The SIFO manuals

The Pharmacist of Research and the Research Pharmacist: Users Guidelines

SIFO
Italian Society of Hospital Pharmacy
and Pharmaceutical Services of Health Authorities

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The Pharmacist of Research and the Research Pharmacist: Users Guidelines

Edited by the Scientific Managers
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When it comes to Research and Clinical Trials...

The future belongs to those who face it, not to those who fear it
Steve Jobs

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MODULE I: PHARMACIST OF RESEARCH

MODULE II: RESEARCH PHARMACIST

MODULO III: NON-PROFIT RESEARCH

Preface

M. Pani, S. Serao Creazzola, A. Cavaliere
Board of Directors 2016-2024, SIFO Presidents

This Manual was established as a functional synthesis of an important training course on Clinical Trials promoted by SIFO. The Project for "National High Level Specialization Course in Clinical Trials" – conceived during the Clinical Trials session in the XXXVIII SIFO National Congress 2017 in Rome and subsequently presented at the XXXIX SIFO 2018 National Congress in Naples which ended in June 2021 with a specific congress session – has foreseen six itinerant meetings (three residential: Rome, Milan and Bari; three via webinair: ex Bologna, ex Turin and ex Palermo) and one web based meeting repeated every month for 7 months. It was an important training and updating project in which SIFO desired to invest heavily, highlighting the attention and value of the hospital and territorial pharmacist as an Health Authority to conduct Clinical Trials. The Manual reports and examines topics and themes dealt with during the training course, starting from the contributions of the Professionals involved, taking stock of the reality and prospects for the pharmacist, in the light of the current regulatory evolution.

The **EU Regulation no. 536/2014**, which due to the pandemic period has delayed its introduction and will be implemented in the first months of 2022 and will constitute an epochal shift in the management of clinical trials, from national to coordinated at European level. This new European regulation will certainly benefit to the Italian research, as it was created to fill gaps and shortcomings of the current Italian legislation, such as complexity, bureaucracy, the long delays times, high costs and approval delay of authorization phases, in particular by Ethics Committees for multinationals clinical trials. **Lorenzin Law no. 3 of 11 January 2018, the Constitution of the National Coordination Center of Territorial Ethics Committees (Ministerial Decree 19 April 2018), the Commission Implementing Regulation (EU) 2022/20 of 7 January 2022 (laying down procedures for application of Regulation (EU) no. 536/2014), the identification of Ethics Committees of national significance (GU no. 63 of 16 March 2022), the measures to adapt the suitability of the structures in which the clinical trial is conducted in accordance with the provisions of Regulation (EU) no. 536/2014 (GU no. 65 of 18 March 2022) and all subsequent rules/regulations that will be issued and applied,** will urge to create an increasingly congenial reality in the "Italian System of Ethics and Research Committees" for the application

of the European Regulation which is a candidate to become one of the most important European milestone law for clinical trials.

The formative intent of this Manual is, first of all, to define and intensify, in the real world of the Pharmacist, both Hospital and Territorial, the operational areas in the future management/realization of a Clinical Trial in Italy.

On the one hand, it wants to highlight the methods of carrying out this operational management, in which Institutions/Actors will be involved, such as **SIFO** and the Hospital/Territorial Pharmacists, can organize themselves, trying to identify and address the possible critical issues on which to intervene in the field of interventional and observational clinical research. On the other hand, by explaining how this regulatory evolution which is required will ensure that the Hospital/Territorial Pharmacist skills and professional and managerial expertise in the administrative, logistic and clinical fields are increasingly more specific and of high quality in the context of Clinical Trials, with a vision more in line with the most recent international GCP and GMP guidelines. Furthermore, specific methodological-statistical skills will be required, in particular when carrying out the Observational studies of Real World/Real Life, given the important therapeutic/clinical impact of the innovation that has occurred in recent years, which is foreseen to increase in the future.

With the elaboration of this Manual, SIFO intends to provide a written and tangible reference, useful and indispensable, in particular for new recruited personnel, for the identification, definition and affirmation of two highly specialized figures in this professional field: **"Pharmacist of Research"** and **"Research Pharmacist"**.

In fact, in the context of Clinical Trials, it is fundamental, opportune and necessary for SIFO, to continue **to invest and implement high professional training** for the two complementary figures, but operating individually:

- the **Pharmacist of Research**: that is the Hospital/Territorial Pharmacist who operates either as a member of the EC and/or as a component/manager of Scientific Secretariat of the ethical committee (EC) and/or as a member/manager of the Regional Clinical Trials Observatory and/or as the manager of the Logistics/Clinical and Administrative management of the Profit or Not-for Profit clinical Trials transiting and stationing in the Hospital/Territorial Pharmacy;
- the **Research Pharmacist**: as a sponsor of Clinical Research in particular by carrying out Observational Studies of Real Life/Real World, with reference to the multiple work/professional activities that the Hospital/Territorial Pharmacist carries out each day: for example Appropriateness, Adherence Pharmacovigilance, Pharmacoeconomics, Quality of Life, Counseling, "Effectiveness", Efficiency, etc.

The present Manual has the ambition to be an updated and complete, comprehensice and clarifying tool for every aspect/area inherent in the world of Clinical experimentation, in a vision for planning in depth:

- **the institutional aspects for a global vision** of the world of Clinical Testing, involving all the Actors/Professionals that for their competence have been involved and have given their contribution in the training and in-depth courses for this SIFO's project of High Specialization in Clinical Trials and all other related activities promoted by SIFO in recent years (National itinerant residency courses, Web and FAD, SIFO Clinical Congress Trial Sessions from 2017 to 2021, other SIFO National-Regional Courses);
- **the operational aspects, addressing in detail areas and criticalities** in which the "Pharmacist of Research" and the "Research Pharmacist" are and can be involved in the various activities that they have to face daily such as planning, solving and possibly writing and/or publishing.

This work results from the effort of making information, knowledge and arguments available derived from reports of chapters/theoretical sessions/ training courses of the highest professional quality needed within the world of Clinical Trials.

Particular attention is given to the issue of the development and implementation of Real Life/Real World Observational Studies, for the activities that the Hospital and Territorial Pharmacist faces daily, providing the theoretical basis, including the STROBE Statement (Strengthening the Reporting of Observational Studies in Epidemiology).

This Manual therefore represents a **reference tool, necessary, useful and indispensable in the world of Clinical Trials**, both under the regulatory profile, for organization and planning, for approval, leadership, management and logistics of Clinical Trials, and from a methodological point of view to stimulate, encourage and implement research projects such as:

- Descriptive observational studies: prevalence studies, case studies, evaluation of diagnostic tests, concordance studies, cross association studies;
- Longitudinal descriptive observational studies: incidence studies, description of the effects of an unwanted intervention, description of natural history;
- Analytical Observational Studies: cause-effect sequence: cohort studies;
- Analytical Observational studies: effect-cause sequence: case studies check.

* When we talk about local or territorial pharmacist we mean pharmacist who works in the pharmaceutical services of the Local Health Authority; when we talk about local o territorial pharmaceutical service we mean the pharmaceutical services of the Local Health Authority.

Preface

A. Marinozzi, G. Polito
Scientific Cultural Clinical Trials Area 2016-2024
Scientific Cultural Pharmaceutical Legislation Area:
Hospital-Territory 2020-2024

Clinical research plays a role of primary importance in the health panorama, it is fundamental for the development of new treatments, constitutes a long-term investment of innovation for the quality of life perspective and it is an engine of economic and social development. It is therefore the lifeline that maintains the NHS, permeates it in all fields and shapes it according to continuous and sudden changes in the standards of treatment and in all therapeutic areas.

The continuous changes consequently entail changes in the European and national legislation, to make the processes more usable and effective allowing on time use of new treatments. At present, we are witnessing an important legislative and regulatory changes due to the entry of the Regulation (EU) no. 536/2014, of the application of the "Implementing Regulation (EU)2022/22", to the heath minister Lorenzin Law no. 3/2018 and to all the implementing decrees that completely revised the management of clinical trials.

In this context, the hospital and territorial pharmacists experience the change due to these new laws for conducting clinical trials and therefore having an intrinsically dual nature: that of the Pharmacist of Research and that of the Research Pharmacist. These two figures show the extremely versatile and multifaceted character of the hospital and territorial pharmacist, that is called to manage to test multiple issues:

- in the management field the **Pharmacist of Research** guarantees the processes relating to the administrative-logistic part of Profit and Not for Profit clinical trials (he is entrusted with the task of receiving and managing the Investigational Medicinal Products (IMPs), either as Pharmaceuticals or as Medical Device), as well as providing his know-how both at level of the Technical-Scientific Secretariat of Ethic Committee and as a member/ manager of the Regional Observatory for clinical trials;
- in the clinical world, as **a Research Pharmacist**, he supports the Researchers in the development and carrying out of projects and to promote observational studies of Real Life/Real World, studies in which the health system has great expectations and hopes that they could reach many areas of hospital practice such as: appropriateness, pharmacovigilance, pharmacoepidemiology, etc.

In light of the importance of the pharmacist's role in these areas, a virtuous national path of high specialization in clinical experimentation was carried out, which led to meetings, webinars, scientific sessions at national congresses, repeated web based meeting and up to this highly specialized manual, which aims to make a strong contribution for all the colleagues that will be involved into clinical trials offering an important tool to think for standard operating methods to colleagues that already work in this field. The manual is ambitious, it aims to be a national reference point on the current panorama of clinical trials, giving a complete overview on the subject and addressing in detail and in-depth all the issues inherent to this world. The manual gives ample emphasis to the regulatory part, relating to the New Regulation (EU) no. 536/2014, to the Lorenzin Law no. 3/2018 and the Implementing Decrees, the legislation concerning clinical trials of galenic and radiopharmaceuticals, to medical devices according to Regulation (EU) no. 745/2017, focusing both on specific areas, such as the Requirements to be accredited as Phase I study centers (Det. AIFA no. 809-2015), and on the logistical aspects and standards for a correct management of Investigational Medicinal Products (IMP).

The second part of the manual is related to research, providing biostatistical bases for the realization of experimental studies, with a focus on strengthening of the Reporting of Observational studies in Epidemiology (STROBE statement) and Real World Evidence, up to a detailed management and design of the Not for Profit clinical trial.

The Manual can therefore be understood as a unique methodological tool of its kind, offering all the necessary information to be able to know and improve the training path of the hospital and territorial pharmacist, helping them in giving the impetus to a continuous improvement in the quality of care, hoping to reach the heart of national institutions and leaders to an ever more prolific collaboration between these bodies and professionals of this field.

With the collaboration of:

- *Scientific Cultural Area Clinical Trials 2016-2020* – A. Marinozzi, S. Borrione, V. Cola, C. Confalonieri, G. De Luca, S. Ferraiolo, G. Orlando and Vergati
- *Scientific Cultural Area Clinical Experimentation 2020-2024* – G. Polito, E. Capone, G. Casini, C. Confalonieri, G. De Luca, R.M. Lobello, M.A. Maselli, A. Maugeri, S. Passacantilli, M. Roperti, M.E. Sellitti and F. Vecchione
- *Scientific and Cultural Area of Pharmaceutical Legislation: Hospital-Territory 2020-2024* – A. Marinozzi, P. Baldo, F. E. Bernardini, G. Blandini, C. R. Borino, V. Drago, C. Hasa, L. Magnani, M. Peverini, A. Renzetti and A. Zovi

Preface

S.E. Campbell Davies, C. Lamesta
SIFO Youth Area 2016-2024

Without clinical trials, conducted on patients to verify the efficacy of the latest therapeutic discoveries or new diagnostic tools, research cannot go on, especially if clinical trials are not conducted rigorously and with a sufficient number of patients. More specifically, in clinical research, it is difficult to analyze its dynamics without contextualizing it in the more general situation of the National Health Service (NHS). This aspect does not appear absolutely irrelevant for the efficiency of a sector such as that of clinical research, which requires ever higher quality standards, as well as ever greater professional skills and availability of time on the part of healthcare personnel. The entry into force of the legislation represents an important turning point in an era in which clinical experimentation has assumed an increasingly central role, hence the idea of us young people to deepen the research and experimentation activity of the hospital pharmacist. I give to the realization of a highly specialized course.

An itinerant course for Italy, which saw the construction and subsequently the realization of an ambitious project, namely the "Pharmacist of Research" and the "Research Pharmacist", thus providing knowledge and preparation to SIFO members, through theoretical and practical sessions. Clinical trials, the purpose of which is to demonstrate through the scientific method the validity of a therapy capable of preventing a disease, improving a diagnosis or treatment or improving the quality of life, are also recognized as an excellent teaching tool for young colleagues in training. Because, every research professional must have in mind that the patient's interests and the advancement of medicine must be the primary goals in conducting a clinical trial.

In this way, the **Youth Area 2016-2020 looked to the younger members to help them integrate and make their way into the world of drug research and development**. It is precisely from this cultural change that the **Youth Area 2020-2024 wants to create a completely new concept of the young hospital pharmacist, highlighting the role it plays not only in educating the patient but also in creating a service that places at the center the "1000 faces" of our profession, including research as a fundamental part of normal daily practice**.

In recent years, research has brought new knowledge into science

biomedical, pharmaceutical sectors by bringing enormous information and new technologies available to young pharmacists who will continue to explore and learn. **The manual will offer new opportunities and perspectives to the profession by ensuring that the Pharmacist of Research retains his key role in the innovative, dynamic models and systems of health care and the provision of health services in which he is involved, and the Research Pharmacist to read, interpret, demonstrate and promote the scientific evidence indispensable for a correct, ethical and appropriate management.**

With the collaboration of:

- *SIFO Youth Area 2016-2020*: S.E. Campbell Davies. G. Bagaglini, F. Brera, C. Cannizzo, C. Confalonieri, M. De Fina, F. Decannas, M. Del Pizzo, C. Lamesta, R. Langella, C. Lodovichi, C. Marella, N. Nigri, C. Procacci, E.M.F. Tempesta.
- *SIFO Youth Area 2020-2024*: C. Lamesta, D. Bazzani, E. Belvedere, S. Berlinghini, D. Cambareri, Y. Cau, A. D'Avino, M. Del Pizzo, C. Della Costanza, F. Decannas, G.B. Di Nardo, M. S. Giurin, C. Crespini, A. Salierno, Staiano.

Introduction and Objectives

Curated by the Scientific Managers
P. Polidori, A. Marinozzi, R. Langella

The realization of this Highly Specialized Manual is intended to be the expression of a training course of high professional, intellectual and regulatory depth, whose design spark was born in the Congress Session of Clinical Trials in the XXXVIII SIFO National Congress 2017 in Rome, with Tutor **Barbara Meini** and report by **Andrea Marinozzi** (Responsible in SIFO ASC Clinical Trial), entitled ***"Il Farmacista di Ricerca e il Farmacista Ricercatore – Istruzioni per l'Uso"***. The Session and the presentation in particular, immediately aroused and aroused great interest in the Scientific Society and in all the stakeholders present, in particular:

- by the SIFO Board in the person of **Piera Polidori,** who, being also a member of the EAHP board, saw the need and opportunity to undertake a training course in the national context with a European eye, for the institutionalization and training of these two highly specialized and professionalizing the category;
- by the SIFO Youth Area, in the person of **Roberto Langella,** an area in which the intellectual and physical energy mixed with the desire to grow and train, inherent in the young part of our Scientific Society, if properly cultivated, educated and professionalized, they could be a source and matrix for the promotion and management of scientific research at 360 degrees, in all areas where the Hospital and Territorial Pharmacist operate.

The project idea, mixed with passion and love for our profession and SIFO, catalyzed by the generosity of all three of *"throwing your heart over the obstacle, always and in any case"*, meant that at the XXXIX SIFO National Congress 2018 Naples was institutionalized and started, in the Clinical Trials Session, a course of **SIFO High Specialization in Clinical Trials, entitled "Il Farmacista di Ricerca e il Farmacista Ricercatore – Istruzioni per l'Uso"** of high professional and educational depth that developed and carried out:

- **in the Congress Sessions on Clinical Trials of the following SIFO Congresses**: Genoa 2019, Florence (via Web 2020), Rome 2021;
- **6 itinerant National Conferences** (3 residential: Rome 2019, Milan 2019 and Bari 2020; 3 via webinair: exBologna 2021, exTorino 2021 and exPalermo 2021;
- **a National FAD** lasting 7 months (the FAD that has had the most adhesions and members in the history of SIFO).

It is a complex, important and highly professionalizing editorial training and updating project, financed through the involvement of about 60 specialized companies, coming from both the drug and medical device world, in which the Scientific Society had the opportunity to be able to involve stakeholders and excellences in the field of National and International Clinical Research, in the context of SIFO, of Institutions (AIFA, ISS, Ministry...), Universities, other Scientific Societies (FADOI, GIMBE...) and others Professions (Clinicians, Researchers, Statisticians, Nurses...), bringing out and highlighting the professional and institutional value of the hospital and territorial pharmacist of the Health Authorities in clinical trials across the board.

The realization of an editorial work at the end of this great, complex and long project is fundamental and indispensable to fix all the themes and topics covered. It has the ambition to be a tangible work of the many sacrifices put in place, of the many information provided, a necessary, useful and practical reference to support the figures of the Pharmacist of Research and the Research Pharmacist, reporting and deepening all the rules, the topics and topics covered, involving as much as possible all the speakers and teachers who were protagonists during the various project activities, dividing into four Macro areas described below:

- **The Clinical Trial in SIFO in the Regional context, by the Regional Secretaries and SIFO Advisers Year 2020-2024.** In which all the scientific, training and planning activities of the Regional SIFO Secretariats are detailed with the aim of being a window of professional comparison-visibility and occasion-opportunity for stimulation and growth in carrying out and promoting research in a systemic and capillary way in Regional scope.
- **Module I: Pharmacist of Research.** In which are listed and updated, up to the time of printing, all the Regulatory, Management, Organizational aspects in the context in which this figure operates, also giving a practical cut of realization and examples of excellence and organizations in the National context.
- **Module II: Research Pharmacist.** In which all the statistical and methodological tools necessary to carry out, read and promote clinical research are provided, detailed and indicated, particularly in the areas where this figure is the protagonist and can express its cultural, professional and scientific value.
- **Module III: Non-Profit Research.** In which we wanted to strengthen all the design potential and to do research expressed in Module II, providing further scientific, methodological and design ideas, to develop more structured and consistent research that can also be a source and promotion of national works, projects and research and International.

Clinical Trial in SIFO in the Regional Area

Curated by the Regional Secretaries and SIFO Councilors
Year 2020-2024

Preface

by the Scientific Tutors U. Trama and A. Vercellone

Clinical trials must be understood essentially as a tool for the protection of citizens' health and therefore, as such, it represents both a professional obligation for all health professionals and a moral imperative for the purposes that a scientific society such as SIFO proposes itself.

In fact, by extension, clinical research on drugs can also be considered as one of the ways that health professionals have to put into practice what is defined by art. 32 of the Italian Constitution which defines the right to health, as the right of the individual and as an interest of the community to promote the health of the entire population, which corresponds to what scientific research proposes in its ultimate goal of creating benefits for the people involved in the research and then, consequently, for all people who will be able to enjoy the results deriving from the advancement of knowledge.

Clinical drug research is a fundamental asset for the National Health Service and the economic system. Participation in controlled clinical research activities translates into important benefits for all the actors involved:

- for patients enrolled in clinical trials, who are offered the possibility of potentially innovative treatments well in advance of their general availability;
- for health companies that host experimental centers as they enjoy an improvement in the quality of health care as well as a notable professional growth of the personnel involved (investigators, doctors, pharmacists, research nurses, trial managers and others);
- for independent clinical research, the dissemination of which is facilitated in facilities that manage high volumes of sponsored controlled clinical trials;
- for the Health System, which becomes the recipient of economic resources, as the delivery of experimental and control drugs administered to patients enrolled in clinical trials, and all the numerous diagnostic services and laboratory analyzes that are performed during the trials, they are entirely borne by the sponsoring companies;
- for the whole Community, both in terms of social utility for the lengthening of the average life span and the improvement of the general quality of life in the population that the development of new drugs can determine both in terms of growth opportunities for operators and new employment opportunities.

Clinical research is therefore an engine of economic and social development for the country. Thus, in this moment of changed international scenario, the elaboration of a new support strategy for clinical trial activities has become crucial, centered on the need for structural reforms also of the regional system, in order to avoid the risk of being excluded from the international circuits of truly innovative research. The legislative and regulatory changes brought about by the introduction of the European Regulation no. 536/2014 if supported by organizational and governance interventions constitute in fact important development opportunities for our NHS. It is essential to implement all effective strategies aimed at guaranteeing attractiveness, competitiveness and innovation:

- guaranteeing the start-up times and costs of clinical trials compatible with international competition, adapting the regulatory and legislative framework;
- strengthen the experimental centers, with an adequate staff of personnel dedicated to clinical research (Pharmacist of Research, data manager, study coordinator…), improving the organization and the ability to enroll a large number of patients;
- promote the presence of networks by pathology and of collaboration between research centers;
- promote and enhance the training of personnel dedicated to research;
- improve access to innovation, with strong digitization strategies of the research centers and the adoption of innovative technologies that will be the drivers of future value, seeing that this area represents one of the strategic axes around which the National Recovery and Resilience Plan is developed.

Surges an urgent need for a strong alliance between politics, institutions, operators in the health sector and the pharmaceutical industry to create the conditions so that clinical research in our country may express itself efficiently in the competitive international panorama.

In this scenario, the pharmacist of the NHS plays a fundamental role as an integral part of the Ethics Committees, as foreseen by the current legislation on the subject (Decree of the Ministry of Health 8 February 2013) and, for this reason, fully involved in being an ethical guarantor the primacy for the wellbeing of the citizen, the freedom of scientific research, the protection of the citizen in his or her dignity and integrity, the maximization of benefits and the minimization of risks, respect for autonomy and consent in format, protection of privacy and the confidentiality of personal data, the protection of vulnerable people, of equal access to treatment and the refusal of all forms of discrimination.

Therefore, the pharmacist of the NHS who is a member of an Ethics Committee has a duty to rigorously assess, in collaboration with the other professionals involved in the CE, the methodological validity and requirements of researchers and test sites for clinical trials on drugs and medical devices.

Furthermore, it is also the main factor for the evaluation of off-label uses (Law no. 94/1998) and for the so-called "compassionate use" (Ministerial Decree of 7 September 2017): indispensable paths to guarantee access to the drug to patients suffering from rare diseases or for whom an effective therapeutic path has not yet been identified.

However, clinical research on drugs or medical devices is not the only type of activity through which the pharmacist can give his contribute to research. In fact, in the broader perspective of the organization of therapeutic paths and the good use of the pharmaceutical asset with the consequent fair allocation of the economic resource, the pharmacist is also engaged in the promotion of those studies that use Real World Data, which are increasingly demonstrating of being an important source of valuable information available for scientific research.

It is, therefore, bearing these principles in mind that the information and training activities by the SIFO Regional Secretariats have been implemented, and in some cases thanks to the collaboration and support of the dedicated Scientific Area, in order to provide all colleagues with a "toolbox" for all aspects related to clinical research, but above all to stimulate in each one the will to actively engage in this field as well.

SIFO SECRETARIAT OF ABRUZZO AND MOLISE REGION
Secretary: F. Santoleri
Councilor: F. Simiele

Scientific Area Coordinator of Pharmacy: Felice Simiele
Collaborator of the Scientific Area of Pharmacy: Fiorenzo Santoleri CURF member: Alberto Costantini
Collaborator in the areas of Pharmacutilization, Pharmacovigilance, Medicinal Gases: Alessia Romagnoli
Radiopharmacy Area Collaborator: Manlio Mascia

Training activities carried out in the years 2017 – 2018 – 2019 – 2020– 2021 – 2022

Insights into the Radiopharmacy area:
April 4, 2022
Role of the Pharmacist in Nuclear Medicine
Conferences in the area of Pharmacutilization:
27 – 28 May 2022
Analysis of real world data and real world evidence through the use of drug-utilization indices
31 December 2021
Management of the patient with haemophilia and ways of accessing new therapies in the Abruzzo Region
10 November 2021
The drug use indices - real-world application in Hemophilia
22 – 29 September 2021
Drug-use indices - application in the biological real world
30 June 2021
The drug use indices: application in real-world oncology
18 September 2020
Interregional SIFO Marche, Abruzzo and Molise: Biosimilar drugs: an opportunity for the sustainability of the health system. Pescara.
9 November 2019
Sustainability and costs in evaluating the therapeutic choice in IBD. Pescara
7 – 8 November 2019
The management of chronicity: analysis models of pharmaceutical prescriptions as a basis for the optimization of the treatment path
24 – 25 May 2019
Analysis of Real World Data and Real World Evidence through the use of drug-utilization indices

14 December 2018
Analysis of data from Real life: comparison on data management methods
24 – 25 May 2018
Analysis of Real World Data and Real World Evidence through the use of drug- utilization indices
26 – 27 May 2017
Adherence to treatment and data analysis in the real world setting: drug-use evaluations.

Projects in place

National multicentre non-interventional pharmacological restrictive study: "ADA_ETA_BIO2021: Pharmacutilization analysis on biologic and targeted synthetic disease-modifying anti-rheumatic drugs: adherence, persistence, switch and costs in real life. Focus on comparison between originator and biosimilar, oral and parenteral therapy".

Projects concluded

1. National multicenter pharmacological non-interventional retrospective study: "Adherence, persistence and efficacy of dasatinib and nilotinib in the treatment of patients in the chronic phase of chronic myeloid leukemia".
2. "Adherence, persistence and efficacy of nintedanib and pirfenidone in the treatment of patients with idiopathic pulmonary fibrosis".

Evidence produced

1. Santoleri F, Ranucci E, La Barba G, Colasanto I, Scaldaferri M, Cattel F, Federici F, Rossi C, Di Biagio K, Scortechini AR, Musicco F, Torquati G, Frazzetto A, Vozza A, de Rosa C, Lanzillo R, Monteverde M, Luciano L, Pane F, Pasquazi A, Celeste MG, Cantonetti M, Franceschini L, Rizzo M, Costantini A. Adherence, persistence and efficacy of dasatinib and nilotinib in the treatment of patients resistant or intolerant to imatinib with chronic myeloid leukemia in chronic phase: an Italian multicenter study over two years in real life. Curr Med Res Opin. 2021 Mar; 37(3):477-481.
2. Santoleri F, Auriemma L, Spacone A, Marinari S, Esposito F, De Vita F, Petragnani G, Di Fabio C, Di Fabio L, Costantini A. Adherence, Persistence, and Effectiveness in Real Life. Multicenter Long-Term Study on the Use of Pirfenidone and Nintedanib in the Treatment of Idiopathic Pulmonary Fibrosis. J Pharm Pract. 2021 Apr 21:8971900211008625.

Scientific activities produced

- Romagnoli A, Santoleri F, Costantini A. The impact of COVID-19 on chronic therapies: the Pescara (ASL) local health authority experience in Italy. Curr Med Res Opin. 2021 Dec 10:1-6.
- Santoleri F, Romagnoli A, Costantini A. Adherence and persistence in the use of statins and ezetimibe over 8 years in a real-life study. Curr Med Res Opin. 2021 Sep 29:1-6.
- Romagnoli A, Santoleri F, Costantini A. Drug utilisation pattern over 3 years in the real-world treatment of type II diabetes. Int J Clin Pract. 2021 Mar 2:e14120.
- Romagnoli A, Santoleri F, Costantini A. Adherence and persistence analysis in patients treated with double antiplatelet therapy (DAPT) at two years in real life. Patient Educ Couns. 2021 Jan 12:S0738-3991(21)00005-7.
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- Romagnoli A, Santoleri F, Costantini A. Adherence and persistence analysis after three years in real-life of inhalation therapies used in the treatment of COPD. Curr Med Res Opin. 2020 Nov 3:1-7.
- Santoleri F, Romagnoli A, Costantini A. Real-life adherence in capecitabine therapy using two analysis methods and persistence after 6 months of treatment. J Oncol Pharm Pract. 2020;1078155220949634.
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- Santoleri Fiorenzo, Romagnoli Alessia, Costantini Alberto. Adalimumab and etanercept adherence, persistence and switch in the treatment of psoriatic arthritis: 10-year real-life analysis. Expert Opin Drug Saf. 2020 Jan; 19(1):93-97.
- Santoleri F., Romagnoli A., Costantini A. Use and costs of originator and biosimilar erythropoiesis- stimulating agents in the treatment of chemotherapy-induced anemia: real-world evidence from an Italian hospital. Future Oncology 2019 15:1, 45-51
- Santoleri F, Lasala R, Logreco A, Ammazzalorso A, Fantacuzzi M, Amoroso R, Costantini A. Time factor in antiretroviral adherence: analysis of adherence to single-tablet regimens versus multipletablet regimens over a 5-year period. Drugs Ther Perspect, 34, 263-268 (2018);

• Santoleri F, Lasala R, Logreco A, Ranucci E, Costantini A. Using a treatment diary to improve the medication adherence in patients with chronic myeloid leukaemia. J Oncol Pharm Pract. 2018 Jan 1:1078155218759184.

SIFO SECRETARIAT OF BASILICATA REGION

Secretary: F.A. Di Cuia
Councilor: M.C. Galizia

In 2021 the Regional Secretariat of Basilicata organized, together with Puglia, an ECM course sponsored by SIFO in Videoconference entitled *Communication in Healthcare: agreement and divergence points between "talking" and "narrating"* held on Friday 26 March 2021 at 2.30 pm.

The meeting saw the participation of many SIFO members with the aim of connecting the different settings in which communication is crucial to standardize quality paths and give information on the best way to relate to give health, focusing the attention to oncology.

Taking a cue from the requests received from many Members, there's a plan to organize a training event in the near future, to be held in the city of Matera with the participation of the Secretariats of the neighboring Regions (Puglia, Calabria, Campania) on the subject of medical devices following the entry into force of the new European regulation and the innovations introduced on the subject.

Another subject on which we are working for the organization of a training event is that of the National Recovery and Resilience Plan (NRRP), which has the declared objective of radically reforming the prevention sector, aligning health, environmental and climatic conditions, as well as to strengthen the territorial settings for taking charge and care of people, given that the pandemic has shown that the better structured regions on the territorial side have reacted to the pandemic emergency with greater effectiveness and appropriateness of the interventions.

The aim of the course is to focus one's attention on key issues necessary for the improvement of hospital and territorial processes and paths such as: Digital Health, management of urgency in Emergencies and above all to highlight solutions aimed at improving the organizational welfare.

All this is in the planning phase with the involvement of our members and it is hoped to make them viable by the end of this year 2022.

SIFO SECRETARIAT OF CALABRIA REGION

Secretary: F. Urso

Councilors: A.E. De Francesco, D. Labate

Regional Quality Referent: Brunella Piro – ASP Cosenza Pharmacist Manager
SIFOweb contact person: Maria Roberta Garreffa
SSFO contact person: Domenica Costantino

Calabria was the first region, together with Emilia-Romagna and Liguria, to undertake the quality certification process of the Regional Secretariats and to achieve this result in 2014. The Calabria Regional Secretary is part of the updating group of the quality system documentation of the secretariats themselves.

The project, which was launched in 2013 with the first staff meeting of the members of the regional secretariats, aimed at achieving certifiable quality standards for the processes of the regional secretariats.

After a series of face-to-face work meetings, in which activities were analyzed and the definition of monitoring procedures and indicators, the certification process was concluded.

The Regional Secretariat has always paid particular attention to Hospital Pharmacy Postgraduates and, since 2016 it has financed every year, through the use of Regional Funds, vouchers for enrollment in the SIFO National Congress.

Furthermore, the Regional Secretariat is very active as regards the interaction with the Regional Institutions. In 2021 the Regional Secretary was authorized to the Health Commission in the Regional Council, where he exposed the various problems of Pharmaceuticals, that represents the second expenditure item of the regional budget, immediately after Personnel.

The Regional SIFOweb Referent takes care of updating the web page, interfacing and interacting with the SIFOweb National Editorial Team.

The objective of the constant updating of the Calabria section of the site is to make the information of greatest interest to professionals in the pharmaceutical sector belonging to the NHS structures easily accessible.

The page has been made functional and easy to consult, as it is divided by thematic areas in "Communications" (notices of particular importance for SIFO members), "Activities" and "Regulations".

The section dedicated to "Activities" contains all the events in which the SIFO Regional Secretariat has actively participated, sponsored by SIFO or SIFO- Provider. Since 2016 to the present day, including seminars, courses, conferences and webinar, a total of 33 events were organized, all important

occasions to address various topics of extreme interest for the profession, to debate with colleagues and exchange their experiences, offering serious reflection and professional growth.

The "Regulations" section is an area treated with particular attention, since it is dedicated to regional legislation relating to regional laws/regulations/regional notes regarding Pharmaceuticals.

It contains all the Decrees of the Commissioner ad Acta issued to regulate the activities concerning the Hospital and Territorial Pharmacy services in the regional context. All documents (over 150) are subdivided by year and by areas of interest; for example, all the measures concerning the Prescribing Centers authorized in our region for the diagnosis and treatment of specific pathologies have been grouped in a single archive, as well as the DCAs relating to the updates of the Regional Therapeutic Handbook and the Framework Agreement for A-PHT drugs, which represented an indispensable tool for the procurement of drugs from the Healthcare and Hospitals of Calabria.

The aim of the work carried out in recent years is the constant updating of the page in order to provide important technical support to the NHS Drug Managers, simplifying access to essential information for the correct performance of the profession in our region. SIFO Calabria members are in fact constantly updated and a notification is sent to them at each update of the section.

The Privacy Requirements are applied, which we now know are of great importance.

There is a continuous and always fruitful collaboration with the School of Specialization in Hospital Pharmacy of the "Magna Graecia" University of Catanzaro. In addition to continuous interaction, periodic meetings are organized in order to be able to confront each other in the common interest of providing the Residents in Hospital Pharmacy with the best possible training. For this purpose, the Manual drawn up by SIFO in the latest version available is sent to the tutors.

The Calabria Region played an important role in FARMAPER, the entirely self-financed SIFO National Project, carried out in collaboration with the Business Management School of the Bocconi University, which sees the participation of 6 SIFO members from the Calabria Region. The project aimed to build a performance management system for the development of the pharmacy and the pharmacist in health and hospital companies, starting from the contextualization of the value produced by SIFO, and then continuing with the subsequent objectives, including redefining the identity of the Profession and the hospital and territorial Pharmacy, to then get to enhance the health role of the NHS Pharmacist Manager.

Calabria has become the spokesperson, together with the other Regional Secretaries of the four-year period 2016-2020, of a request to the Board of Directors to address the problem of drug unavailability.

This phenomenon of "unavailability", distinct from "deficiencies" (recorded on the AIFA portal), the result of distortions in the distribution chain, is in fact added to these and constitutes the overall unavailability of the drugs.

SIFO, on the proposal of the Regional Secretariats, has decided to start a project called "DruGhost" which plans to activate and provide a national database of drug unavailability in order to map and quantify a phenomenon that is perceived as important, share with AIFA the reports contained therein and to network with all the NHS structures a tool that could also be very useful for "validating" and "evaluating" suppliers in tender procedures.

Calabria plays a fundamental part in the Working Group as the National Coordinator of the Project is the Regional Secretary for 2016-2020 and 2020-2024.

The Project was carried out in partnership with AIFA, and there is in fact a link to DruGhost on the AIFA portal in the section dedicated to drug shortages.

The project was then joined by Egualia - Industrie Farmaci Accessibili, with whose contribution it was possible to finance a scholarship for a resident in Hospital Pharmacy dedicated to the Project.

The Database was then modified so that upon entering an unavailability of a product distributed by a company belonging to the Egualia Consortium, the company is notified of the unavailability registered.

The Regional Secretariat focuses heavily on the involvement of Members: in this perspective, taking advantage of the technological innovations and the telematic platforms made available by the National Secretariat, Regional Assemblies are held every 2-3 months, in order to expand the opportunities for discussion between the Calabrian members.

SIFO SECRETARIAT OF CAMPANIA REGION

Secretary: P. Maiolino
Councilors: M.N. Diana, M. Fabbrocini, A. Lalli, M. Mercaldo, M. Scarpato, P. Zuppardi

Since September 2020, the SIFO Campania Regional Council has met 15 times, dedicating itself to the promotion and fulfilment of numerous ideas, passing from editorial projects, to training events, and to communication initiatives. The work carried out and the future prospects were also presented during the first SIFO Campania Regional Assembly, held on 2 December 2021.

As for the editorial projects, they were presented by the Regional Council SIFO Campania and approved by the national SIFO Board of Directors:

1. Project **Ca.RA Regione Campania Rheumatoid Arthritis,** which sets itself the ambitious goal of evaluating the total costs of patients affected by Rheumatoid Arthritis in the Campania Region, abandoning the logic of "silos", in order to be able to evaluate the overall cost of the pathology.
2. **Speed Info** Project, whose purpose is to provide, through a single regional web page, information relating to: points of direct dispensing of drugs, medical devices, aids and nutrition; hours and days of opening to the public; type of drugs, MD, aids and nutrients supplied.
3. **Campania Vaccination Project,** with the aim of evaluating the vaccination coverage of the Campania Region 2019/2020, identifying for which vaccinations the coverage has not yet reached the objectives set by the PNPV, creating strategies to raise awareness among the population and health professionals on usefulness of vaccinations and its importance in the prevention of non-eradicated infectious diseases.

With regard to training events, five courses were organized in 2021:

1. *Calls for tenders for blood products and devices* – Interregional course, webinar
   The aim of the course was to illustrate how to attribute a tender, with the support of numerous practical examples.
2. *Ministerial and regional flows* – Regional course, webinar
   The purpose of the course was to provide correct data of real life that would allow, through the correct monitoring techniques, is to obtain information regarding the state of the population health, and to plan the improved interventions of the existing paths.
3. *Narrative Pharmacy Days* – Regional course, webinar
   This initiative was created with the intention of describing an important tool such as narrative pharmacy, sharing experiences and hypothesizing possible future scenarios for our profession.

4. *Insuline: management of hospital and territory* – Interregional course, webinar The course represented an important opportunity for discussion on how to build a hospital memorandum suited to the needs of patients undergoing hospitalization; to manage the therapeutic continuity of diabetic patients in polytherapy; establish needs, purchasing cycle and physical management of insuline; set up protocols for "special" diabetic patients, such as oncological ones.
5. *Access to oncological and onco-haematological treatments: from decrees to clinical practice* – Regional course, hybrid modality
   The aim of the conference was to allow the various participants involved in the access to care to have a clear vision of the current context, to trace and undertake a single and homogeneous path, through the support of regional directives, safeguarding the patient and supporting the SRG in compliance with the rules.

Furthermore, the SIFO Campania Regional Council, since December 2020, has been editing a periodical, **iPharma.zine,** now in its thirteenth edition. **iPharma.zine** is a magazine of interest for Hospital and Territorial Pharmacists, which collects the voluntary contributions of all colleagues from Campania: work, study and research experiences in the field of Territorial and Hospital Pharmaceuticals. Furthermore, voluntary contributions by experts on topics of interest to the Hospital and Territorial Pharmacist are published. The magazine also includes "*Thematic Sections*" such as that of the Schools of Specialization in Hospital Pharmacy, Covid experiences, Radio Pharmacy and other topics considered current for the Hospital and Territorial Pharmacy; at the end of the mandate of the current SIFO Campania Regional Council, in 2024, a paper collection of the Magazines developed over the four years and disseminated to all Campani members will be produced.

Finally, there are numerous projects of the SIFO Campania Regional Council scheduled for 2022 and proposals for future initiatives: in addition to the courses already scheduled for 2022 ("*I flussi ministeriali e regionali*", The Ministry and Regional Flows, II edition; "*Global health evaluation della Sclerosi Multipla: dalla presa in carico del paziente al confronto tra le figure sanitarie ed istituzionali*", Global health evaluation of Multiple Sclerosis: from undertaking care of patient to the evaluation of the health and institutional figures), topics of great interest for subsequent developments are Radiopharmacy in the Campania Region, Scientific Writing, Plaque Psoriasis - Farmacological Therapy and Expenditure management, the activity of the Umaca and UFA laboratories within the Campania Oncological Network, rare diseases, data analysis and medical devices.

SIFO SECRETARIAT OF EMILIA ROMAGNA REGION

Secretary: A. Marra
Councilors: C. Confalonieri, G. Valentino

The four-year period 2020-2024 led to the election of the new SIFO Emilia Romagna (ER) Regional Secretary Dr. Anna Marra, former Director of the Operating Unit of Hospital Pharmacy of the University Hospital of Ferrara and former coordinator of the scientific-cultural area SIFO of Pharmacovigilance and SIFO Emilia Romagna Regional Councilors Dr. Corrado Confalonieri and Dr. Guido Valentino.

To date, the SIFO ER Regional Secretariat wants to represent an important contact-point to guarantee its member answers relating to the activity of the Scientific Society and guarantees from the training point of view, all aimed at guaranteeing the members comparison and possible solutions to eventual problems in the workplace. Recent developments make it necessary to create a network of professional active research sponsors, a virtual meeting and discussion venue.

In a context marked by the pandemic, the SIFO ER Regional Secretariat managed to guarantee important events and opportunities for discussion. During the year 2021, an important event such as FAD Webinar is organized on 23 June relating to the economic evaluation of health programs.

The increase in health expenditure, the continuous development of new diagnostic and treatment technologies, the growth of expectations towards the NHS require an ever increasing use of resources. The economic evaluation of health programs therefore fills the need to know whether, given the clinical efficacy, there is also an economic efficiency. The Hospital Pharmacist cannot exempt himself from this evaluation and therefore a fluency of the terms used and of the tools apparent to the world of assessment becomes fundamental. The aim of the webinar was to acquire the basic concepts and terminologies used, how to perform an economic drug evaluation of a drug/ medical device and lay the foundations for a correct evaluation of the main online databases. In view of the above mentioned, the interventions of Dr. Luca Degli Esposti relating to the economic impact on health policies and Dr. Andrea Messori on the tools of applied pharmaco-economics were particularly valuable and appreciated.

When dealing with the problem of AMR, very often we talk about prevention programs, which are essential to limit the phenomenon. Prevention is indeed a key aspect of AMR. But although recently research has once again been producing new antibiotics, there is a problem in the appreciation of new molecules and in recognizing the investment of those who develop them.

On 21 July, again through webinar modalities, Dr. Marra and Dr. Confalonieri, as SIFO regional representatives, were invited to take part in a round table organized by Motore Health "Dal 'Cutting Edge' della Ricerca in Antibiotico Terapia al Bisogno di Nuovi Antibiotici, dalla Valutazione del Valore al Place In Therapy Appropriato" with the involvement of various stakeholders of the Emilia Romagna Region, a moment of important discussion.

Still in 2021 the SIFO high specialization course in clinical testing "*Il Farmacista di Ricerca e il Farmacista Ricercatore: istruzioni per l'uso*", involved Dr. Anna Marra and Dr. Corrado Confalonieri in the FAD Webinar course respectively on the issues relating to "*Ricerca No Profit: progettazione, eticita, farmacovigilanza, pubblicazione, scelta delle fonti e bibliografia*" (Research No Profit: planning, ethics, drug vigilance, publication, choice of sources and bibliography) and to the "*Strobe Statement per gli Studi Osservazionali*" (Strobe Statement for the Observational Studies). The national event had a great participation of all the members involved and it was particularly engaging to bring the regional skills acquired up to date to the attention of the learners.

At the end of the year (2-4 December 2021) it was possible to propose and organize an inter-regional course in Rimini, sponsored by SIFO, with the involvement, among others, of important exponents such as Prof. Domenico Motola, Dr. Roberto Raschetti and Dr. Marina Maggini as Speakers. Evidence-based Health Care has been shown to influence all areas of health care by applying the best scientific evidence to clinical practice and the organization of health services. However, the ability to critically analyze the results of the proposed research is necessary: from systematic revisions to meta-analyzes and observational studies, providing tools for a critical reading of scientific articles, in order to assess the appropriateness of drug prescription, which represents one of the most important tasks of the NHS operators involved in the epidemiology sector and the monitoring of pharmaceutical prescriptions. The event, which had a full turnout by colleagues from the whole Region, was structured to comprehend the main aspects of the planning and conduct of pharmacy-epidemiology studies and acutely analyze the results of published studies in order to identify methods for conduction and statistical analysis of randomized/observational clinical trials and critically reading and commenting articles on clinical trials and/or systemic reviews.

The year 2022 finds the SIFO Emilia Romagna Regional Secretariat directly involved in the organization of the next National Congress "*Clinica, Etica, Managerialità. Costruiamo insieme la salute di domani*" (Clinic, Ethic, Management: Building together the future Healthcare) (27-30 October), Bologna, Palazzo della Cultura e dei Congressi, President of the Congress

Dr. Alessandro D'Arpino with Dr. Marra as President of the Scientific Committee, Dr. Mauro Mancini President of the Organizing Committee and the SIFO Regional Councilors Dr. Confalonieri and Dr. Valentino involved respectively in the scientific and organizational committee. Only by basing ourselves on strong and scientifically unassailable clinical values and processes, only by referring to a crystalline professional ethics and by relying on effective and shared management qualities, will we be able to transform NRRP into an opportunity for the health of the future. It shall be Bologna, a city of extraordinary cultural and academic tradition, that will be the seat of our demanding study.

Research and continuous training become a daily working tool with a view to planning activities and a functional tool aimed at increasing the efficiency of the system in order to generate data that have a positive impact on the National and Regional Health Service as well as on the health of the citizens.

SIFO SECRETARIAT OF FRIULI-VENEZIA GIULIA REGION

Secretary: C. Roni
Councilor: L. Virdis

Who we are

The regional section SIFO Friuli-Venezia Giulia (FVG) counts with 55 members, in March 2022, derived from all entities of the Regional Health Service: Azienda Sanitaria (Health Agency) Friuli Occidentale (AS FO), Azienda Sanitaria Universitaria (University Health Agency) Friuli Centrale (ASU FC), Giuliano Isontina University Health Authority (ASU GI), IRCCS Cancer Reference Center (CRO) of Aviano, IRCCS Burlo Garofolo of Trieste and Regional Coordination Agency for Health (ARCS).

Subscribers are thus distributed among hospital pharmacists, local pharmaceutical services, trainees and other types (pharmacists operating for example within the Regional Health Coordination Agency, the Regional Pharmaceutical Service, etc.):

Pharmacists	Number of subscribers
Hospital	30
Territorial	5
Other	10
Trainees	10
Total	**55**

Working groups

During 2021, the Regional Secretariat promoted the activation of a joint **working group** between SIFO members of the FVG and Veneto **on the class of antisense oligonucleotides (ASO)**, still in operation.

Objectives of the working group:

- in-depth analysis of the class of ASO drugs already available on the market and in the phase of forthcoming approval, identifying, through an analysis of the literature available on the subject, the salient aspects that affect the entire class or the single molecule in relation to the mechanism of action, safety and management of these drugs;
- in-depth study of two pathologies (spinal muscular atrophy for the area of rare diseases and hypercholesterolemia for the area of chronic diseases), on which to focus a definition of the place in therapy of the new ASO molecules compared to other therapies available.

The project, aimed mainly at young members, aims to be a way to share a way of working on and analyzing the literature of new therapies, and will result in training events/publications for SIFO members, in order to disseminate information emerged from the working group.

Meetings for members

During 2021, the Regional Secretariat organized two meetings for the presentation of the OsMed 2020 National Report on the use of drugs in Italy, entitled "*Quattro chiacchiere sul Rapporto OSMED 2020*" (A talk on the OSMED Report 2020), aimed at seeing together with the members the main data on the use of medicines in Italy, with a specific focus on the FVG Region, on how this compares to other Italian Regions and on the possible areas of intervention.

The event was enthusiastically welcomed by members and, for 2022, the organization of other similar events is planned, also with a focus on clinical outcomes as well as consumption, by analyzing together, for example, the data made available by the "System for evaluating the performance of regional health systems" (Target project) of the Scuola Superiore Sant'Anna in Pisa and the National Outcome Program (PNE) of the National Agency for Regional Health Services (Agenas).

ECM events

With regard to the organization of ECM accredited events, the Friuli-Venezia Giulia Regional Secretariat in 2021 organized, in collaboration with the Veneto Regional Secretariat, the webinar event "*Dibattiti in dermatologia: approccio multidisciplinare. L'alleanza farmacista SSN e clinico*"

(Dermatology debates, multidisciplinary approach. The alliance between NHS pharmacist and physician), sponsored by SIFO.

Scientific rationale for the event

Dermatological diseases, by diffusion and impact on quality of life, represent a health challenge that not only includes clinical commitment but extends to professional components that can guarantee the efficiency of the entire treatment path. Among these, the pharmacist of the NHS, for the tasks and responsibilities in the processes of evaluation of access, procurement and management of the treatment flow (from purchase to delivery) is an undisputed protagonist. The educational path, built to concentrate within the main care environments (reference hospitals for specialist dermatology, treatment centers for disabling diseases and prescription of innovative drugs) provides for the focus on the main novelties in the dermatological therapeutic field (diseases disabling, psoriasis, etc.) and a wide debate on the treatment, selection and access to innovative therapies (especially the use of biotechnological drugs) of a multidisciplinary nature.

The speakers included both clinicians and pharmacists operating in FVG and Veneto, to encourage the exchange of opinions, good practices and problems on the management of patients suffering from dermatological diseases.

SIFO SECRETARIAT OF LAZIO REGION

Secretary: E. Scotti
Councilors: G. Bagaglini, M. Canonici, M. Cecchi, G. Gambarelli

In September 2020, with numerous difficulties related to the Covid-19 pandemic situation, a new "team" gets involved for the SIFO LAZIO section.

On 29 September 2020, Dr. Arturo Cavaliere, newly elected president of SIFO for the four-year period 2020-2024, as well as former Secretary of SIFO Lazio for the four-year period 2016-2020, expresses his congratulations to Dr. Emilia Scotti in an official letter for the conferral of the elective office of SIFO Lazio Secretary for the four-year period 2020-2024.

The number of Lazio shareholders is equal to 211 (update III quarter 2021, including defaulting shareholders).

Our team is ready to start on the new "adventure", convinced that collaboration, transparency and sharing are the right "ingredients" to face and win challenges together and that the different experiences and skills will lead to an enrichment of ideas, solutions and possibilities, making the path more stimulating.

Our strength is the continuous confrontation in order to make shared choices, approved unanimously; therefore we try to organize meetings, face to face or via WebMeeting, on a monthly/bimonthly basis or whenever a need arises.

In this sense, in July 2021 we identified, by direct choice, without following an expression of interest, three regional offices:

- Dr. Alessandra Mecozzi - SIFO Lazio SSFO contact reference
- Dr. Martina Canonici - SIFO LAZIO Quality Reference
- Dr. Marco Cecchi - Sifoweb contact reference SIFO LAZIO

Training

During the year 2021, also thanks to the collaboration of many partners, we coordinated and implemented various scientific-cultural training and professional updating projects approved and also included in the PFA ECM Agenas 2021:

- *"Il moderno management multidimensionale della patologia emicranica"* (The modern multidimensional management of migraine pathology) – Regional refresher course by the regional section of the SIFO Lazio
  FAD webinar - September 30, 2021
  Scientific managers: *Dr. Luigi Bellante – Dr. Assunta Staiano*
  Dr. Bellante, sponsor of the project, involved in a multi-thematic focus all health professionals dealing in the management of migraine pathology (GPs, specialists, pharmacists, etc.). All this shared by the point of view of patients and their associations.
  Objective: to clarify the areas of intervention for acute and chronic forms of migraine, following current pharmacological therapy and what are the economic-health effects and the methods of access to drugs, highlighting the critical issues and the eventual possibility of resolution.
- *"Il farmacista ospedaliero nella gestione delle terapie oncologiche: le realtà provinciali della regione Lazio" – Prospettive per la costituzione di una rete galenica oncologica regionale* (The Hospital Pharmacist in the management of oncological therapy - The provincial reality of the Lazio region - Perspectives for the establishment of a regional oncological galenic network)
  Residential course - November 12-13, 2021
  Scientific managers: *Dr. Gabriele Bagaglini, Dr. Emilia Scotti, Dr. Gabriella Bonanni*
  A highly specializing course, whose sponsor was Dr. Bagaglini, with the involvement of various stakeholders of both regional and interregional origin and had as a purpose the training of learners from the various provincial realities of the Lazio Region on the regulatory, technical- pharmaceutical framework and on the risk management of oncological drugs.

Objective: to create the necessary conditions for the establishment of a regional network of oncology galenics, thus favoring a single management system.

In November 2021, always more convinced that the comparison/collaboration with other realities is the basis of our professional growth, we welcomed with great pleasure the request for involvement from the SIFO Campania section, carrying out the Lazio edition of the following course:

- "*Insuline: la gestione tra ospedale e territorio*" (Insuline: the management between hospital and territory) – Refresher course of a itinerant regional nature by the regional section SIFO Campania - FADWebinar with the involvement of the Lazio and Puglia Region November 17, 2021 - date of the Lazio edition
  Scientific Manager: *Dr. Piera Maiolino*
  In addition to the secretary, all the advisers of the SIFO Lazio section were actively involved, as well as many regional members.

Another example of project and scientific sharing/collaboration, in this case between areas and regional secretariats, was effected, thanks to the request for active participation by the scientific managers of the event, in the Itinerant Course national webinar (central Italy) on clinical trials:

- SIFO high specialization course in clinical trials "Il Farmacista di Ricerca e il Farmacista Ricercatore: Istruzione per l'Uso" – In memoria di Stefano Bianchi, Stefano Federici e Francesco Paganelli – 16 April 2021
  Scientific Managers: *Dr. Andrea Marinozzi, Dr. Roberto Langella, Dr. Piera Polidori*
  The RS participated as moderator, together with the RS of Tuscany, in module 2 "The Research Pharmacist".

With regard to this topic, as SIFO Lazio Referents we have also released to all regional members (via e-mail and via WhatsApp) the communication relating to the national distance training project – Asynchronous FAD "Corso di Alta Specializzazione SIFO in sperimentazione clinica – Il farmacista di ricerca e il Farmacista ricercatore: istruzione per l'uso" (SIFO Highly Specialized Course on Clinical Testing – The Pharmacist of Research and the Research Pharmacist – Users Guidelines), online from 1 December 2020 to 30 June 2021.

In the press release, shareholders were explicitly requested to disseminate them also to non-shareholder colleagues in order to sensitize them to these initiatives and stimulate their interest in our scientific society.

Subsequently, we gladly accepted the request for the participation from the SIFO Umbria section:

- FAD Interregional refresher Webinar course by the regional section SIFO - Umbria "*Terapie effettuate secondo legge 648/96 e 94/98: esperienze a confronto tra benefici e rischi*" (Therapies effected according to the legislation 648/96 and 94/98: comparison of experiences between benefits and risks) – 24/25 November 2021

Scientific managers: *Dr. Silvia Di Marco, Dr. Maria Antonietta Calzola, Dr. Nicola Nigri*

The RS Lazio was involved as moderator in the session relating to special use in infectious disease and CR Dr. Bagaglini as moderator in the session dedicated to special use in pediatrics.

With regard to participation in regional/interregional workshops and technical round tables:

- RS intervention at the Central-South Macro-regional Workshop - *Multistakeholders Working Group of the* Emoforce Project – 25 February 2021 *online event*
- RS intervention at the *multi-stakeholder macro-regional Workshop,* with a specific focus on Diabetic Macular Edema (EMD) – 16 December 2021 *online event*
- RS intervention at the regional table on "Pharmacological therapies in the treatment of severe osteoporosis in postmenopause women at high risk of fracture" – 22 September 2021 *online event*

Stimulated by the experience in the year 2021 and moved by the awareness that training and updating activities are essential for our profession, we have proposed several projects on the occasion of the proposal of 2022 planning.

These project proposals have been implemented in the framework of the activities that will be launched in 2022 and have been included in the Annual Training Plan ECM, upon positive evaluation of both the CURF and the CD:

- *"Il Farmacista dei Servizi Farmaceutici delle Aziende Sanitarie: ruolo strategico per garantire una* governance *farmaceutica efficiente"* (The Pharmacist of the Healthcare Pharmaceutical Services: a strategic role to ensure an efficient pharmaceutical governante)
- *"WOUND CARE 2022: standard di cura, innovazione e gestione"* (WOUND CARE 2022: treatment level, innovation and management)
- *"CARENZA ED INDISPONIBILITÀ DEI MEDICINALI: stakeholder a confronto"* (Lack and unavailability of drugs: discussion by stakeholders) (in collaboration with SIFO Lombardia)
- *"Valutazione d'uso, impatto farmacoeconomico e profilo di sicurezza dei farmaci biologici vs biosimilari: confronto tra la realtà di Latina e Frosinone"* (Usage Evaluation, farmacoeconomic impact and the biological versus biosimilar drug safety profile: discussion of the realities between Latina and Frosinone)
- *"Il Farmacista Ospedaliero nella gestione delle terapie oncologiche (II edizione) - le realtà provinciali della regione Lazio: sviluppo della rete di galenica oncologica regionale"* (The Hospital Pharmacist in the

oncological therapy management (II Edition) – the Lazio provincial and regional reality: development of the regional oncological galenic network)

- "*Medical Device alla luce delle novità introdotte dal Nuovo Regolamento: aspetti regolatori e normativi – emergenza Covid-19 a conferma dell'importanza dei processi di governance*" (Medical Device regarding the innovation introduced by the New Legislation: regolatory and law aspects – COVID-19 emergency confirming the importance of the governance processes)

An attempt was made to embrace various sectors, both in the hospital and territorial fields, in consideration of the different roles and multiple activities of the pharmacist.

A project that differs from those organized up to now, is the "WOUND CARE 2022", highly specialized, residential with a national target, proposed by Dr. Claudio Pisanelli, and unanimously shared with great enthusiasm by the whole Regional Council.

The course aims to frame the types of lesions that are treated in the hospitals of the NHS and to assess the market availability of products for which a classification and an in-depth analysis of the appropriate use and cost-effectiveness ratio in the choice is required of the same for the purpose of implementing the standards of assistance in compliance with sustainability.

The decision to propose a second edition of the course dedicated to the Pharmacist in the management of oncological therapies was made in the light of the great success aroused in the previous edition and for this we must, first of all, thank Dr. Bagaglini.

A further proposal for the year 2022 comes from Dr. Luigi Bellante and regards a regional refresher course organized by the Lazio section (webinar mode), which involves various professionals, including the oncologist, hospital pharmacist and geneticist: "*Precision medicine applied to oncology, a challenge for the present*".

The coordinators/collaborators of the relevant national Scientific and Cultural Areas, as well as many colleagues from other regions, were informed and involved in all projects, simply because we believe that "joining forces" means optimizing resources and obtaining the best results.

Now it is up to all of us to work to be able to realize what has been proposed; it is our goal and we will try to do our utmost, thanks also to the valuable support of many partners, who likewise believe that training, the "stubbornness" and the constant desire to improve are fundamental for our professional growth.

Institute of Specialization

As SIFO Lazio we are very confident in the role of the scientific society at the Residency Institutes in Hospital Pharmacy (SSFO) and we strongly feel the need to integrate the academic path with the "information baggage" coming from real practice.

Dr. Alessandra Mecozzi, as SIFO Lazio SSFO Referent, fulfilling the important role of connection between the Academy and the Profession, from the beginning of her assignment has stressed the importance for the trainee of both the carrying out of the practical internship and of the seminars highly professionalizing held by hospital teachers within the study program.

For this reason, thanks to the constant relationship with Academic Universitary Professors and with the various tutors of the Health Authorities hosting the trainees, the referent is devising *ad hoc* paths to guarantee a wide variety of skills, experiences and realities, both cognitive and applicative.

And always with a view to giving greater prominence to the "figure" of the trainees and to his training, as SIFO Lazio both in 2020 and in 2021, we have welcomed the possibility of making a share of the Regional funds available to support their enrollment at the two National SIFO Congresses.

Our message

Active and conscious participation in SIFO represents an important step to translate scientific quality into concrete daily action more effectively.

Lazio is a large region and the support of all colleagues is needed in order to promote new scientific activities as much as possible and face the numerous challenges that await us in the immediate future.

We must be **MANY, UNITED and COLLABORATIVE,** because only in that this way we can stimulate the growth of our business.

A sincere thanks to you Scientific Managers for having involved us in this great project, demonstrating that we are a real "team" and the union represents the first great means to achieve our common goals.

Coming together is a beginning, keeping together is progress, working together is success.

(Henry Ford)

SIFO SECRETARIAT OF LIGURIA REGION

Secretary: A. Brega
Councilor: S. Borgna

The SIFO Regional Section of Liguria, as of 15th December 2021, has 70 members and it is also composed by:

- Regional Referent for SSFO University: Dr. Barbara Rebesco
- Regional Quality Referents (RQr): Dr. Karen Bertolotto and Dr. Rosaria Canevari
- SIFO WEB referents: Dr. Eugenia Livoti and Dr. Sara Bianchi

The SIFO Liguria has two activated Regional Scientific and Cultural Areas (ASC):

Medical and in vitro diagnostic devices
Dr. Eugenia Livoti (coordinator)
Dr. Irene Marasca
Dr. Giulia Agosti Dr. Sara Bianchi
Dr. Pietro Gazzola Dr. Elisa Fondrini

Rare Diseases
Dr. Annachiara Cericola (coordinator)
Dr. Chiara Garbarini
Dr. Elisa Fondrini Dr. Irene Marasca
Dr. Giulia Agosti Dr. Giorgia Bo
Dr. Sara Bianchi Dr. Pietro Gazzola
Dr. Carmen Beatrice Traversi Dr. Eugenia Livoti

Training activities have been carried out and are planned with SIFO Provider:

- EMICRANIA: BEST PRACTICE, INNOVAZIONE E COINVOLGIMENTO DEI PAZIENTI NELLA PRESA IN CARICO
  (Migraine: Best Practice, innovation and patient cooperation in the follow-up period)
  Webinar, May 26, 2021
- HTA, EVIDENCE BASED PHARMACY E FARMACIA NARRATIVA
  (HTA, EVIDENCE BASED PHARMACY AND NARRATIVE PHARMACY)
  FAD Asincrona August 1, 2021- July 31, 2022
- TERAPIE INNOVATIVE: DALLA CLINICA ALLA GOVERNANCE
  (Innovative therapy: from the Clinical to the Governance)
  Webinar, September 17, 2017

- LA GESTIONE DELLE MALATTIE RARE ALLA LUCE DELLE INNOVAZIONI TERAPEUTICHE: LA FIBROSI CISTICA
  (The management of Rare Disease focus on the therapeutic innovations: Cystic Fibrosis)
  Webinair, October 1, 2021
- LA GESTIONE DELLE MALATTIE RARE ALLA LUCE DELLE INNOVAZIONI TERAPEUTICHE: EMOFILIA
  (The management of Rare Disease focus on the therapeutic innovations: Haemophilia)
  Webinair, November 27, 2021
- EMICRANIA: INNOVAZIONE, RWD E COINVOLGIMENTO DEI PAZIENTI NELLA PRESA IN CARICO
  (Migraine: Innovation, RWD and patient cooperation in the follow-up period)
  Webinar May 20, 2022
- INFETTIVOLOGIA & MULTIRESISTENZA: SFIDE CLINICHE E FARMACEUTICHE
  (Infectivology and Multiresistance: Clinical and Pharmaceutical challenges)
  Webinar June 20, 2022

The sponsored courses organized by the regional secretariat:

- IL PAZIENTE EMOFILICO AL CENTRO DELL'IMPIEGO DI TUTTI GLI STAKEHOLDERS
  (The Haemophilic patient at the centre of attention of all stakeholders)
  Webinair, April 27, 2021
- I BANDI DI GARA SUI FARMACI, EMODERIVATI E DISPOSITIVI SECONDO IL NUOVO CODICE DEGLI APPALTI
  (The Tender Notices on drugs, blood products and medical devices according to the new procurement procedures)
  Webinar March 3, 2021

Initiatives/ activities developed or in progress:

- AWARD FOR THE SCIENTIFIC PRODUCTION AND CULTURAL GROWTH OF PHARMACISTS - "SI pubblica in Farmacia Ospedaliera" Award
  In 2021, the first edition of the AWARD FOR THE SCIENTIFIC PRODUCTION AND CULTURAL GROWTH OF PHARMACISTS Award "It is published in Hospital Pharmacy" which has issued a voucher for training support to the two best articles presented for the SIFO Bulletin magazine.
  The article: "Nutrizione enterale domiciliare e *low value lists*: l'*audit* clinico per monitorare l'appropriatezza della terapia nutrizionale" (Artificial

feeding and low value lists: the clinical audit to monitor the appropriateness of the nutritional therapy) was published on Vol. 67, no. 4-5, of the SIFO Bulletin.

With the second edition of 2022, the awards have been increased to 3 training support vouchers and 3 three-year SIFO membership and they have been awarded Ligurian Members who have produced a manuscript. The announcements are published on the Ligurian page of Sifoweb https:// www.sifoweb.it/2013-07-25-09-57-61/comunicazione.html

- REGIONAL AND NATIONAL NEWSLETTER
  From 2020 a newsletter was published in the regional section of Sifoweb. The Newsletter concerns both the regional legislation and main news of pharmaceutical interest selected by the *Gazzetta Ufficiale* della Repubblica Italiana. The news are also conveyed through the mailing list of the members. Regional legislation link: https://www.sifoweb.it/2013-07-25-09-57- 61/normativa-regionale.html; National Law link: https:// www.sifoweb.it/newsletter/normativa- nazionale.html
- OP-ED COLUMN IN THE SIFO BULLETIN
  Since 2022 the SIFO Liguria Regional Secretariat together with ASC Pharmaceutical Legislation Hospital-Territory with Young People Area collaboration, decided to create a periodic compilation of normative references which will be insert in the SIFO Bulletin so that it can provide a compendium of new guidance, reimbursement schemes, Regulatory references focus on the hospital and territorial pharmaceuticals Services. The collaboration between the Regional and National sections, with the support and involvement of the SIFO Youth Area, aims to provide all Hospital and Territorial Pharmacists with a complete training/information program in the Regulatory field to respond to their legislative needs, with the intent to build a knowledge base essential for carrying out the profession, full of ideas, reflections and opportunities.
  Be ready in Healthcare in regulatory and/or informational terms means encouraging and supporting all those values of sustainability, appropriateness and hold up the healthcare world that are indispensable, creating and supplying professionals with increasingly skills, up-to-date and able to face the challenges of the present with a look into the future.
- PROMOTIONAL VIDEO ON SPECIALIZATION INSTITUTES IN HOSPITAL PHARMACY (SSFO)
  The Secretariat collaborated with the University of Genoa in the creation of the promotional video on the School of Specialization in Hospital Pharmacy (SSFO) available on the http://youtube/uuZQXQ8w3TU link

Research project

"Aderenza terapeutica nel paziente diabetico: SIFO e FAND si incontrano per rilevare e pianificare azioni di miglioramento" (Therapy adhesion of the diabetic patient: SIFO and FAND meet to identify and plan improvement actions)

The 2021 project born from the collaboration between SIFO and the Italian Diabetic Association (FAND) intends to photograph and to analyze adherence to therapies in the adult diabetic population, through the administration of a validated questionnaire (MMAS-8 Morisky scale) and to present the results to the institutions in order to promote improvement actions.

Meeting between NHS pharmacists and university students

The training and information event: "I Farmacisti Ospedalieri incontrano gli studenti universitari" (The Hospital Pharmacists meet university students), which will be held on 6th May, 2022 at the Gaslini Hospital, aimed to promote knowledge of the important and strategic functions of the Pharmacist of the Hospital Pharmacies and Territorial Pharmaceutical Services with the National Health Service; furthermore, it presented the modalities and the path whereby the graduates in Pharmacy or Chemistry and Pharmaceutical Technologies have to follow to access the School of Specialization in Hospital Pharmacy.

SIFO SECRETARIAT OF LOMBARDY REGION

Secretary: R. Langella
Councilors: E. Albini, S. Cattaneo, M. Gambera, A.A. Nisic, A. Iezzi, A. Zovi

"Real-World Effectiveness of calcitonin-gene-related peptide binding monoclonal antibodies for preventive migraine treatment: systematic review and meta-analysis": a research project developed by SIFO Lombardia.

The ability to conduct systematic reviews and study the evidence present in the scientific literature by performing a meta-analysis study are skills that, if acquired, can be of great support in the daily activity of the hospital pharmacist and of the Territorial Pharmaceutical Services. In fact, the skills in collecting scientific data and the subsequent evaluation of the same can guarantee the pharmacist the opportunity to work and confront in multidisciplinary teams within the operational and professional context of reference, with the aim of contributing to the best possible choices for purposes of protecting the patient's health and at the same time having a positive impact on the resources of the National Health Service. The Lombardy regional section

of SIFO in February 2021 launched a project with the aim of involving 15 members and setting up a working group aimed at scientific research within the professional category, competent in the field of auditing systematic activities and meta-analysis of the data published in the literature.

Once selected, the members of the working group could participate in the proposed activities, in order to obtain the necessary knowledge to develop the skills to independently conduct a systematic literature review study with subsequent application of a meta-analysis. The selected topic was focused on a new pharmacological class recently authorized for marketing and for which the evidence published in the literature was still rather borderline: monoclonal antibodies for the prevention of migraine attacks.

The members involved participated in three educational workshops, conducted by colleagues with expertise in the sector and held from May to November 2021. The first didactic laboratory, held by Dr. Ruggero Lasala (hospital pharmacist with statistical skills and member of the SIFO CURF), introduced the production means, reporting and critical appraisal methodologies useful for carrying out a systematic review; he also explained how to search for scientific studies in the literature by using data banks (Pubmed, Scopus, Embase, etc.). At the end of this first meeting, in the weeks that followed the participants extracted the studies from the available databases would then be the subject of the statistical analysis of the endpoints established in the logic of the project. The results of this first extraction were then reviewed by the coordinators and scientific managers of the project.

In the second didactic laboratory, held by Prof. Patrick Maisonneuve (Director of Epidemiological Clinic of the European Institute of Oncology), the related statistical analysis techniques were deepened to conduct a meta-analysis study, with the aim of providing participants with the necessary knowledge to apply meta-analysis on the data collected through the systematic review of the literature carried out during the first phase of the project.

In the third didactic laboratory the participants got into the heart of the activities. Dr. Ruggero Lasala and Dr. Andrea Zovi (member of the Regional Council of SIFO Lombardia) assigned the previously selected and evaluated studies to the partners, giving indications on how to set up the search for outcomes within the texts through a guided simulation and then providing information on how to structure the last phase of the project or the drafting of the scientific article, the final result of the research activity which would then describe all the activities carried out during the work period. All the partners involved actively participated in the collection of data and in the drafting of the article, thanks also to the supervision by the project coordinators, establishing a daily relationship of effective professional confrontation and contributing

to the discussion on the subject being dealt with. The article produced by the working group is currently being published in an international indexed journal.

It is auspicious that the working group is reconstituted during this mandate to develop new similar projects, being able to put into practice the knowledge and new skills acquired in order to establish a spirit of collaboration and sharing within the scientific society.

The SIFO Secretariat of Marche Region has always been very careful in providing an increasingly specialized and professionalizing Scientific training in the many healthcare realities in which the Hospital Pharmacist is actively involved, creating stimuli and perspectives to develop ideas and do research, also thanks to a close collaboration and sharing with the School of Specialization in Hospital Pharmacy of the University of Camerino.

SIFO SECRETARIAT OF MARCHE REGION

Secretary: L. Scoccia
Councilors: A. Caprodossi, F. Ciuccarelli

During 2021 the SIFO Regional Secretariat of Marche organized and/or collaborated in the following courses:

a) TREATMENT AND PREVENTION OF COVID-19 DISEASE SARS-COV-2: STATE OF THE ART AND FUTURE DEVELOPMENTS
21 September 2021

The Covid-19 pandemic is a global emergency linked to the emergency of a new virus (SARSCoV-2) that has rapidly spread around the world and has been able to overload even the most resilient health systems with a strong social and economic impact. The clinical management of patients affected by Covid-19 SARS-CoV-2 has evolved over time, reflecting the progressive collection of information relating to the symptoms presented by patients and the knowledge that has been acquired in the field of efficacy and toxicity related to different therapies. In particular, the treatment was based on differentiated approaches: drugs with potential antiviral activity against SARS CoV-2, drugs with prophylactic/therapeutic activity against thrombotic manifestations, drugs capable of modulating the immune response, plasma infusions aimed at a transfer of antibodies neutralizing the link between the new corona virus and its receptor expressed on human cells (ACE2). It should be remembered that, to date, there are large margins of uncertainty about the efficacy and safety of some of the aforementioned therapies and based on the results of the ongoing clinical trials, AIFA periodically updates the authorizations for the use of drugs

for Covid-19 regulating the use of the various therapeutic options in different care settings; furthermore, for patients with the most severe symptoms, AIFA recommends inclusion in clinical trials whose direction is aimed at defining the role of the various treatment options. Although the clinical management of the patient has improved thanks to the experience gained and the results of clinical studies that have evaluated the efficacy and safety of the drugs, vaccination against Covid-19 will be crucial to put an end to the global pandemic. The development of vaccines against Covid-19, based on different technologies, with different characteristics in terms of storage methods and preparation before administration, requires a multidisciplinary approach to their management to ensure maximum efficacy and safety. Among the professional figures involved in the clinical management of the pandemic that of the hospital pharmacist has proved essential both to ensure access to therapies in compliance with the recommendations actions by the regulatory bodies and regulations in force, so as to coordinate vaccine preparation activities (training of the operators involved) guaranteeing the quality of the same through continuous monitoring of the correctness of temperatures and of the validity times during storage, transport and preparation phase. Furthermore, the pharmacist carries out a very important activity in encouraging the reporting of suspected adverse reactions to drugs and in particular to vaccines for which, given the rapidity of development and authorization, it is necessary to continuously collect data on safety and efficacy.

b) INNOVATIVE TOOLS FOR NEW CARE AND ORGANIZATIONAL MODELS IN THE HOSPITAL-TERRITORY CONTINUITY
16 November 2021

The Covid-19 pandemic highlighted the need to rethink the care and organizational models in hospital-territory continuity through a more concrete use of innovative systems such as digital technologies. The use of digital technology can help improve the quality of the assistance, particularly in chronic patients, by facilitating communication (more immediate access to information), the setting up of a network between specialist, patient, general practitioners and pharmacist, computerization of paper documents and patient care, optimizing access to therapies and prescribing aptness. Furthermore, digital technologies can promote patient empowerment and therefore therapeutic adherence, patient monitoring, the prescriptions and adherence. To obtain the maximum benefit from digital in terms of efficiency and sustainability of the National Health System, it is essential to dedicate economic and human resources and equip health professionals with new skills for an appropriate and more conscious use of digital technologies.

c) OFF LABEL THERAPIES, COMPARING EXPERIENCES: BETWEEN BENEFITS AND RISKS

In collaboration with SIFO Umbria 23/28 September 2021

The use of off-label drugs, that is in a manner that does not comply with the provisions of the summary of the characteristics of the authorized product, is becoming more and more widespread in daily clinical practice, mostly in various areas of medicine, such as, for example, oncology, rheumatology, neurology and psychiatry and affects both the adult and pediatric populations. In the pediatric field, especially at the neonatal level, a large part of the prescriptions both in the hospital and on the territory are off-label, mainly due to the scarce clinical trials carried out on patients of this age during the drug registration phase. The law allows a "different" use of the drug if the treating physician, on the basis of the evidence documented in the literature and in the absence of better therapeutic alternatives, deems it necessary to administer a drug outside the authorized indications for use. Therefore, if on the one hand the prescription of off-label drugs exposes the patient to potential risks, considering that the efficacy and safety of these drugs have been evaluated in populations other than those subject to the off-label prescription, on the other hand side represents the only therapeutic alternative for the treatment of some pathologies. As pharmacists, guarantors of the therapeutic appropriateness and correct use of the drug, we strive every day to ensure that patients receive quality, safe and effective therapies, especially in the case of off-label therapy. This course aims to sensitize doctors on the off-label use of drugs, trying to eliminate the fear that makes them avoid requesting it but in their eyes becomes a limit, imposed by pharmacists, to their prescribing freedom while instead it represents a protection for the patient in first place and thereafter for the doctor and pharmacist. During the course we will face the whole process that leads to the use of an off-label drug, starting from the correct compilation of the company forms and presentation of the right scientific documentation to support off-label use, passing through the legal medical implications, up to obtaining the true "informed consent" from the patient to finally arrive at the authorization of the health management, because, let us remember, off-label drugs are not charged to the NHS.

d) FROM SYSTEMATIC REVIEWS TO OBSERVATION STUDIES

2/4 December 2021

Evidence-based Health Care has been shown to influence all areas of health care by applying the best scientific evidence to clinical practice and the organization of health services. However, the ability to critically analyze the results of the proposed research is necessary: from systematic reviews to

meta-analyzes and observational studies, providing tools for a critical reading of scientific articles in order to assess the appropriateness of drug prescribing, which represents one of the most important tasks of the NHS operators engaged in the field of epidemiology and of monitoring the pharmaceutical prescriptions.

While for the year 2022, we have:

THE SIFO-FARE PROJECT IN THE CONTEXT OF THE REALITY IN THE MARCHE REGION: APPLICATION OF THE QUALITY INDICATORS IN THE PROCEDURES FOR THE PURCHASE OF ONCOLOGICAL DRUGS

The SIFO-FARE project was created to find shared rules on the procurement process of drugs and medical devices in the light of the new procurement code which at the center of the entire changing process foresees the choice of new procurement criteria that adapt to the tendering sector of health goods. The first objective of the working group was to identify qualitative criteria to be included in a technical specification contract relating to health goods, and the oncological drugs of the ATC L01 group were chosen as the sample class. In the complex field of oncological drugs, the factors to be considered are many: the technical-pharmaceutical characteristics and the elements related to the safety of the operator are fundamental, but the aspects concerning the delivery at the place of order, the post-marketing assistance are equally important, as well as the provision of additional services. In a context of the need to rationalize pharmaceutical expenditure, the challenge is to identify objective and measurable indicators to be included in the tender evaluation. In a logic of co-design between Universities and professionals, the Center on Economics and Management in Health and Social Affairs of the Carlo Cattaneo University - LIUC, assisted by hospital pharmacist colleagues from various realities in the Marche Region, will be involved in simulating the application of the objective parameters identified by the national SIFO-FARE project to the award of the drug tender carried out by the contracting authority ASUR for the Marche Region. The exercise will be carried out on batches of drugs belonging to the ATC L01 class not covered by a patent. An attempt will also be made to identify the most appropriate and balanced quality level with respect to economic offer received. Subscribers will be asked to fill in a questionnaire, to be sent to the Scientific Secretariat, prior to the event, in order to analyze the results obtained and present them during the conference, in order to open a discussion and bring out elements of consensus.

SIFO SECRETARIAT OF PIEDMONT AND VALLE D'AOSTA REGION

Secretary: M. Boni

Councelors: L. Bagnasco, E. Caiazza, F. Cattel, L. Infante

Regional Referents for the University:
Dr. Andreina Bramardi, Dr. Laura Lanzone

The SIFO Piedmont Region Secretariat, which in the previous four-year period, 2016-2020, had the same composition as the current one, except for the position of Paolo Abrate, now occupied by Dr. Francesco Cattel mainly carried out training activities, offering to its members the opportunity to participate in different residential ECM courses, all with SIFO as Provider, with great participation, also by Trainees of Specializing Pharmacists. The topics were selected for their relevance and innovativeness.

It was decided to involve, both in the relations and in the "round tables", many pharmacist colleagues, experts in the field, thus favoring the aggregation of members and technical comparison, in order to increase the debate and consequently, the professional enrichment.

Since 2020, due to the pandemic, training initiatives have decreased compared to the past, the workload of pharmacists has significantly increased to supply the new required drugs and to produce disinfectant gels in order to balance the lack on the market during the first wave, and to manage the arrival of monoclonal antibodies and vaccines thereafter.

In 2017, a residential course on immunotherapy was organized entitled "*L'immunoterapia, primo appuntamento per il farmacista ospedaliero, il polmone: innovazione, efficacia e sostenibilità* (The Immunotherapy, first appointment for the hospital pharmacist, the lung: innovation, effectiveness and sustainability) – Turin, March 29, 2017"), with the goal of identifying new technical-organizational formulas to address the need for sustainability and, at the same time, to meet the demand for health and illustrate how to apply HTA methods in the evaluation of innovative drugs.

Another topic that required a quick update was about disinfectant and biocide solutions, due to the recent transposition of European legislation. The residential course "*Nuove disposizioni europee in materia di antisettici, disinfettanti e biocidi: lo stato dell'arte in Europa e in Italia* (New European regulations in antiseptics, sanitizers and biocide: the state of art in Europe and in Italy) – Turin, 25 May 2017", had the aim of describing the new european regulations about antiseptics, disinfectants and biocides, describing their correct use and application in clinical practice and defining the skills and

methods of collaboration between pharmacists, Health Departments and users.

Since botulinum toxin represents today a first-choice treatment in a large heterogeneous set of pathologies, transversal to many different specialized branches, with indications for use still increasing, in the last ten years there has been a considerable activity of publishing articles on pharmacology and clinical applications, which today are mainly neurological, dermatological, physiatric and urological. We therefore wanted to provide elements of knowledge on the mechanism of action, on the possible and realistic therapeutic objectives in the various pathologies and on the treatment and follow-up protocols that maximize their effectiveness, with a view to better management of the patient and the appropriate management of resources associated with its diagnostic-therapeutic path. All this was discussed in the residential course: "*Dalla patologia cronica all'obiettivo terapeutico: l'impiego multi specialistico della tossina botulinica e la sua gestione multidisciplinare nella partnership medico-farmacista* (From the chronic pathology to the treatment objective: the multi-specialistic use of the botulinum toxine and its multi-disciplinary management within the doctor-pharmacist partnership) – Turin 21 September 2017".

In 2017, the Secretariat also granted sponsorship for the following residential courses: "*La sostenibilità dell'innovazione: strategie a confronto* (The sustainability of innovation: discussion strategies) – Turin 31 March 2017"; "*Mediafill quale strumento di controllo del processo in asepsi* (Mediafill as an aseptic process control tool) – Turin 24 March 2017", "*L'importanza dell'aderenza delle terapie oncoematologiche per via orale* (The importance of the adherence to oral oncohaematologic therapies) – Turin 20 December 2017".

In 2018 we wanted to organize a course on oral therapies in onco-haematology, since, being in constant growth, even if, on the one hand, they improve the patient's acceptability due to ease of the intake and to the absence of intravenous administrations, on the other hand it must be considered that these therapies could result in important side effects, and therefore require great attention by healthcare professionals in terms of prescription, dispensing and patient compliance. With the introduction of oral therapies, it is also necessary for the pharmacist to improve communication skills with the patient: "*Dall'ormono-terapia alle target-therapy: l'evoluzione della terapia orale in oncologia* (From hormone to target therapy: the evolution of oral therapy in oncology) – Turin 19 June 2018".

Subsequently, in the course "*La gestione dei registri AIFA in oncologia* – (The management of the AIFA registers in oncology) -Turin 15 November 2018", the current situation was assessed on the structuring of the registers of

AIFA monitoring drugs, which are a constantly evolving tool, the experiences of pharmacist colleagues were discussed, studied any changes that could improve the IT structure and improvement elements for management were analyzed.

The aim of the course "*Il servizio farmaceutico oggi tra tradizione e innovazione* (The Pharmaceutical service today between tradition and innovation) – Turin 11 December 2018" was to sum up the situation at the current state of territorial pharmaceutical assistance, to illustrate future developments and to improve the quality of provision of the territorial pharmaceutical assistance.

In 2018, the Secretariat also granted sponsorship for the following courses: Presentation of the book "*La sabbia negli occhi* (Sand in the eyes)– Turin 14 May 2018", "*La sfida: sanità 4.0 per un sistema sanitario sostenibile e inclusivo* (The challenge: health 4.0 for a sustainable and inclusive health scheme) – Turin 2 October 2018", "*Il paziente al centro e la rete al suo fianco: dubbi tra aspettative di vita e sostenibilità* (The patient in the centre and the network beside him: doubts between life expectancy and sustainability) – Turin 19 September 2018".

The residential course "*Ruoli e responsabilità di provveditori e farmacisti nei processi pubblici di acquisto* (Supervisors and Pharmacists' roles and responsibilities in the public procurement processes) – Turin 14 June 2019" was about the drug value and the new procurement code, indirect healthcare costs and LEA objectives, drug supervision and risk management, all of which require a comparison between technicians with different skills and responsabilities. The objective is to obtain a best rationalization in the phase of defining the needs, a more effective management of the goods and services purchased and greater economy of scale. The performers of the procurement processes must promptly adopt a system and dialogue logic aimed at building structured multi-disciplinary relations and with the goal of building a shared relational strategy with the other actors.

In June 2019, a national course "*Pratiche di HTA per il farmacista ospedaliero* (HTA practices for the hospital pharmacist) – Turin 19-20 June 2019" was organized. Thanks to its HTA Laboratory, SIFO has disseminated knowledge and pragmatic skills to its associates on the principles and use of HTA, to support decisions at regional and hospital level to integrate the more traditional skills of the hospital pharmacist. The training model proposed is "engaging" and aims to achieve the "transformation" of the competency model of the participants both from a technical and professional profile and from a behavior profile in line with the management model based on competencies (Spencer & Spencer). The structure of the course includes a residential part (1.5 days) and

a FAD part. The residential part is dedicated to the presentation of the main themes and intervention tools as well as laboratory activities in small groups. It aims to provide knowledge and the development of skills both of a technical, professional and behavior nature with particular attention to the aspects of "negotiation". The residency of the course also guarantees an opportunity for sharing among the participants and gives the possibility of using the dinner provided to insert an activity to be shared (e.g. a cooking class rather than a discussion "fireplace").

The objectives of the residential course "*Dalle sperimentazioni alla pratica clinica in oncologia, il farmacista in laboratorio e nei gruppi interdisciplinari* (From testing to oncology clinical practice, the pharmacist in the laboratory and in the interdisciplinary groups) – Turin 18 September 2019" were to deepen the methods of managing experimental drugs according to GCP in the laboratories set up for cytotoxic drugs, to acquire the rationale of clinical trials in oncology, as to how they are transferred into clinical practice and their discussion in interdisciplinary care groups (GIC), to assess the current situation on the presence of the pharmacist in the GICs and discuss the added value of his professionalism.

The course "*La documentazione e l'utilizzo dei sistemi informatici in radiofarmacia* (The documentation and the use of IT systems in radiopharmacy) – Turin 3 October 2019" the Regional Secretariat of Piedmont and the Scientific Area of Radiopharmacy, from organizational and economic point of view, with the contribution to financing the course with regional funds. The course provided an overview of the computerized systems useful for the management of the documentation related to the activities of Radiopharmacy in Nuclear Medicine, in compliance with the current legislation on data processing, the results of the experiences were presented with the most widespread commercial software systems and adopted in some hospitals.

"*Il progetto SIFO FARE nel contesto della realtà piemontese* (The project SIFO FARE in the context of the reality in Piemonte)– Turin 6 November 2019" dealt with the practical analysis of the regulatory aspects, simulating the application of the objective parameters identified by the national SIFO-FARE project to the award of the drug tender carried out by the station SCR contractor for the Piedmont Region. The exercise will be carried out on batches of drugs belonging to ATC L01 not covered by a patent. It will also try to identify the most appropriate and balanced quality level with respect to the economic offer.

In 2019, the Secretariat also issued patronage for the following courses: "*La continuità assistenziale tra acuzie e cronicità: focus di confronto tra*

aziende sanitarie e tra medici e farmacisti (The uninterrupted healthcare between acute and chronic: focus on the debate between doctors and pharmacists) – Turin 15 February 2019", "Road MAP e CAR-T: prospettive attuali e future dell'uso delle CAR-T in Italia (Road MAP e Car-T: current and future expectations of using Car-T in Italy) – Turin 17 July 2019".

In 2021, the Secretariat granted sponsorship for the following courses: "*Corso di alta specializzazione SIFO in sperimentazione clinica "Il Farmacista di ricerca e il farmacista ricercatore: istruzioni per l'uso"* (SIFO Course of high specialization in clinic testing "The Pharmacist of Research and the Research Pharmacist – users' guideline") – Webinar, 14 May 2021"; "PDTA regionali in oncologia. Il ruolo del farmacista e dell'oncologo (Regional PDTA in oncology. The the pharmacist and the oncologist's roles) – Webinar, Turin 7 July 2021"; "*Bandi di gara su farmaci emoderivati e dispositivi secondo il nuovo codice appalti* (Calls for Tender on blood products and devices in accordante with the new bids) – Webinar, Turin 15 September 2021"; "*Dibattiti in dermatologia: approccio multidisciplinare. L'alleanza farmacista SSN e clinico* (Debates in dermatology: multidisciplinary approach. The alliance of the NHS pharmacist and the doctor) – Webinar, Turin 18 September 2021".

In 2022, the Secretariat granted sponsorship for the course: "*Il valore del dato: come trasferire l'innovazione dalla teoria alla pratica* (The value of data: how to transfer innovation from theory to practical) –Turin 18 March 2022".

In 2022 the following course is scheduled: "*Real World Data e polifarmacoterapia nel paziente fragile: due ambiti critici di intervento del farmacista ospedaliero e territoriale* (Real World Data and polipharmacotherapy on a fragile patient: two critical intervention areas of the hospital and territorial pharmacist) – Turin 23 May 2022". Real World Data is becoming increasingly important to measure the appropriateness of care in different areas. The data extracted from the AIFA registers, the NHS prescriptions on the territory, the computerized medical records represent databases to be compared with the RCT outcomes to obtain highly significant data on the efficacy and safety of treatments. Fragile patients, oncologic or not, are often forced to take a large number of drugs contemporaneously: according to Ministerial Recommendation 17 the pharmacist together with doctor and nurse must carry out the recognition and reconciliation prior to any change in the care setting, to prevent any toxicity and improve compliance, and therefore effectiveness of treatments.

The objectives of the course are to provide tools to assess the appropriateness of treatments using Real World Data in different care areas and carry out analysis of drug use and persistence/adherence to treatments.

Research projects

- *"The Information and Communications Technology (ICT) applicate al percorso del medicinale in ospedale"* (The Information and Communications Technology (ICT) applied to the drug itinerary within the hospital).
- *"Aggiornamento a livello regionale degli standard del servizio pubblico per l'area di Farmacia nelle due articolazioni Farmacia Ospedaliera e Servizio Farmaceutico Territoriale"* (Update at regional level of the public service standards in pharmaceuticals be it in hospital and territorial pharmacy services).

A training-research project is being studied, to be carried out in collaboration with the Regions of Lombardy and Liguria, structured in such a way as to form some mixed working groups, that is, formed by colleagues from all three Regions, to study some specific issues concerning Hospital and Territorial assistance.

A training project on the implementation of Patient Blood Management programs is being studied.

SIFO SECRETARIAT OF PUGLIA REGION

Secretary: P. Trisolini
Councilors: R. Lombardi, G. Mingolla, M. Cetrone

The SIFO Regional Section of Puglia consists of 161 members, in 12/15/2021:

Date	Members	Supporters	Trainees	Females	Males
03/11/2020	156	5	43	126	30
04/10/2021	161	3	40	127	34

The organization chart of the secretariat is composed as follows:

- Regional Secretary: Dr. Pietro Trisolini
- Regional Councilor: Dr. Grazia Mingolla
- Regional Councilor: Dr. Michela Cetrone
- Regional Councilor: Dr. Renato Lombardi
- Regional Referent for the SSFO University: Dr. Domenica Ancona
- Regional Quality Referents (RQr): Dr. Pietro Trisolini
- SIFO WEB contact person: Dr. Maria Colamonico

During 2021, the work of the Puglia regional section of SIFO focused on stimulating the formation of collaboration networks between members and stakeholders (Scientific Societies and Institutions) in compliance with professional ethics and generational continuity. The presence in the regional technical tables was constant and pro-active, as well as the presence in the training events promoted by other scientific societies, an opportunity to consolidate new relationships and highlight the professional peculiarities of the hospital pharmacist and the territorial services.

In this vein it was organized, in collaboration with the Apulian section of the scientific society of supervisors (FARE), an ECM course in modality webinar entitled: "*Bandi di gara sui farmaci, emoderivati e dispositivi secondo il nuovo codice degli appalti*" (Calls for tender on drugs, blood products and devices in accordance with the new bids code). The course's motto was aimed to address some critical aspects of the procurement code in order to make it easier to understand by addressing some technical aspects of a tender procedure such as the definitions of RUP, DEC and RES, of the tender lots, requirements and award procedures. The course saw the participation of Tuscan colleagues allowing a comparison between the experience between the two regions in relation to the procurement procedures for drugs and medical devices in order to understand similarities and differences. It was an opportunity to dispel, through concrete examples, various doubts that arise in everyday practice. The event also represented an important training opportunity for young pharmacists, given that tendering is not a curriculum subject in the university training course.

In the same way, a course was organized, in presence, together with the Italian Association of Medical Oncology (AIOM) entitled "*Oncologia e Malattie rare in tempo di Covid*" (Oncology and rare diseases in COVID times). The occasion was propitious to discuss together with Oncologists and doctors dealing with Rare Diseases of the consequences that the Covid-19 pandemic has had on the care capacity of the NHS foremost and of the SSR in particular. It was interesting to discuss the need to create a network between the professional figure of the pharmacist, the specialist doctor and the general practitioner to tackle the patient's care process together in a singular assistance.

Still in the directive to create a network also within SIFO, collaborations with other regional SIFO secretariats in the organization of courses have been favored.

The Apulian SIFO was present at the *Corso di alta specializzazione SIFO in sperimentazione clinica* (SIFO Course of high specialization in clinical trials) "*Il farmacista di ricerca e il farmacista ricercatore: istruzioni per l'uso*"

Webinar (ex Ed. Sud) and collaborated in the realization of the FAD course "*Insuline: la Gestione tra Ospedale e Territorio*" (Insuline: the Management between Hospital and Territory), for an itinerant regional update by the SIFO - Campania regional section, in collaboration with the Lazio secretariat. The course represented an essential opportunity for discussion, between colleagues from different regions, on strategic issues for the profession, in particular on the key function of monitoring the prescriptive-therapeutic appropriateness in order to optimize economic resources and guarantee rapid access to the drug. A constructive interregional debate has also been created between pharmacists and specialists, addressing the main issues of care for patients with diabetes in hospital.

An ECM residential event, SIFO provider, was organized by the regional secretary of Puglia on the theme "Plaque psoriasis, Pharmacological Therapy and expenditure management". Together with doctors specializing in dermatology, the issue of prescriptive appropriateness was addressed, focusing attention on drugs with a high impact on pharmaceutical expenditure for direct purchase of drugs. The measures for the rationalization of pharmaceutical expenditure that the Puglia Region has developed for the correct use of drugs in the treatment of moderate to true plaque psoriasis and the guidelines for the prescription of immune-modulatory drugs were analyzed encourage the use of therapeutic options with a lower economic impact.

The priority objective of the regional secretariat in 2022 will be to enhance support for SIFO cultural areas, create working groups on specific issues that want to be developed with annual plans and create a direct channel with decision-makers at the regional level to encourage the recognition of professional pharmacists' profiles not yet recognized/planned and the launch of *ad hoc* funded projects.

SIFO SECRETARIAT OF SARDINIA REGION

Secretary: P. Chessa
Councilors: S. Tonina, M. Rivano

The SIFO Sardinia Section has sixty-six members with a prevalence of Hospital Pharmacysts (65%). It is interesting that a component of Trainee colleagues which has reached 22%, that denotes the attractiveness towards those who choose a career path that has gained a lot of prominence, especially from the fateful March 2020. Since then, in fact, Sardinian pharmacists have been a keystone on which the containment of the pandemic was based; both with

the commitment of finding the indispensable drugs for patients admitted to intensive care during the first wave, with the dissemination of evidence on suitable therapies, on the management and preparation of antiviral drugs and of monoclonal antibodies and, last but not least, in the management of the precious anti SARS-COV2 vaccines. Colleagues Pharmacists have been involved at the forefront in the preparation of regional guidelines on the vaccination plan and also in the organization of vaccination hubs.

Naturally, such a dynamic context, with the news on the simplification of the procedure for clinical trials addressed to SARS-COV2 positive patients and with the constant documentary research on the most recent evidence regarding the subject of therapy with the consultation of *interim* data, has made us more confident with the clinical research subject and with the most accredited resources available on the net. To facilitate our daily routine as "evidence researchers", the Region of Sardinia in collaboration with CRS4 surl - Center for Research, Development and Advanced Studies in Sardinia, with the project aimed at the Regional Scientific Library, have provided to health professionals, an interesting search engine with the possibility of free full text access to a large database of scientific publications of field training, on the possibilities of data extraction. In 2021, the Sardinia Section proposed various training events, and also in presence when the legal constraints allowed it.

- The webinar course entitled "LEAN MANAGEMENT PER L'OTTIMIZZAZIONE DEI PROCESSI DI APPROVVIGIONAMENTO E LOGISTICA DEL FARMACO" (LEAN MANAGEMENT FOR THE OPTIMIZATION OF THE SOURCING AND LOGISTIC OF DRUG PROCESS) with six meetings from 8 September 2021 to 22 October 2021 aimed at stimulating analysis and planning in a lean perspective thanks to the comparison with expert teachers and high-level technicians
- The in-person course "LA GESTIONE CLINICA DELLE SIDEROPENIE" (THE CLINICAL MANAGEMENT OF SIDEROPENIA) of 2 October 2021 for an update and debate exchange between pharmacists and clinicians on the latest scientific evidence.
- The 2021 edition of the SIFO Regional Congress - Association of Economic Providers of Sardinia. An appointment that has now become a tradition and strongly anticipated and attended by the audience, Pharmacists and Administrators, but also by teachers who take the opportunity to exchange experiences, visions, perspectives during moments of dialogue and round tables that characterize each edition of this event. The theme of the year was "I FUTURI RAPPORTI ISTITUZIONALI TRA AZIENDE SANITARIE ED IL SOGGETTO AGGREGATORE. IL FUTURO MODELLO DI APPROVVIGIONAMENTO DELL'HUB DEL FARMACO E DEI

DISPOSITIVI: ANALISI BEST PRACTICE" (THE FUTURE INSTITUTIONAL RELASHIONSHIPS BETWEEN THE HEALTH COMPANIES AND THE AGGREGATOR SUBJECT. THE FUTURE MODEL OF PROCUREMENT OF THE DRUGS AND DEVICES FOR THE HUB: BEST PRACTICE ANALYSIS).

2021 ended with an in-person event entitled "L'ASSISTENZA AL PAZIENTE ONCOLOGICO. FOCUS REGIONALE" where on 5 November, an audience made up of Pharmacists, doctors and nurses, were presented the different regional realities with the peculiar characteristics of the four UFA Laboratories in operation and the latest evidence on the subject of agnostic therapy. The course also saw a large participation of postgraduate colleagues and was characterized by being the first moment of collegial meeting between pharmacists involved in the management and preparation of oncological and oncohematological therapies.

2022 is bringing a lot of news to our Section. It opened with the official start of the lessons of the second School of Specialization in Hospital Pharmacy of the Region, within the University of Cagliari, which complements the SSFO of the University of Sassari. The Hospital and Territorial Pharmacists will therefore be engaged in teaching and tutoring the postgraduate colleagues. On the organizational side for the Pharmacists of the NHS, significant innovations are emerging with the perspective of the trainees two logistics hubs of health assets and with the consolidation of the changes due to the SSR Reform (Law 20/2020) with the termination of the Health Protection Company and the restoration of autonomous ASLs.

From a training point of view, as a consequence of the scenario described above, spring will see the SIFO-ARPES Congress anticipated. In May, the Sardinia section will take its contribution to the multi-regional webinar "Emicrania: Innovazione, RWD e coinvolgimento dei pazienti nella presa in carico"; a first time experience for our remote joint course section. The happy experience of November 5, 2021 in the field of assistance to the oncologic patient, stimulates a second edition with a focus dedicated to the evolution of the organization of the Molecular Tumor Boards. The pharmaco-economic side will then see us engaged in a training meeting, in process of definition, which will draw our attention to the relevant therapeutic category of drugs dedicated to haemophilia. The high impact on regional and national expenditure and the high incidence of the disease in the Sardinia Region have inspired an *ad hoc* project.

Our commitment and our hope are placed in an elaboration of the new skills acquired during a demanding two-year period, in a renewed spirit of body and, we hope, in a consolidated awareness of our identity as women and men of science.

SIFO SECRETARIAT OF SICILY REGION
Secretary: V. Di Giovanni
Councilors: E. Garaffo, S. Arena, C. Russo, B. Busà, H. Aliferopulos

SSFO CATANIA
Maria Anna D'Agata, Director of the Pharmaceutical Department ASP Catania
SSFO PALERMO
Maurizio Pastorello, Director of the Department of Pharmacy ASP Palermo
SSFO MESSINA
Alfina Rossitto, Director of the UOC Territorial Pharmaceutical Assistance ASP Messina

The scientific activities set up by the Regional Secretariat includes the annual organization of:

- a regional conference as a moment of comparison and strong professional growth for all pharmacist members of the Sicily region;
- one or more days of training dedicated to SSFO trainees involving the three schools of Hospital Pharmacy located in Sicily (Catania, Palermo and Messina);
- "Silvana Mansueto" Award in memory of a colleague, aimed to young Sicilian members for the assignment of vouchers to be used for training.

Moreover, there are different kind of training sessions both on input of the SIFO members and on the sponsor companies.

Activities

- FAD updating webinar course by the SIFO Sicily regional section entitled: "Le nuove tecnologie nella gestione del paziente diabetico e nuove opportunità distributive" (The new management technologies related to the diabetic patient and the new distributive opportunities) 2 July 2021 (4.5 ECM);
- for awarding prize vouchers, first edition of the "Silvana Mansueto" merit award, aimed at young people who have prepared the best specialization thesis in Hospital Pharmacy, for the academic year 2019- 2020 of the graduate schools in Hospital Pharmacy of the Sicily region. Publication in the SIFO Bulletin volume 67, number 6, November- December 2021 of the thesis: "Budget impact analysis del nuovo sistema di flash glucose monitoring per l'autocontrollo della glicemia nei pazienti diabetici" (Budget impact analysis of the new Flash glucose monitoring system of the glycaemia self-control in diabetic patients) and "Emergenza sanitaria Covid-19: ruolo del farmacista ospedaliero/territoriale ed esperienza presso l'ASP

di Caltanissetta" (Health emergency COVID-10: the hospital/territorial pharmacists' role and experience at ASP of Caltanissetta);
- for awarding prize vouchers, second edition of the "Silvana Mansueto" merit award, no. 3 vouchers worth € 500 each for participation in the 26th EAHP Vienna Congress 23-25 March 2022 for the IV year post graduates of the Graduate school in Hospital Pharmacy of the Sicily Region.
- Contribution to the XLIII SIFO National Congress programme, held in Bologna 27-30 October 2022, with the work titled: "Introdurre la gentilezza in sanità rappresenta la vera riforma del sistema sanitario. Mettere in primo piano nei percorsi sanitari la dimensione umana della cura attraverso dei percorsi per gli operatori sanitari in cui imparare a relazionarsi al meglio con il paziente e i suoi familiari" (To introduce courtesy in health represents the true health system reform. The need within the health path, to place the human dimension in the forefront for all health staff, where they learn to interact with the patient and their families);
- Residential ECM course "Aderenza e appropriatezza nelle patologie respiratorie croniche: istituzione della nota AIFA 99" Catania 27 May 2022 (event sponsored by SIFO);
- Participation in the SIFO editorial project: application of Regulation (EU) 2017/745 on MD and Regulation (EU) 2017/746 on in vitro diagnostic medical devices;
- Update of the SIFO web page in the Sicily regional section: regional legislation, activities, communications and activation of a regional email.

SSFO training days

"Update terapie e vaccini anticovid" (Update of anti-Covid therapies and vaccines) Dr. MA D'Agata - Referent of the Specialization School of Catania - Catania, 11 November 2021.

Work in progress

- SIFO Regional Spring Meeting "Il Farmacista tra scienza e cultura: esperienze a confronto" (The Pharmacist between science and culture: exchange of experiences) 12-14 May 2022 Mazara del Vallo (event sponsored by SIFO);
- SSFO Catania training day year 2022;
- SSFO Messina training day year 2022;
- SSFO Palermo training day in 2022;
- Refresher webinar course organized by the Sicily region "Gare d'appalto in ambito sanitario – problematiche e criticità" (Procurement procedures in the health sector – challenges and concerns).

SIFO SECRETARIAT OF TUSCANY REGION

Secretary: F. Del Santo
Councilors: P. Giambastiani, A.M.F. Calvani

The SIFO Secretariat of Tuscany Region, in particular in the last two years, has tried to work intensively by providing a Scientific training increasingly specialized and varied, raising awareness of a professional aggregation and a sharing of ideas and initiatives that are the basis of doing and encouraging research in multi-specialized scientific activities in which the Hospital Pharmacist operates and is actively inserted.

In the year 2021 the following SIFO INTER-REGIONALI PROVIDER COURSES:

- "EMICRANIA: BEST PRACTICE, INNOVAZIONE E COINVOLGIMENTO DEI PAZIENTI NELLA PRESA IN CARICO" (Migraine: Best Practice, innovation and participation of the patient in care) (Event Code 313-319658) FAD Webinar, 26 May 2021
- "TERAPIE INNOVATIVE: DALLA CLINICA ALLA GOVERNANCE" (Innovative terapie: from clinical to governance) (cod. F23/2021) FAD Webinar, 17 September 2021
- "LA GESTIONE DELLE MALATTIE RARE ALLA LUCE DELLE INNOVAZIONI TERAPEUTICHE: LA FIBROSI CISTICA" (Management of rare diseases in view of innovated terapies: cystic fibrosis) (cod. F21/2021) FAD Webinar, 1 October 2021
- "LA GESTIONE DELLE MALATTIE RARE ALLA LUCE DELLE INNOVAZIONI TERAPEUTICHE: EMOFILIA" (Management of rare diseases in view of innovated terapies: haemophilia) (cod. F29- 38/2021) FAD Webinar, 27 November 2021

Also in 2021 there were the following events with involvement SIFO TOSCANA and patronage:

- "HORIZON ACADEMY" FARMACIA DEI SERVIZI SANITARI: CICLO DI ALTA FORMAZIONE: (Pharmacy of the Health Services: high level training cycle): 9 days
- "BANDI DI GARA SU FARMACI, EMODERIVATI E DISPOSITIVI SECONDO IL NUOVO CODICE APPALTI-Liguria" (Calls for tender on drugs, blood products and devices according to the new procurement code – Liguria) FAD Webinar 3 March 2021
- "BANDI DI GARA SU FARMACI, EMODERIVATI E DISPOSITIVI SECONDO IL NUOVO CODICE APPALTI-Campania" (Calls for tender on drugs, blood products and devices according to the new procurement code – Campania) FAD Webinar 15 April 2021

- "CORSO DI ALTA SPECIALIZZAZIONE SIFO IN SPERIMENTAZIONE CLINICA 'IL FARMACISTA DI RICERCA E IL FARMACISTA RICERCATORE: ISTRUZIONI PER L'USO'" (SIFO High specialization course in clinical trials "the Pharmacist of Research and the Research Pharmacist: Users' guide") ID ECM: 313-284987 FAD Webinar (ex Ed. Bologna), 16 April 2021
- "BANDI DI GARA SU FARMACI, EMODERIVATI E DISPOSITIVI SECONDO IL NUOVO CODICE APPALTI-Piemonte" (Calls for tender on drugs, blood products and devices according to the new procurement code – Piemonte) FAD Webinar 15 September 2021
- "BANDI DI GARA SU FARMACI, EMODERIVATI E DISPOSITIVI SECONDO IL NUOVO CODICE APPALTI-Lombardia" (Calls for tender on drugs, blood products and devices according to the new procurement code – Lombardy) FAD Webinar 14 December 2021
- "TERAPIE OFF LABEL, ESPERIENZE A CONFRONTO: TRA BENEFICI E RISCHI" (OFF LABEL THERAPY, debate on experiences: benefits and risks) FAD Webinar, 24-25 November 2021

While for the Year 2022 the following scientific activities have been planned and will take place:

- MIGRAINE: INNOVATION, RWD AND IN TAKING CHARGE OF THE PATIENT.

Migraine is a complex neurological disease, with a strong genetic component on which other factors are inserted, mainly linked to lifestyle, which can modify its course and severity. According to the World Health Organization (WHO) it represents the third most frequent pathology and the second most disabling for mankind; in fact about 1 billion people in the world (12% of the population), of which 136 million in Europe, suffer from this disease which affects three times more women than men, particularly in the age group between 25 and 55 years old. Law no. 81 of 14 July 2020 *(the Official Gazette* no. 188 of 28 July 2020) recognizes some forms of chronic primary headache, including migraine, as disabling social diseases and provides for the identification of projects aimed at experimenting innovative methods of taking in charge people with headache. In this context, the course was drawn up and has three main objectives: to know the best practices and innovative pharmacological treatments, to support the use of RWDs in the monitoring of migraine disease and to build a network that allows the sharing and creation of projects for taking care of patients.

- THE MANAGEMENT OF INTOXICATIONS AND ANTIDOTES.

Intoxications represent a frequent cause of recourse to emergency structures and the treatment of intoxications always associates symptomatic treatment and purifying/evacuating treatment with, when available, an antidotic treatment. The use of these medicines is not always supported by strong clinical evidence, nor can their use have a predictable and constant trend, and last but not least, their supply is often difficult and problematic: it should be remembered in this regard that antidotes are real life-saving drugs. The efficacy of antidotes is strongly influenced by the precocity of their administration; this makes us understand how important a good knowledge on the part of health workers of an intoxication symptom and the ease with which the procurement of antidotes. Until a few years ago these were mainly classified according to their mechanism of action of the drug, today however it is following the criteria proposed by the International Program on Chemical Safety (IPCS) and of some directives of the World Health Organization (WHO), it is preferable to adopt a classification based on the urgency with which the antidote is administered and obviously on its proven effect. University training of health personnel often does not go in-depth or does not dedicate the necessary space to the topic of intoxications, which nevertheless plays a primary role in Emergency-Urgency Services, with important health implications in the case of mass intoxication. The purpose of this course is to deepen the knowledge related to the mechanisms of action and use of antidotes, as well as their correct management in the equipment in health facilities. In addition to these aspects, the event will analyze aspects relating to hospital management in the clinical practice of antidotes. The objectives of the course are: to illustrate all the major causes of intoxication focusing on those of the acute type and their respective management; improve knowledge on antidotes; get to know the main mechanisms of action.

- INFECTIOUS DISEASE & MULTIRESISTANCE: CLINICAL AND PHARMACEUTICAL CHALLENGES

The Covid-19 pandemic has focused in the eyes of health professionals and general population how infections can pose a serious threat to the overall health of people and can also heavily impact the economic and social well-being of countries, as well as the life expectancy of people. Furthermore, the spread of multidrug-resistant pathogens seriously jeopardizes any possibility of effective treatment in numerous clinical settings, in relation to many etiological agents, bacterial but also viral. In fact, it is known that bacterial infections are sustained by resistant microorganisms, such as *Enterobacterales* resistant to carbapenems. Regarding these infections the therapeutic weapons available

to clinicians are reduced and a change of pace in clinical research is urgently needed. Also other areas of infectious disease – for example HIV – are daily grappling with problems related to the reduced availability of therapeutic options. Among HIV-positive patients, for example, there is a group of subjects with a long history of antiretroviral therapy who have developed resistance to the various drugs on the market and therefore need new therapeutic options; others, on the other hand, often burdened by multiple co-morbidities, have very limited therapeutic options which they can benefit from, and are in urgent need of new classes of drugs. Extended drug resistance tuberculosis is also a real clinical challenge, for which new therapeutic opportunities seem to be opening up at the moment. The training event aims to outline the extent of the spread of drug resistance in relation to the different types of infections, with particular regard to: bacterial infections, HIV, tuberculosis. Furthermore, the event aims to highlight the clinical and therapeutic weaknesses related to multi-resistances. Finally, the event will provide knowledge tools on the therapies available, on the chances of treatment with current therapies, and on the clinical needs that still await effective strategies from clinical research.

SIFO SECRETARIAT OF TRENTINO-ALTO ADIGE REGION
Secretary: R. Ciaghi

With the scientific support of A. Pasqualini

1. The Pharmacist in the role of DEC and facilitator in the purchasing processes of the related to the new procurement legislation

The New Procurement Code has imposed an integrated vision of the pharmacist in an area where skills are increasingly fluid and intertwined. The Supervisor, the Pharmacist, the Clinical Engineer and the IT Colleague are evermore interconnected figures and to whom it is always more required to integrate their expertise, to bring their added value to the resolution of wide ranging problems and to participate to the design for the implementation of the skills and professional activities of one's own company.

The role that the figure of the pharmacist can still be strategic to the extent in which his profession challenges him with other professional figures on which he is partly forced to measure himself and with whom he is integrated and dependent.

We would like to design a new working method with the Superintendency and Management Control to develop a method for monitoring contracts, an epidemiological assessment procedure such as to generate estimates of needs

as realistic as possible, a proposal for a better integration of information pre and post tenders and the creation of a work group dedicated to the Horizon scanning of innovative technologies close to its arrival on the market.

The work would consist of an operational phase to be shared with the Company and thereafter, a mini training course for DEC Pharmacists and Pharmacist facilitators for DEC Clinicians.

2. Innovative drugs in cystic fibrosis: how much and how they improved the lives of patients in the first year of treatment

The introduction on the Italian market of modulating drugs aimed at the functional recovery of the CFTR protein capable of favorably affecting the course of patients suffering from cystic fibrosis marked a step forward in the fight against this disease.

We would like to evaluate together with the referring Pediatric Clinicians of the CF Center in Rovereto how much and how the introduction of modulators has changed the course of our patients' disease and what were the possible side effects recorded in the first year of treatment.

3. Reduction of thrombotic complication: adherence to the guidelines on drugs and MD of the APSS company. Where are we at?

Starting from the requests made by the company PICC Team, we would like to evaluate how much and how company procedures are in line with the main guidelines for the use of drugs and MD.

From the analysis, we would then like to submit to the relevant Commissions the company's current most suitable corrective actions to align with international gold standards.

4. Reception of Covid-19 vaccines from the commissioner

From 27 December 2020, the Provincial Agency for Health Services (APSS) of the Autonomous Province of Trento (PAT) is engaged in the vaccination campaign to fight Covid-19.

The current company organization foresees that the Hospital Pharmacy manages the procurement and distribution of the Medical Devices necessary for the administration, the storage of vaccines for Covid-19 with surveillance and monitoring of the storage temperature (24h-24h), the reception the "vaccination agendas" and urgent "extra-system" requests for the relative organization/management of the distribution of vaccines for Covid-19 in the provincial territory (> 130 destination points in PAT) and the thawing and preparation of doses for sending to the vaccination points with labeling of the validity date after thawing, batch and expiry date.

The current company organization provides that the Hospital Pharmacy is considered a HUB for the Autonomous Province of Trento and manages the reception/distribution of monoclonal antibodies and antivirals sent by the Commission Structure.

The Commissioner Structure in collaboration with the Ministry of Health and AIFA has begun to distribute monoclonal and antiviral antibodies for Covid-19 throughout the country.

Monoclonal antibodies:

- Bamlanivimab in monotherapy (Eli-Lilly)
- Bamlanivimab + Etesevimab (Eli-Lilly)
- Casirivimab + Imdevimab (Ronapreve-Regeneron/Roche)
- Sotrovimab (GlaxoSmithKline)

Antivirals:

- Molnupiravir (MSD)
- PF-07321332 and Ritonavir (Pfizer)

The Hospital Pharmacy participates in weekly meetings with the Commissioner Structure, the Ministry of Health, AIFA, the Autonomous Regions and the Provinces for the monitoring of consumption and the management of monoclonal antibodies and antivirals for Covid-19 (about 52 meetings per year).

The Hospital Pharmacy sends the stocks of monoclonal antibodies and antivirals for Covid-19 weekly to the Commissarial Structure, the Ministry of Health and AIFA, which are constantly monitored in order to guarantee therapies to patients (approximately 52 monitoring per year).

Collaboration in answering questions from the Trento PA Council.

Elaboration of a procedure for the management of monoclonal antibodies provided by the commissioner structure to the covid wards of community hospitals:

- collaboration between Covid wards department, specialists;
- guarantee the patient treatment in a short period;
- avoid squandering resources (e.g. ambulances) for the transport of the medicine;
- avoid wasting time at the department and at the pharmacy for the transfer organization.

5. Respect for the procurement plan

Carrying out of activities necessary for compliance with the Procurement Plan through the identification of members of working groups for the drafting of the specifications/components of Judging Commissions and the promotion of their participation in such groups/Commissions of Medicinal GASs.

Participation of the Hospital Pharmacy in the working group "Procedura per la fornitura di gas medicali e tecnici e gestioni degli impianti centrali e di rete per la distribuzione dell'ossigeno, dell'aria medicale e del vuoto - nomina componenti gruppo di lavoro" (Procedure for the supply of medical and technical gas and the management of central systems and network for the distribution of oxygen, of healthcare and of the emptiness - nominates working group elements) since 28 October 2020 MARKING/ ID: 123642151.

6. Objective: quality and safety policies

Compliance with the actions envisaged in the patient quality and safety plan, also for the purpose of renewing JCI validation.

7. Antibiotic stewardship and broad spectrum antibiotic monitoring to counteract antibiotic resistance

Monitoring, in collaboration with the Management Control Service, of the consumption of antibiotics for systemic use (ATC J01) according to the indicators:

- PNCAR (DDD/100 days of hospitalization)
- S. Anna di Pisa (DDD/100 days of hospitalization)

Pre-authorization with validation of justified requests per patient (in some cases with AIFA prescription paper form) provided, among the antibacterials for systemic use, for ertapenem, moxifloxacin, daptomycin, tigeciclina, ceftobiprole medocaril, dalbavancin, ceftaroline fosamil, ceftolozane + tazobactam, cefadizime + avibactam, iv fosfomycin and tedizolid. Registration in the database.

Alert in Tecum proposal to clinically re-evaluate an antibiotic therapy 72 hours after the first prescription, under development and possible with the next release, the clinician will be left with the possibility of setting the alert for re-evaluation for any drug, not just an antibiotic. Once set, it will present itself, at the time set initially, to those who are validating the therapy.

ATB prophylaxis in Surgery and Interventional Medicine in adults – participates to a new evidence-based multidisciplinary review (September 2021).

SIFO SECRETARIAT OF UMBRIA REGION
Secretary: S. Di Marco
Councilor: N. Nigri

If we had to describe SIFO Umbria with a title, we would call it "a nice group of friends"!

This is what I already found at the beginning of my first term as Regional Secretary in 2016. And this is what we were lucky enough to find, thanks primarily to two examples of 'passionate' professionals, Dr. Fausto Bartolini and Dr. Alessandro D'Arpino, Regional Secretary before me and then a member of the SIFO Board.

Over the years, with their passion for the profession, their 'perseverance', the involvement of us all, even outside the SIFO area, have made it possible to structure an increasingly united regional group, able to share everyday life and at the same time to create training courses that over the years have allowed the implementation of events of excellence!

The two editions of the National Conference on Cannabis for medical use entitled *Cannabis Terapeutica e Preparazioni Galeniche 2017 - Cannabis Terapeutica e Preparazioni Galeniche lo stato dell'arte al 2018* (Medicinal Cannabis and Galenic Preparations 2017 - Medicinal Cannabis and Galenic Preparations the state of the art 2018) (Dr. Bartolini, Dr. Calzola, Dr. Di Marco) attended by experts from numerous regions, representatives of institutions, parliamentarians and scientific societies who discussed the proposed reform of the law relating to the right to treatment and the use of therapeutic cannabis, on the actual risk/benefit ratio, on the dosages, on the masterly to be arranged and on the relative availability of the active substance in the various pharmaceutical forms and, consequently, on the role that the pharmacist of the National Health Service will have to assume in relation to therapeutic indications and clinical galenic.

The Inter-regional event entitled *Terapie effettuate secondo Legge 648/96 e 94/98: Esperienze a confronto tra Benefici e Rischi* (Therapies carried out accord to Law 648/96 and 94/98: Expeirences comparing Benefits and Risks) (Dr. Nigri, Dr. Calzola, Dr. Di Marco) in which the intervention was discussed of doctors, pharmacists and institutions, on the special use of drugs, aimed at guaranteeing the possibility of treatment in the absence of therapeutic alternatives or the need for early access, is of central importance in numerous therapeutic areas, in particular for the pediatric, oncological, infectious areas and for rare diseases.

The two editions of the *Corso teorico-pratico sulla "Farmacia clinica"* (Theoretical-practical course on "Clinical Pharmacy") (Dr. Bartolini) held in

Assisi inspired from the analysis of the complex scope of contents and actions that define the safety and efficacy of pharmacological treatments and to promote appropriateness in all its dimensions. Appointments sponsored by the National Health Institute and the Umbria Region, carried out with the scientific-cultural collaboration of the Italian Society of Hospital Pharmacy and Pharmaceutical Services of the Health Authorities – SIFO.

SIFO-Fare Event *Il farmacista nel percorso degli acquisti: esperienze e responsabilità* (The Pharmacist in the purchasing process: experiences and responsibilities) (Dr. Bartolini) in which aspects related to the value of the drug and the new procurement code, indirect health costs and LEA objectives, drug supervision and risk management were analyzed with the aim of achieving greater rationalization in the phase of defining needs and more effective management of the goods and services purchased and greater economies of scale.

Despite the difficulties of the pandemic period, now behind us, combined with those each day, we are convinced that, thanks to the strength and unity of our "group of friends", we will still be able to devise and organize many.

Participation in IOC meetings.

SIFO SECRETARIAT OF VENETO REGION

Secretary: V. Lolli
Councilors: F. Sconza, I. Toffanello

In 2021, this Veneto Regional Secretariat took charge of the requests presented by some members regarding the necessary training with respect to the innovations introduced by the entry into force in May of the new European Regulation on Medical Devices.

The articulation of the various chapters and the complexity of the arguments covered by the legislation was very difficult to interpret according to the vast categories of devices and also for the professionals, whether it was an application in the drafting of the tender specifications or evaluation of the relevant documentation or for the management of instances for clinical trials, many interpretative doubts arose and many questions remained open regarding the correct application of the text.

By way of example, the following topics were proposed to be addressed.

1) Definitions (art. 2): which are the most important changes introduced in the definitions. Classification of Devices and Classification regulations: what changes (Annex VIII).
2) Tracking of medical devices by using a mandatory unique identification

number (UDI). Deadlines for application of the UDI on the label for the different classes of MD (class III, class II b, II a, I). Checks to be carried out by the Health Authorities. Healthcare professionals must register the UDI code upon entry. Operational management of DMs with UDI code (e.g. for class III and implants). UDI database accessible by healthcare professionals?

39How do the conformity assessment procedures applicable to each risk class of medical devices change according to art. 52 of the MDR (Annex IV and Annex V).

4) The technical documentation during the tender to be requested by the Buying Authorities: what to ask for "new" in the tender specifications. For example, following the increased production of clinical evidence (articles 61-82) what to expect from manufacturers for evaluations during the tender. Again, the new regulation introduces a new figure as head for the Manufacturer responsible for compliance with the legislation (art. 15). Do the tender specifications starting from May 27, 2021 have to take into account compliance with the legislation?

5) Strengthening of the supervisory and post-marketing surveillance system. What changes for health professionals in the field of device-supervision. New definitions of accident and serious accident. How to report? New forms? What changes for manufacturers, agents and importers.

6) The transition period and application dates. Transitional provisions (art. 120).

Starting from these ideas, with the unconditional contribution of two Venetian companies: Santex and Clinilab, we managed not without difficulty, to put together a pool of experts of considerable caliber to seek answers to the training needs expressed, organizing an CME webinar course sponsored by SIFO, from the following program.

With the patronage of SIFO the LIVE WEBINAR: LA NUOVA NORMATIVA DEI DISPOSITIVI MEDICI (THE NEW LEGISLATION OF MEDICAL DEVICES) - 21 May 2021 - *Scientific Director Dr. Vincenzo Lolli.*

In proximity of the new European legislation on medical devices entering into force, many aspects relating to the regulatory part are still little known, such as, for example, regarding classification, traceability and conformity assessment.

Again what should be requested in the technical documentation in tendering headquarters, or what changes for health workers in the field of device surveillance, also relating to the new definitions of accident and in the field of clinical trials?

With the participation of colleagues and expert consultants, we will try to illustrate the new regulations and answer questions.

Program

- *Introduzione* (Introduction): Alessia Lazzaro, Vincenzo Lolli;
- *Introduzione generale: il nuovo regolamento* (General Introduction: The new regulations): Antonella Garna, Director of the Pharmaceutical and Logistic ESTAR Department
- *La sperimentazione clinica* (Clinical trials): Filomena Vecchione, Director of the Pharmaceutical and Logistics Department of ESTAR;
- *La vigilanza sui dispositivi medici* (Surveillance on medical devices): Daniela Minella, Inspection and supervision activities on medical devices, Ministry of Health;
- *Organismi notificati* (Notified Bodies): Roberta Marcoaldi, Director of the Notified Body 0373 National Health Institute;
- *Il nuovo regolamento europeo dei DM: innovazione e sicurezza terapeutica* (The new European regulation of the MD: therapeutical innovation and safety): Cecilia Giron, University researcher/Adjunct Professor of Pharmacology, Department of Pharmaceutical Sciences, University of Padua;
- *Fabbricanti e operatori economici tra regole, concorrenza e mercato* (Manufacturers and economic operators between rules, competition and market): Mauro Crosato, Lawyer;
- *Aspetti cogenti e regolamentari nella* supply chain. *Identificazione e rintracciabilità, vigilanza e sorveglianza del mercato* (Mandatory and regulatory aspects in the supplì chain. Identification and traceability, supervision and market surveillance): Riccardo Dainese, Sole director Eumed srl;
- *Discussione e Tavola rotonda Aspetti regolatori: opinioni a confronto* (Discussions and Round Table Issues: Comparing opinions): Speakers: Alessia Lazzaro, Cecilia Giron Discussant: Mauro Crosato, Riccardo Dainese, Antonella Garna, Roberta Marcoaldi, Daniela Minella, Filomena Vecchione.

The initiative met with considerable interest and the participation initially addressed to the members of the Triveneto was finally extended to all the regions through the involvement of the regional secretaries, obtaining the adhesion of as many as 150 members.

Following the CME accredited training event, the presentations carried out by Drs Marcoaldi and Minella respectively were made available to SIFO members, within the reserved profile on the website.

Furthermore, it was possible to verify how there is a social forum set up in the reserved area of the Sifoweb site by the previous area working group, which should be re-launched by the new national area group

on medical devices, identifying contacts for correct management, in order as such to stimulate fruitful discussions involving all the members professionally concerned, and gathering useful elements for the in-depth and understanding of the topics dealt with in the new European Regulation which only by application and experience in the field can find a right and complete meaning and classification. Another important updating activity is carried out at the Department of Pharmaceutical Sciences of the University of Padua, with the *Corso di Alta Formazione in Dispositivi Medici* (Advanced Training Course in Medical Devices), Director Prof. Maria Cecilia Giron, SIFO member.

The course is aimed at providing specific knowledge in the field of general and specialist medical devices. The operational tools that the course aims to offer to those who work in the medical devices sector are aimed at their correct evaluation, selection, information and use in compliance with current legislation and the clinical needs of patients.

Information and registration can be made by consulting the website: https://www.dsfarm.unipd.it/corso-di-alta-formazione-dispositivi-medici-aa-20202021.

Module I: Pharmacist of Research

Preface

Edited by the Scientific Tutors G. Muserra, P. Serra, F. Cattel, A. Esposito, R. Moscogiuri, E. Omodeo Salè, C. Masini

Dealing with clinical research and organizational research is one of the institutional tasks and prerogatives of the pharmacist that works in the NHS. The main places areas are represented by the Ethics Committees (present *ex officio* - Legislative Decree no. 211 of 24 June 2003) and the clinical trials in which the reference Health Authority is directly involved (monocentric and/or multicentric studies). This professional space is considered highly qualifying and deserves the recognition of a specific operational areas that we will try to detail in this manual.

In this part of the manual we want to clarify the role of the Pharmacist of Research: the Hospital/Territorial pharmacist has always been a member of the Ethics Committee as a healthcare specialist in Controlled Clinical Trials due to his technical and scientific skills. He is responsible for the management of the experimental sample, in most cases he is member/manager of the scientific secretariat, expert of the regional/national Observatory of clinical trials and responsible for the management and monitoring of Profit and Non-Profit trials. Given the complexity and multiplicity of the processes relating to the management of experimental samples, the pharmacist is also a key figure for the drafting of operational procedures and/or guidelines to support the process. The Pharmacist of Research is a figure that stands out but collaborates synergistically with the Research Pharmacist (Module II of the Manual), promotes of observational studies of Real World Evidence, epidemiological, and the use of innovative drugs and technological devices. In fact, the Hospital/Territorial Pharmacist, carrying out daily clinical trials, therapeutic attitude and adherence, pharmacovigilance, pharmaco-economics, in order to improve the quality of care through counselling both to professional colleagues and to patients, being considered an important figure in the realistic application of the topics under consideration.

Clinical research is constantly evolving either from the point of view of new models of clinical studies (for example, the new adaptive study models are being joined by other types of studies such as decentralized trials introduced with the pandemic), to facilitate more and more the access to innovative therapies, or from a regulatory point of view. Indeed, on January 31, 2022, Regulation (EU) no. 536/2014 had the aim of standardizing and simplifying the processes both at national and at European level.

The pharmacist, as an expert, in addition to being involved in the practical management of experimental drugs/devices is a relevant figure since the initial stages of authorization of a trial, being a member of the Technical-Scientific Secretariats of the Ethics Committees, interfacing with Clinical Trials Centers, providing support to investigators in the study design and carrying out a monitor activity of activated clinical trials.

With this manual, SIFO as a Scientific Society intends to provide Hospital and Territorial Pharmacists with information, useful clarifications and insights so that the category is ready to face and safely overcome this significant steps included in the world of Clinical Trials. In producing this manual, there was the participation in this draft of expert professionals from the Ministry of Health, National Health Institute, AIFA, Farmindustria, CRO and members of various Ethics Committees and obviously Hospital and Territorial Pharmacists engaged in clinical research.

In addition to the aforementioned Regulation (EU) no. 536/2014, the manual will also deal with Regulation (EU) no. 745/2017 on medical devices, an ambitious regulation that overlaps various directives. The world of medical devices is a very large and a growing sector, crossed by various problems regarding their management and their trials which, as within drugs, must be conducted in compliance with current regulations in order to evaluate the validity of the devices, with the hope that, as is the case for drugs, there will be soon a national and an international consultation platforms for clinical investigation pre-marketing, post-marketing and their therapeutic indications.

We hope that, as well as the High Level of Specialization Path, this manual will also be useful for the training and updating of professionals dedicated to the topic of clinical research. The primary objective is to guarantee not only the quality requirements for conducting clinical trials according to GCP but also to a greater attraction of the country, Italy, for clinical research and therefore of competitiveness at European level, in which the Pharmacist of Research is a central player within the complex world of clinical research, without which the system itself risks being penalized and limited, not only due to a delay in the application of European legislation, but also due to a lack of expertise of our own professional figure.

Both national and regional SIFO clinical research working groups continue to promote comparison activities on clinical trials. The pharmacist represent a central player in Clinical Trials (research and researcher) conduction and its absence could delay in Italy the regulatory application of the EU recommendation.

We believe that this text can represent an important starting point for us

Pharmacists, leaving room for a constructive dialogue between the various players involved.

We can therefore conclude that the pharmacist, properly trained, is the guarantor of quality and safety in the correct management of clinical trials, as well as becoming a strategic consultant for the clinician in conducting them through the clinical trials.

1. The role of the Istituto Superiore di Sanità (National Health Institute) in evaluating applications for admissibility to the Phase I clinical trial

M.F. Cometa, P. Popoli

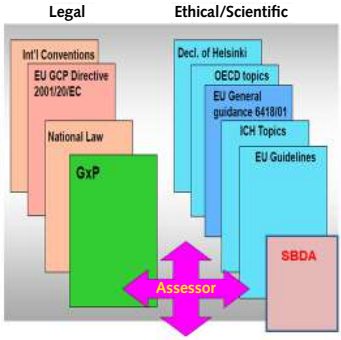
The drug is the result of an integrated development process which identifies: the scientific research and discovery phase (drug discovery), the non-clinical phase, the clinical trial phase and the surveillance phase after placing it on the market (post-marketing). From a regulatory point of view, it is possible to divide these phases into two main instances: the authorization process (which follows all the experimental phases of the drug) and the registration process (which allows it to be placed on the market).The Regulatory Authority must ensure the quality, safety and efficacy of an investigational medicinal product or of a drug to be placed on the market. The authorization process of a clinical trial is the prerogative of the Competent Authority (CA) which, on the basis of the evaluation of the documentation submitted by the "Owner" of the investigational medicinal product for the admissibility of the trial, issues the authorization or denial of the proposal in a clinical study. The scientific evaluation of data (Scientific Based Drug Assessment - SBDA) is the tool to protect public health both during the authorization phase of the development of a medicinal product and for its registration and requires the application of a coded "regulatory methodology" and adhering to international standards and guidelines.

The regulations governing the development of drugs have established in the last twenty years that the development of an Investigational Medicinal Product (IMP) must meet the requirements of the GxP including the rules of Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Good Clinical Practice (GCP). The fundamental ethical principles with which studies in clinical trials on medicinal products must comply originate from the Declaration of Helsinki and the requirements of the international standards of GCP developed to design, conduct, record and communicate the results of clinical studies that involve human subjects.

Downstream of the regulatory methodology, the SBDA cannot disengage itself from the regulatory guidelines that are issued by the European Medicines Agency (EMA) for Europe and the International Conference of

Regulatory methodology

- Legislation (*legal provisions*)
- GxP system (*regulated by regulatory decrees*)
- Regulatory guidelines (*are never mandatory*)
- SBDA (Scientific based Drugs Assessment): *Scientific evaluation of data is the tool to protect public health during the development of a medicinal product (clinical trials) and for its registration (AIC).*



Regulatory guidelines

THEY ARE NOT THE GUIDELINES OF SCIENTIFIC SOCIETIES

Scientific guidelines on the quality, safety and efficacy of medicinal products for human use, adopted in Europe by the CHMP (Committee for Medicinal Products for Human Use) (**EMA guidelines**) and by the International Council for Harmonization (**ICH guidelines**) (Europe/USA/Japan)

http://www.ema.europa.eu

http://www.ich.org/products/guidelines.html

The absence of shared guidelines increases the discretion of the regulatory authorities of the various States, highlighting divergent interpretations and non-homogeneous evaluation approaches.

Harmonization (ICH) created with the aim of harmonizing all production and registration processes, including non-European ones (including a consensus between Europe, Japan and the United States).

By way of example, a framework of the reference regulatory guidelines for the evaluation of the first dose to be administered to humans in Phase I "First in man" studies is provided.

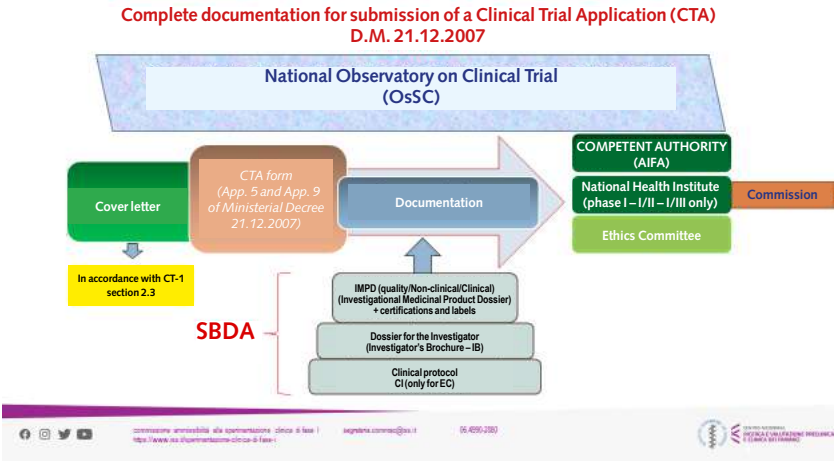
The calculation of the first dose is directly linked to the *target of the* population and the nature of the IMP:

- **IMP Chemical/Healthy Volunteer:**- LG FDA (2005) *Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers.* - NOAEL approach (*No Observed Adverse Effect Dose*) with calculation of the human equivalent dose (HED, *Human Equivalent Dose*) which will be divided by an SF (Safety Factor).
- **Chemical IMP/Sick subject (e.g. oncology)** - LG ICHS9 - 1/10 STD_{10} (*Severely Toxic Dose* in 10% of the animals, rodent) or 1/6 HNSTD (*Highest Non-Severely Toxic Dose,* non rodent).
- **Biotechnological IMP (e.g. MoAb)/Healthy Volunteer** - LG ICHS6 and LG CHMP *on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products:* MABEL approach (*Minimal Biological Effect Level*) (PK/PD).
- **IMP biotechnology/sick subject** LG ICHS6 and ICHS9.
- **Cell/gene therapy** (*Case by Case approach*) at times *Proof of Principle studies* (without going through the preclinical, directly in humans).

US Department of Health and Human Services Food and Drug Administration • Center for Drug Evaluation and Research (CDER) July 2005 • Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers • EMA/CHMP/ICH/731268/1998 Committee for medicinal products for human use (CHMP) • ICH guideline S6 (R1) • Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals • EMA/CHMP/ICH/646107/2008 • ICH guideline S9 on Nonclinical Evaluation for Anticancer Pharmaceuticals • EMA/CHMP/ICH/453684/2016 • Committee for Human Medicinal Products • ICH S9 Guideline on Nonclinical Evaluation for Anticancer Pharmaceuticals - Questions and Answers • EMEA/CHMP/SWP/28367/07 Rev. 1 Committee for Medicinal Products for Human Use (CHMP) • Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products.

In the last twenty years, in Europe, the legislation put in place to re-launch clinical trials under a more unitary framework is linked to directives 2001/20/EC, 2003/94/EC and 2005/28/EC. However, the nature of the legal instrument of the "Directive" has not effectively affected the achievement of the primary objective of incentivising clinical trials in Europe, leaving the authorization status the responsibility of the individual competent authority of the Member States (MS). In Italy, the Directives were implemented with

Legislative Decree no. 24 June 2003, no. 211, with the Legislative Decree 24 April 2006, no. 219 and with Legislative Decree 6 November 2007, no. 200. With the Ministerial Decree of 21 December 2007, the formalities relating to the documentation to be submitted to the CA and the Ethics Commitee (EC) for admission to the clinical trial of a drug were regulated in detail and starting from 1 July 2013, the documentation concerning clinical studies on Medicines is managed exclusively electronically, through the standard models of the AIFA National Observatory on Clinical Trials.

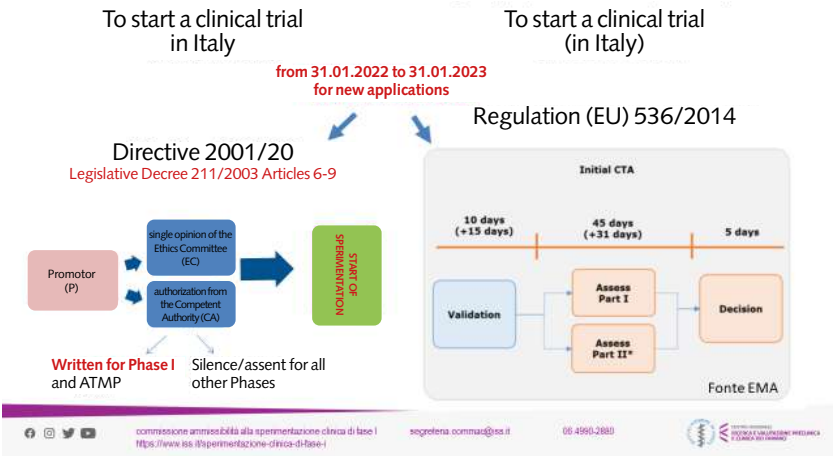


In 2014, the Regulation on clinical trials of medicines (EU) 536/2014 was issued. The Regulation, repealing 2001/20/EC, represents a turning point for the simplification of regulatory procedures but above all it is a provision that aims to fill various regulatory gaps on clinical trials through the creation of a uniform framework for authorization of clinical studies by all Member States concerned, with a single evaluation of the results. The evaluation therefore changes its way of being and becomes a shared work also from a regulatory point of view among the MS, promoting interaction between all the European CAs, involving the Ethics Committees in the evaluation procedure and bringing all the member countries involved to a joint authorization according to a single agreed assessment schedule.

The full application of the Regulation will take place after the transition period of 3 years defined starting from January 31, 2022. The Sponsors of clinical trials until January 31, 2023 will be able to choose whether to submit an application for authorization of clinical trials pursuant to Directive 2001/20/EC through the national procedures for submitting Clinical Trial

Applications (Ministerial Decree 21.12.2007) or pursuant to the Regulations through the European portal CTIS (Clinical Trials Information System).

From January 31, 2025, the trials still in progress approved pursuant to Directive 2001/20 will have to be transferred to the CTIS in accordance with the Regulations.



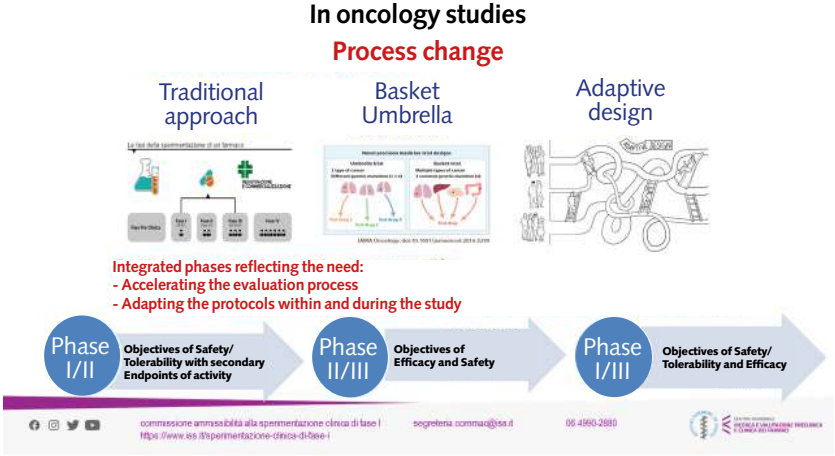
Role of the Istituto Superiore di Sanità (ISS) (National Health Institute) in clinical trials in Italy: Phase I clinical trials

The Phase I clinical trial typically represents the transition from preclinical trials (*in vitro* and/or on animals) to the first administration of a drug in humans (First in Man - FIM). FIM experiments can also take place on the sick subject in the case of products intended for serious pathologies and for which it would be unethical to treat a healthy subject.

The transition to the FIM trial is the most critical moment in the development of a new drug as it is potentially the most risky clinical phase for trial participants.

In the last sixty years there has also been a major evolution in the type of IMPs, starting from small chemical molecules to biological/biotechnological drugs up to advanced therapies (cell, gene and engineered therapy) which represent the most innovative type of products present today in the panorama of experimental medicines. Above all in the field of oncological drugs, moreover, to this is added an increasing complexity of Phase I clinical studies which not infrequently, especially for Phase I/II "seamless" designs, often of

an adaptive type, represent real registration studies. The acceleration of the development of such drugs (which is justifiable in light of the important unmet need), is also associated with the growing complexity of the molecular profiles of some tumours, which has led to the development of particular clinical designs such as the *basket* and *umbrella studies.* The combination of these elements makes the evaluation and authorization of Phase I clinical trials an increasingly complex task, which requires increasingly qualified and multidisciplinary skills.

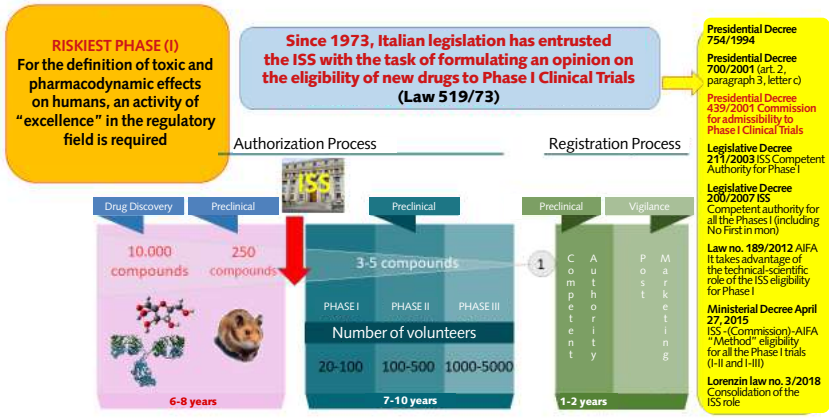


In order to judge whether a new drug can be used in humans, it is necessary to examine the data relating to the pharmaceutical quality of the product, the results of the preclinical studies and the proposed clinical protocol.

The evaluation of the aforementioned data, for the purpose of defining the toxic and pharmacodynamic effects on humans, is therefore an activity of "excellence" in the regulatory field, for which it is necessary to make use of experts with high competence in determined sectors (production of drugs estimated in quality, pharmacology and forecast toxicology) and consolidated experience in drug evaluation.

Due to the complexity of the evaluation process, Italian legislation has since 1973 assigned the Istituto Superiore di Sanità (National Health Institute) **the task of formulating an opinion on the admissibility of new drugs** to Phase I clinical trials according to Law no. 519/73 and subsequently with the Presidential Decree no. 754/1994 and then the Presidential Decree no. 70/2001 to art. 2, paragraph 3, lett. c, the ISS was called upon to ascertain the composition and harmlessness of the newly established pharmaceutical products before clinical trials on humans. Currently, the ISS opinion is expressed through the examination by the **Commission for admissibility to the Phase I Clinical Trial**

established by Presidential Decree no. 439/2001 (art. 7), which began its work in March 2002, operating in compliance with the indications of the legislation itself, with principles of independence, transparency and scientific rigor in the evaluation of individual proposals. The Legislative Decree no. 211/2003 confirmed the role of the abovementioned Commission and introduced art. 2 for the ISS (National Health Institute) the competence to authorize Phase I FIM clinical studies. With the Legislative Decree no. 200/2007, the competence extends to all Phase I clinical trials including *Non First In Human Trials.* With the Law no. 189 of 8 November 2012, the "*Competences in the field of Clinical Trials of medicines attributed by the legislative decree of 24 June 2003, no. 211, the Istituto Superiore di Sanità (National Health Institute - hereafter referred to as NHI) were transferred to AIFA, leaving the "evaluation" function to the ISS (NHI). With the Decree of the Ministry of Health of 27 April 2015, the procedures for exercising the functions, in the field of clinical trials of medicines, carried out by the Istituto Superiore di Sanità (NHI) and by the Italian Medicines Agency, which continue to make use of the Commission for the evaluation of the documentation submitted in support of the admission requests to all Phase I, I-II and I-III trials (to be understood regardless of the phase in which it is carried out or studied in Italy)*".



With the advent of the "Lorenzin" Law no. 3/2018 which foresees the "Delegation to the Government in the matter of clinical trials of medicinal products" is intended, in the spirit of the Regulation, to strengthen the principle that "*the procedures for evaluating and authorizing a clinical trial must take place through the guarantee that the people in charge of validating and evaluating the application are free from personal and financial conflicts of interest and ensure their impartiality by means of a declaration made*

pursuant to articles 46, 73 and 76 of the consolidated act as per the decree of the President of the Republic on 28 December 2000, no. 445".

A broader view at Regulation no. 536/2014 the role of the ISS can be considered for the aspects of competence consolidated over the years, still fundamental taking into account what is foreseen in the written motivations in the following three fundamental points:

- Member States (MS) must establish the appropriate body or bodies for the purpose of the assessment;
- MS must ensure that the people in charge of validating and evaluating the application have no conflicts of interest, are independent of the sponsor, of the institution to which the trial site belongs and of the investigators involved, and are free from any undue influence;
- The MS must ensure that the assessment is carried out jointly by a reasonable number of people who collectively have the necessary qualifications and experience.

How the Phase I activity is organized

- **The Commission** (Presidential Decree no. 439/01) is appointed by Ministerial Decree and remains in office for 3 years, meeting on a monthly basis. It is made up of 3 external experts and 3 internal ISS(NHI)/AIFA experts, is chaired by the President of the ISS (NHI) and has the Director General of AIFA as a member by right. It avails itself of the contribution of the experts (to date 52) appointed by the President of the Istituto Superiore di Sanità (NHI), the support of the Technical-Scientific Secretariat and an Administrative Secretariat.
- The Commission Experts are ISS (NHI) employees and appointed by the President of the ISS (NHI) belong to a list renewed every six months as part of the three-year mandate of the Commission. They carry out scientific research activities on a daily basis in the areas of quality and safety and pre-clinical pharmacology. They are called, with the support of the Technical-Scientific Secretariat, to elaborate scientific technical opinions and to train themselves on the guidelines issued by the International Conference on Harmonization (ICH) and by the Committee for Medicinal Product for Human Use (CHMP) of the European Medicines Agency (EMA) on regulatory procedures.
- **The Technical Scientific Secretariat (STS-F1)** on behalf of the President of the ISS (NHI) represents the regulatory interface for ISS (NHI)/ Commission/AIFA Experts, takes care of the preliminary investigation of the Procedures, organizes *pre-submission sessions* for Proposers and promotes the training of experts in the regulatory field.

- **The Administrative Secretariat (SA-F1)** on behalf of the President of the ISS (NHI) takes care of documentary and administrative management of the requests.

COMPOSITION OF THE COMMISSION

(2021-2024) Ministerial Decree 07.05.2021

MEMBERS ENTITLED
Prof. Silvio BRUSAFERRO (President of the ISS and of the Commission)
Dr. Nicola MAGRINI (AIFA General Director)
Both can appoint a delegate

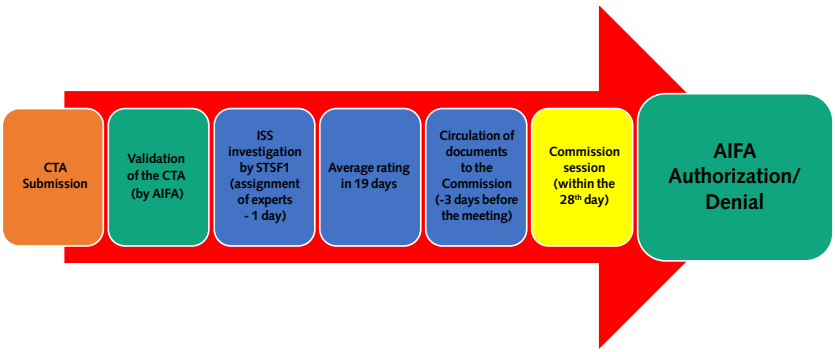
EXTERNAL EXPERTS
Prof. Carla CANNIZZARO (Full Professor Bio/14-University of Palermo)
Prof. Pietro MERLI (Doctor expert in haematopoietic transplantation and cell therapies, Bambino Gesù Hospital in Rome)
Prof. Francesco PERRONE (Oncologist at the National Cancer Institute IRCCS Pascale Foundation - Naples)

INTERNAL EXPERTS (AIFA OR ISS)
Dr. Paolo FOGGI (League II Medical Director - Pharmaceutical Innovation and Strategy Sector - AIFA)
Dr. Patrizia POPOLI (Director of the National Centre for Research and Preclinical and Clinical Drug Evaluation, CNRVF, ISS)
Dr. Mauro BIFFONI (Director of the Department of Oncology and Molecular Medicine, ISS)

SECRETARY
Dr. Maria Francesca COMETA (Director of Preclinical and Clinical Drugs Evaluation Unit, CNRVF, ISS)

The Commission's main task is the assessment of **applications for admissibility to the Phase I, I/II and I/III clinical trials (SC) and related substantive amendments (SA).** From the institution **of the Commission, over 1,900 applications for admissibility to the Phase I clinical trial and over 10,000 ES** have been examined to date.

The Commission examines the reports prepared by the technical-scientific secretariat on the basis of the experts opinions.



Simplification of the phases of the authorization process from the submission of the CTA to the issuance of the AIFA provision in accordance with the national legislation for Phase I clinical trials (Presidential Decree no. 439/2001, Ministerial Decree 12.21.2007, Legislative Decree no. 211/2003 and 200/2007).

It remains the task of AIFA (as CA) to validate the CTA and to authorize or not a Phase I clinical study based on the opinion expressed by the Commission.

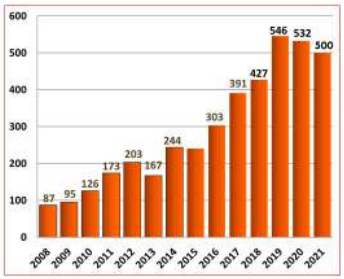
Starting from January 31, 2022, for requests for admissibility to clinical trials sent through the European CTIS Portal, the aforementioned procedure follows the same phase order of the process with the timing dictated by Regulation no. 536/2014.

Initiatives to support the Phase I trial in Italy

Having the opportunity to experiment with new drugs in the initial stages of development represents, other than a possible opportunity of treatment for patients, an important opportunity for growth and development for the entire country.

Applications for Phase I eligibility assessment

Substantive amendments – Phase I –



For this reason, over the years the Istituto Superiore di Sanità (National Health Institute) has implemented a series of initiatives aimed at supporting the Phase I clinical trial, such as:

- optimization of procedures in order to provide the qualified opinion in a certain time frame;
- strengthening of the technical-scientific and administrative secretariat and the involvement of a growing number of experts/evaluators;
- meetings with AIFA managers, representatives of the IRCCS, the Academy and the Industry;
- *pre-submission* hearings for proposers;

- activation of training projects (e.g. Masters, specialization courses) together with AIFA, University, Industry, IRCCS;
- promotion of cultural debates through the organization of conferences on the scientific, ethical and regulatory aspects of Phase I trials.

These initiatives, together with the advanced technical-scientific level of the evaluations, have ensured that the Institute was increasingly perceived as a reliable interlocutor, resulting in a significant increase in requests for evaluation of admissibility to Phase I clinical trials.

Other activities

The Commission, in addition to playing a key role in evaluating applications for admissibility to the Phase I clinical trial, is responsible for the "*Database for monitoring gene therapy and somatic cell therapy*" established by the Ministerial Decree of 2 March 2004 for patients enrolled in respective authorized clinical trials with advanced therapy products. Furthermore, according to the Ministerial Decree of 16 January 2015 "Provisions regarding drugs for advanced therapies prepared on a Non-Repetitive basis", it is established that "*the authorization for the use of the medicine is issued by AIFA, on the assent of the Commission referred to art. 7 of Presidential Decree 439/2001*". The authorization of non-repetitive uses is applied to subjects **not** included in clinical trials; AIFA evaluates the documentation relating to the production of the proposed product and the Commission authorizes its use on a single patient, under the conditions of lack of valid therapeutic alternative, in case of urgency and emergency that places the patient in danger of life or serious damage to health.

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2. Research and clinical trials in Italy: Farmindustria's point of view. How the hospital pharmacist fits into the life of the drug

M. Zibellini, G. Caruso

1. Relevance of research and clinical trials: the Italian data

In the last two years, also due to the Covid-19 pandemic, clinical research has been frequently brought to the fore in the mass media, mainly due to the large amount of studies that have been promoted in order to produce effective vaccines and medicines.

This has allowed this issue to emerge from its natural specialist niche to transfer it to public debates and social networks.

The important awareness on the part of institutions and public opinion has contributed to making it even more evident how an effective, well-organized and highly scientifically valuable clinical research ecosystem can become a crucial factor for the country both as a society and as an economic system, in the awareness of the value of science for the safety and well-being of individuals and the community.

Beyond this sudden notoriety, the relevance of clinical research is well known to all those who work in the sector, in its various aspects: scientific, economic, social and human.

In fact, it constitutes a crucial stage in the process of generating new drugs because it represents the longest, most complex and costly phase of the entire process and a precious opportunity of treatment for patients, since it guarantees early access to the drug in conditions of strict scientific and regulatory control.

For decades it has been an engine of development and advancement for the entire country. The most recent AIFA data (December 2020 Report), show that, in 2019, 672 clinical trials were authorized in Italy, in a context of constant and general contraction of trials conducted in Europe, with an increase in the percentage of authorized trials in Italy (equal to 23%) compared to the rest of Europe.

One of the main differences compared to the previous year was the reversal of the trend of purely national trials, with a decrease compared to the international ones, which instead increased also in absolute number, confirming how in Italy multicentric and multinational are the prevalent typology.

The distribution of the trials by therapeutic area confirms the data of previous years, with about half of the trials in the oncology and blood-oncology fields.

A raise of the trials in rare diseases continues significantly, representing 32.1% of the total, of which almost 82% are Profit trials, with a prevalent distribution in phases II and III and a representation equal to 39% of all phases I. The No Profit trials, compared to the total number of trials conducted in Italy, amounted to 23.2% of the total.

2. Direct benefits of clinical trials

The direct benefits of clinical research relate to its usefulness for patients and for health facilities where clinical trials are carried out. In fact, subjects enrolled in clinical trials mainly benefit from the possibility of taking innovative drugs, with therapeutic advantages compared to current treatments and several years in advance of their availability on the market.

This leads to an early improvement in their condition and quality of life, even for the families involved. Considering that the drugs available today are the result of research initiated in previous years, the current development also contributes to increasing life expectancy and quality of life of the new generations.

Furthermore, the correlation between research and quality of health care is widely recognized. Clinical centres enjoy a notable professional growth of the personnel involved (investigators, doctors, research nurses, trial managers and others). Where research is done, better care is taken.

3. Socio-economic value of clinical trials

The socio-economic value of clinical trials is expressed by several factors, both directly and indirectly:

- direct investments by public and private entities;
- related activities and the positive economic effects of investments;
- the effect on employment;
- cost savings and indirect benefits for the National Health System and for the health facilities where clinical trials take place.

Clinical trials and related activities, in addition to the direct economic contribution, allow for significant cost savings. The main beneficiaries are the National Health Service (SSN) and the community.

The most immediate case of avoided cost is due to the free supply of investigational medicinal products and control drugs administered to patients enrolled in clinical trials, the costs of which are entirely borne by the sponsor.

To these, must be added all the numerous diagnostic and laboratory tests performed during the trials. If patients were not enrolled in a clinical trial, drugs and services should be provided by the NHS, bearing the relative costs.

An ALTEMS research from 2020 shows that, for each euro invested by the sponsor for clinical trials, the NHS obtains overall benefits equal to € 2.77. And at € 3.08 if we consider only oncology trials.

4. Clinical trials: the new rules

The evaluation system of clinical trials in Europe is in full change. In fact, starting from 31 January 2022, Regulation (EU) no. 536/2014 on clinical trials is in force.

With this standard, the European Union intends to promote the efficiency of clinical trials, especially in the case of those carried out in several Member States, stimulating at the same time innovation and research and limiting duplication of evaluation and repetition of trials without added value.

The Regulation is intended to create a favourable environment for the conduct of clinical trials in Europe, through harmonization of the rules and evaluation processes. At the same time it guarantees the highest standards for the safety of the enrolled patients and the transparency of information, thanks to the publication of data concerning authorization, execution and results of the trials.

Therefore, the publication of the still long-awaited implementing decrees will be of fundamental importance, in accordance with the provisions of Law no. 3/2018 and by Legislative Decree no. 52/2019, to make European Regulation fully operational also in our country and to increase Italy's levels of competitiveness and attractiveness in clinical research in the international context.

5. Evolution of hospital pharmacists

The pharmaceutical sector is facing a phase of profound evolution and change that leads to rethinking the role, functions and responsibilities of the professionals involved in the management and conduct of clinical research. One of these is certainly that of the pharmacist.

The skills required and the activities of the pharmacist have gradually diversified over time, and not only according to the tasks performed in the structure in which they operate, but also based on the institutional context, the background of the clinical centres and the geographical location.

This scenario includes the complex mission of the hospital pharmacist who, in compliance with current legislation, is an active part of the care process, making services and information available to ensure effective, safe and economically compatible therapeutic interventions.

But not only. Over time he has acquired new skills in three major areas of intervention:

- logistics, regarding the acquisition and distribution of drugs and medical supplies;
- technical, in the field of preparation and handling of medicines;
- clinical from pharmacoeconomy to risk management clinical governance to clinical trials, implemented by the introduction of the figure of the clinical or ward pharmacist.

Over the years, the role of the hospital pharmacist has undergone a very specific reconfiguration: from a preparer and dispenser of the drug it has evolved to:

- ward pharmacist, managing an activity oriented to the pathology and, therefore, to the optimization of the therapy;
- pharmaceutical care provider, function aimed at taking charge of the therapy of the individual patient by intelligently balancing the allocation of resources, thanks to the knowledge and experience with respect to the drug and the evaluation of its appropriateness of use.

In the panorama of an increasingly complex and evolving healthcare facility, the figure of the hospital pharmacist is continually enriched with new skills and is also often the crucial link in new challenges.

He becomes a health professional capable of treating aspects of the drug ranging from pharmacoeconomics, cost rationalization, to pharmacovigilance, as a sentinel of adverse events; from bioethics to clinical trials, to the development of HTA.

A range of activities so wide that many times it becomes difficult to manage all aspects, but which is necessary to obtain the assistance goal of correct patient care with a view to economic sustainability.

6. Hospital pharmacist in research, clinical trials and care

Among the activities that have seen a significant increase in the involvement of the hospital pharmacist, the most important is certainly the collaboration in the management of clinical trials.

In fact, design, coordination and analysis of a clinical trial requires the involvement of a multidisciplinary team that includes the pharmacist.

In Good Clinical Practice, the pharmacist is indicated as being responsible for the various steps of the drug testing process.

It is responsible for the management of the experimental drug in all its phases: reception of the experimental samples for the qualitative and quantitative verification and the correct management of them; eventual preparation and packaging, randomization, masking and re-labelling procedures, logistical aspects (orders, stock management, destruction, accounting) as well as technical aspects such as, for example, those related to the pharmacovigilance of drugs in clinical trials.

In terms of logistics, experimental products must be stored in an easily identifiable area, with access reserved to the personnel involved in the trial, and separated from other drugs and/or devices to prevent products intended for experimental use from being used for the clinical practice.

It is essential to keep the experimental samples at the correct expected temperature and thus give the sponsor a guarantee; it is necessary to continuously monitor the expiry dates of the products being tested and, in the event of imminent expirations, notify the sponsor to receive information through formal communication about the fate of the product (re-labelling, return, disposal).

If the hospital pharmacy is required to produce experimental samples, it is necessary to keep in mind the provisions of reference legislation and that the production of Investigational Medicinal Product (IMP) is more complex than the production of the drug on the market, since there are some particular conditions:

- need to adopt standardized production and control schemes;
- need to structure fully validated production processes;
- variety of clinical trial designs;
- procedures to guarantee randomization and blindness;
- any additional packaging problems;
- additional risks for cross-contamination and mix-up.

The pharmacist is required to register upon arrival and dispensing of samples (all documentation must be kept in a dedicated cabinet). And to keep track of the documentation relating to the movements of the experimental samples within the health facility (delivery to the investigator, possible return to the pharmacy, etc.). And is also responsible for its correct archiving and conservation (in paper or electronic mode), making it available in case of inspection or monitoring visits.

As the main person in charge of the experimental drug management process, he participates in periodic monitoring visits, internal and/or external audits (pharmaceutical companies and/or CROs) and inspections by the regulatory authorities, providing an important professional contribution in terms of pharmacological and technological knowledge.

Subject to the need for constant monitoring of the expiry dates of the experimental drugs, at the time of the clinical trial being concluded, the pharmacist must take care of the control of returning or the possible disposal of the unused experimental drugs, guaranteeing their traceability.

7. Pharmacists of Research

The Pharmacist always more often is the sponsor of Clinical Research and participates in the drafting of experimental No Profit protocols with clinicians and statisticians as well as observational studies (Real Life/Real World, pharmacoeconomics, pharmaco-vigilance, quality of life of patients).

In such context, the Pharmacist of Research today becomes essential in the whole system because he applies the experimental methodology to the various areas of pharmaceutical assistance with the aim of collecting real world data and evidence, which are used at local and regional levels and by regulatory agencies to monitor the safety of drugs, adverse events and to make decisions as far as they are concerned.

The AIFA Resolution 809/2015 establishes the minimum requirements necessary for the operation of health facilities that carry out Phase I No Profit clinical trials, underlining the importance of the Clinical Trial Quality Team (CTQT) and the need for the existence in the hospital of a site dedicated to the delivery, storage and management of the drug, accessible only to authorized personnel.

Among the figures involved in the Team it is envisaged that of the hospital pharmacist who must deal with the management of the experimental drug and, in collaboration with other healthcare personnel foreseen in the organization chart, the quality of the No Profit trials in compliance with

the GCP, assisting the No Profit sponsor and the investigators, both in the authorization process and in the monitoring phase. Examples of CTQT activities include the revision of the protocol, the formulation of a monitoring plan and the verification of all the equipment and instruments involved in the study.

The pharmacist can also be a relevant figure within the Ethics Committees in the phase of protocol authorization, contract agreement between sponsor and clinical centres, and in feasibility check:

- of the study, according to the existence of the requirements envisaged by Law and Good Clinical Practice (GCP);
- of the trial site, according its resources and facilities present, also verifying that there is no additional burden on the structure and that the drug is actually provided by the sponsor where scheduled.

Very often the pharmacist is also found within the Technical-Scientific Secretariats of the Ethics Committees. In this case pharmacist is required to:

- define the working methods of the Scientific Secretariat, providing operational support in the preparation phases of the sessions of the EC and all other activities attributed to it;
- interfacing with the Clinical Trial Centres, both in the phase preceding the presentation of the studies to the EC, and in the phases following the session for their approval;
- provide support to investigators in the design, presentation, conduct and reporting phases of the studies – systematically record, through an appropriate database, the activities of the EC and information relating to clinical studies;
- carry out monitoring activities for activated clinical trials.

8. Pharmacists and advanced therapies

Gene therapy, which represents a new approach for treating rare genetic diseases, defines new responsibilities for the hospital pharmacist.

Due to their nature as biologically active drugs and the frequent use of live viruses such as vectors, the consequences of errors or accidents are potentially more severe than with standard drugs. Although the management of gene therapy involves specific and distinct problems compared to other medicines, there are currently no specific guidelines from the International Scientific Institutions or professional associations, relating to the manipulation, preparation and administration of gene therapy products.

In the absence of defined guidelines, individual institutions develop local

procedures, which should take into consideration the risk group of the viral vector used for gene therapy and the level of biological safety required, as well as the potential risk associated with the transplanted gene.

The Managers of the Hospital Pharmacy can contribute decisively to the development of standardized operating procedures which, taking into account the level of risk, define the minimum safety requirements and the infrastructures and equipment necessary to ensure the correct handling of gene therapy products, as well as to provide for adequate training of the personnel involved.

With the progressive increase in the number of gene therapy products, the role of the hospital pharmacist is destined to become increasingly important to ensure the correct management of the drug and to implement an effective collaboration between pharmacists and doctors.

This necessarily requires the development and implementation of training programs that allow hospital pharmacists to deepen the right knowledge for the correct manipulation of gene therapies.

9. Pharmacists and digitization

Telemedicine, artificial intelligence, apps and digital therapies. The horizon of the hospital pharmacist is broadening, also including the latest generation innovations to transform the profession in the next decade on a global level. The digitization of healthcare constitutes a new paradigm and a tool available to healthcare services around the world.

Digital therapies also fall within the sphere of competence of the hospital pharmacist as regards both the experimental phases and the clinical application, evaluating technical-scientific aspects, also participating in the activities of the Ethics Committees, and helping to promote a widespread, appropriate, safe and effective digital quality system for patients, within the multidisciplinary team present in the healthcare facility.

Among the activities related to digital health that involve the hospital pharmacist include the evaluation of medical apps, the use of various technologies to track medical devices, the implementation of databases and information systems that make it possible to detect and analyze specific indicators of effectiveness and safety of drug therapy.

It becomes therefore essential that digital training can start from the first phase of the pharmacist's education, equipping university faculties with advanced tools to transfer knowledge and skills to students on their use in professional practice.

Digital skills should integrate with scientific ones, becoming a standard of the profession. Already today, part of the pharmacist's activity makes use of various digital tools, more or less diffused according to geographical areas and were often used due to the pandemic: electronic medical records, dematerialized prescriptions, e-commerce of pharmaceutical products are only some examples of tools that pharmacists are learning about.

10. Patient-centered care: focus of clinical pharmacy

The revolution compared to the classic approach is the shift of the pharmacist's attention from the single drug to the patient's health in clinical trials and practice.

The vision is therefore no longer pharmacocentric but has as its epicentre the well-being of the patient.

It is a discipline that is carried out in any field in which drugs and medical devices are researched, developed, prescribed, dispensed and recommended. Clinical pharmacists treat patients in any healthcare setting, as they possess – in addition to the consolidated basic knowledge related to drugs – adequate skills in clinical and biomedical matters.

In the healthcare contexts in which it is applied, the clinical pharmacy contributes to the generation of new knowledge and allows the optimization of the patient's medical therapy to promote and improve health and quality of life.

Clinical pharmacist can contribute to favouring adherence to therapy, promoting therapy reconciliation activities, active pharmacovigilance projects, epidemiological studies, information and educational health programs, prevention and screening campaigns.

It is also able to carry out a correct differential clinical classification of minor disorders using standardized diagnostic algorithms and to recommend rational therapy through first-line drugs and healthy lifestyles.

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3. Clinical Research during a pandemic: the point of view of the INMI Lazzaro Spallanzani Ethics Committee, the Hospital Pharmacist and the Pandemic emergency

*F. Ciccopiedi e S. Murachelli**

"In a clinical trial, the rights, safety, dignity and well-being of subjects should be protected, as well as reliable and robust data should be produced. The interests of the subjects should always have priority over all other interests".

Thus states the art. 1 of Regulation (EU) no. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials of medicinal products for human use. The dictation of the aforementioned article was the guiding principle of the activity carried out by the Single National Ethics Committee for Covid-19 during the entire period of its mandate.

Since March 2020, the epidemiological emergency from Covid-19 has imposed on health systems, worldwide, the need to face an unprecedented challenge.

The scientific community, faced with the rapid spread of a pandemic of considerable size, in a fight against time has been called to identify, experimental pharmacological therapies in order to try to counteract such a dramatic impact on people's lives, in particularly the vulnerable, and in general for the protection of society.

The pandemic emergency has led government sectors, legal and health workers to face problems that have involved various constitutional principles, including the protection of the health of the entire community.

In fact, in this last period, public health has gradually acquired more and more importance, to the point of becoming a foundation of the security of States.

In the absence of effective ordinary therapies in the face of the spread of an unknown virus and the cause of severe pathologies, hope has been placed on a global level in clinical trials that have extraordinarily multiplied in all scientifically advanced countries. Our country has also done its part very well, activating studies throughout the national territory, in Regions traditionally

* The authors thank Cinzia Caporale, president of the single National Ethics Committee for Covid-19, for the discussion on the contents and the critical review of the article.

engaged in this kind of experimentation and in those where previously these activities were residual.

In carrying out the research, all the precautions necessary to guarantee the participants were put in place, in constant compliance with the applicable national and European standards and the general ethical criteria envisaged in the sector such as: the scientific justification of the validity of the experiments (which is the first ethical criteria to be observed), the balance of risks/benefits, the protection of the patient's health, safety and well-being, respect for individual autonomy and informed consent to treatments and the use of biological samples, the protection of privacy and the protection of personal data, as well as transparency, honesty, rigor, reliability and objectivity in conducting research.

During the emergency period, the simplification of European and national administrative procedures, as well as some methodological devices, made it possible to achieve the expected results quicker than in other periods, but this never occurred to the detriment of compliance with ethical standards in the conduct of research activities, which was constantly guaranteed also thanks to the action of the Ethics Committees. However, several unpublished scientific and ethical criticalities have emerged, in particular here, due to the very special circumstances in which the studies were conducted; critical issues that sometimes required responses also from a legal point of view. To respond efficiently to the needs of clinical research in Italy, with the Law Decree no. 18/2020 – converted with the law of 28 April no. 27 and, subsequently with the Law Decree of 8 April 2020, no. 23, the Ethics Committee of the National Institute for Infectious Diseases Lazzaro Spallanzani – IRCCS of Rome – was appointed "*as the single National Ethics Committee for the evaluation of clinical trials of medicinal products for human use, of observation studies on drugs, programs of compassionate therapeutic use for patients with COVID-19, expresses the national opinion, also on the basis of the AIFA CTS evaluation*".

Centralization was aimed at ensuring greater speed and consistency in the pronouncements, a better connection with the investigators in multicentre trials and a more effective interaction with AIFA.

The main task of the Single National Ethics Committee was the formulation of authorizing, mandatory and binding opinions on the research that involved the Covid-19 pandemic and were carried out in our country. Hundreds of opinions were issued, among which on studies and on amendments.

The Committee whose multidisciplinary composition coincided with that of the IRCCS Ethics Committee operated in its collegiality and independence, taking all decisions unanimously after extensive in-depth analyzes and

collegial discussions, essentially met in permanent plenary session from 17 March 2020 to 31 May 2021.

The activities directly involved all the members of the Committee, both on the basis of their skills and in order to supervise every single aspect with multiple verification stages, with the aim of avoiding delays and errors in objectively very difficult circumstances. The active contribution of the members also partly vicariates the work of the Secretariat, which unfortunately remained substantially unchanged in terms of resources dedicated even after the Committee assumed a national role (in addition to the local one not limited to studies on Covid-19, which was maintained throughout the period).

The path and management methods followed by the Committee were characterized by some features such as the speed in placing the study submissions on the agenda, the holding of online meetings, the very long hours of daily work and the carrying out of sessions also during holidays. These measures, together with the establishment of a single committee in itself and some administrative requirements, have transformed the approval times of the trials, which previously were calculated in months but in the pandemic period were calculated in weeks and even in days.

The protocols submitted to the Committee presented very different profiles of complexity and articulations and some systemic criticalities, probably also due to the commotion of the pandemic period. Among these, the drafting of information sheets and consent forms which overall resulted inadequate and incomplete, drafted with inappropriate language and some major deficits, also with regard to the protection of personal data. In all these cases, the Committee played a fundamental role in protecting the participants and intervened even in support of the researchers in order to allow them to rapidly reach an ethically acceptable and legally congruous formulation of informed consent.

Overall, it can be said that the establishment of the single National Ethics Committee for Covid-19 has contributed in guaranteeing the quality of clinical research and its ethical sustainability, concepts that are inseparable and interdependent, in the most dramatic health period of the last century and has constituted a useful experience for the creation of further single National Ethics Committees according to the needs that will gradually arise.

The Hospital Pharmacist and the Pandemic Emergency

During the Covid-19 pandemic, the hospital pharmacist played a key role in containing and managing the virus.

In the case of an interventional study that involves the use of an experimental drug, approval is subject to the presence of a robust scientific ration, a methodologically correct design, compliance with current regulations. In the case of the many observational studies conducted during the pandemic, already authorized drugs were used, but with other indications. In fact, in the first phase of the pandemic, no drugs with specific indication were available, but inhibitors of proteases active against the HIV virus, cortisone, anti-inflammatory drugs, inhibitors of the activation of cytokines, vitamin D, hydroxychloroquine were used in clinical practice. Since the risk/benefit ratio is connected to the use of any drug, it is important to determine the efficacy of the drugs used in Cov-2 infection with methodologically valid studies.

In addition to the irreplaceable activity carried out within the Ethics Committee, the hospital pharmacist is a figure who is increasingly integrated with the other healthcare professionals present in the hospital.

Even if in Italy this integration has not yet reached the levels present in other countries, especially Anglo-Saxon, there's a reality that begins to exist in our Country too in which the pharmacist, rightly defined *clinical pharmacist,* is present in the wards and works in close contact with doctors and nurses.

Even outside the hospital ward, as occurs in the context of most Italian health facilities, and without claims of invasion of the field, the training acquired during university and specialization studies provides the pharmacist with the requisites and tools to collaborate in correct drug management at all phases, so that *the right drug can be guaranteed to the right patient at the right time.*

The pandemic emergency determined an increase and acceleration of the activities that are part of the professional background of pharmacists and, in our opinion, have made them very visible within the structures and above all more cohesive with other health professionals.

The areas of intervention that the pandemic has most stressed were:

1. Logistic activity

Complete traceability of the drug must be guaranteed (number of packs/doses, lot, expiry date) from the moment of receipt to the moment of distribution. Paper-based tools can be used but preferably IT tools.

Furthermore, it is necessary to ensure the correct storage temperature, which must be documented using certified measuring instruments, calibrated and subjected to periodic reviews. This applies to all drugs but, in particular, it is an obligation for experimental drugs. The documentation must be kept and available for possible inspections.

It is necessary to adjust stocks to actual needs.

Especially in the first phase of the pandemic there was no lack of problems of serious shortages of both drugs, medical devices and personal protective equipment (PPE). Unfortunately, it is not an exhaustive list but by way of example: opioids and curarics indispensable for patients undergoing endotracheal intubation, medical devices for ventilation, flushing pumps for infusion pumps, P2 facial filters and other PPE.

The pharmacist must know the procedures to follow so as to remedy these shortcomings; we refer, in particular, to the methods of importation from abroad, which require specific authorization from AIFA in the case of drugs with AIC or narcotics.

Logistics is sometimes considered the Cinderella of activities. Instead, it is useful to remember the importance of a correct logistical organization if you want to administer *the right drug to the right patient at the right time.* This principle is always valid but it is all the more compelling to respect the "right time" for drugs and monoclonal antibodies to be used in Covid-19 patients, which provide a limited time lapse for their effective administration.

2. Galenic activity

Whenever the drug is not administered as is, galenic-type operations are required, which can range from simple dilution or to more complex operations that require calculations, compliance with certain methods of execution and the presence of dedicated equipment. As an example, the first anti Covid-19 vaccine and the procedure for its use may apply: storage in the freezer – thawing – dilution – taking the correct dose – administration. All this strictly respecting the times, maintenance of sterility, rules of good preparation according to (F.U.).

Not only procedures and preparation sheets must be available, but also documentation relating to the equipment used and maintenance interventions.

3. Pharmacovigilance

Medicines and vaccines must be effective and safe. During the trial phase, it is the responsibility of the investigator to report adverse events. The clinical trial is conducted on a small number of selected patients, which may

not be sufficient to highlight uncommon adverse effects. Post marketing vigilance is essential to unequivocally determine the profile of a given drug or vaccine. Both serious, non-serious, unexpected or already described adverse effects should be reported. In the first phase of the pandemic emergency, no specific drugs against the Sars-CoV-2 virus were available and antiviral drugs be it protease inhibitors or anti-inflammatory were used, both off label and in observational studies and in compassionate use programs, cytokine inhibitors, hydroxychloroquine, vitamin D, etc. It was essential to determine the risk/benefit ratio. While the benefits can only be assessed by the clinician, the pharmacist plays a crucial role in the risk assessment. In each healthcare company, a pharmacist is identified in charge of the drug surveillance activity, who can collect the reports directly from the patient or inform and stimulate clinicians and nurses to transmit the reports. Paper records or IT tools can be used. It is the task of the pharmacovigilance manager to enter the reports in the national network, from which they are subsequently transferred to the European network. Sometimes clinicians and nurses are reluctant to report because not knowing enough about the functioning and sometimes the very existence of the networks, they may have the false perception that the single report, especially if not serious or already described, is useless. It has been observed that, if the pharmacist carries out information/training, the number of reports is destined to increase and their quality to improve significantly.

As a major consequence, information on the safety of drugs and vaccines is increasing.

In conclusion, the pandemic period marked a phase of significant enhancement of the hospital pharmacist figure. The extent of the change is not yet fully determinable; however, it is important that among the lessons learned from the pandemic remains that of the re-evaluation of the functions of this central figure for health structures, for skills and role of guarantor, for the benefit of the hospital organization and operators, but above all of individual patients and definitively of the company.

4. AIFA Observatory of Clinical Trials: setting and explanation

P. Aita

The National Observatory on Clinical Trials of Medicines (OsSC) is the operational tool for managing the authorization process of clinical trials (Phase I-IV) which take place in Italy and allows you to photograph in real time the progress of clinical research in our country, as well as acting as an interface for sending information to the European EudraCT database.

OsSC: functions

Its function is to allow the submission of clinical trial applications and substantial amendments to clinical trials already started, including all the supporting documentation, simultaneously to AIFA as Competent Authority and to the Coordinating Ethics Committee, as well as to all the Ethics Committees of reference for the individual trials.

OsSC: model

At European level, the OsSC represents a platform modality of e-submission, workflow and database on clinical trials of medicines, both as regards the telematic management of authorization flows and documentation among Regions, Competent Authority (CA), Ethics Committees (EC), Sponsors, Contract Research Organizations (CROs), clinical sites and the European EudraCT database, and for the information periodically addressed to operators and citizens through the National Report on Clinical Trials.

OsSC: primary objectives

The OsSC aims to guarantee unity to the clinical research system and constitutes:

- the analysis and support tool for policy makers at national, regional and local levels;
- the management tool at the service of Sponsors, CROs, EC, AIFA, ISS, Regions;
- the link between Italy and the other EU Agencies and EMA (EudraCT DB).

OsSC: registered users

The registered users who access the OsSC are the Applicants (Sponsors and CROs), as well as the ECs. In addition, CA users also access (AIFA and ISS

in support of AIFA's activity for Phase I clinical trials) as well as the Regions for the qualification of the ECs and for the consultation of the data on the clinical trials of their own territorial competence as foreseen by Ministerial Decree of 21 December 2007 "*Procedure for forwarding the request for authorization to the competent Authority, for the communication of substantial amendments and the declaration of conclusion of the clinical trial and for an opinion request to the Ethics Committee*" (Annex 1, par. 5).

OsSC: registered users

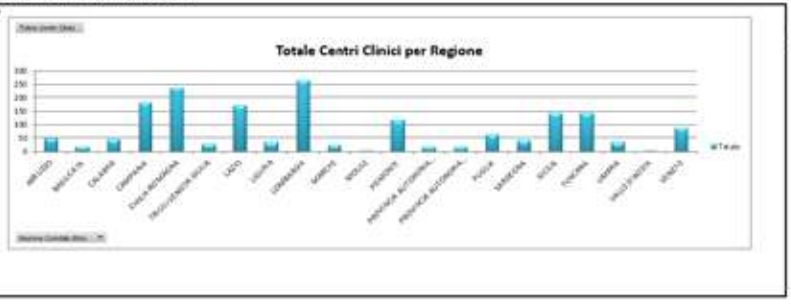
(Updated 27.12.2021)

	User records		
	Italy	**Foreign**	**Total**
Sponsors	405	905	1310
CRO	124	102	226
Ethics Committees			91

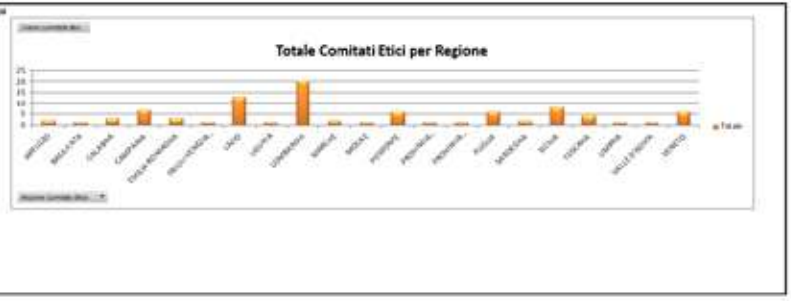
OsSC: detail of Ethics Committees and Clinical Sites (updated to 22 March 2022)

National Register of Clinical Sites and Ethics Committees

Regioni	Totale Centri Clinici
ABRUZZO	46
BASILICATA	12
CALABRIA	46
CAMPANIA	180
EMILIA-ROMAGNA	235
FRIULI-VENEZIA GIULIA	27
LAZIO	171
LIGURIA	33
LOMBARDIA	266
MARCHE	27
MOLISE	1
PIEMONTE	119
PROVINCIA AUTONOMA DI BOLZAN	17
PROVINCIA AUTONOMA DI TRENTC	17
PUGLIA	63
SARDEGNA	41
SICILIA	141
TOSCANA	143
UMBRIA	33
VALLE D'AOSTA	1
VENETO	67
Totale	**1718**



Regioni	Totale Comitati Etici
ABRUZZO	2
BASILICATA	1
CALABRIA	3
CAMPANIA	7
EMILIA-ROMAGNA	3
FRIULI-VENEZIA GIULIA	1
LAZIO	10
LIGURIA	1
LOMBARDIA	20
MARCHE	2
MOLISE	1
PIEMONTE	6
PROVINCIA AUTONOMA DI BOLZAN	1
PROVINCIA AUTONOMA DI TRENTC	1
PUGLIA	6
SARDEGNA	2
SICILIA	8
TOSCANA	4
UMBRIA	1
VALLE D'AOSTA	1
VENETO	6
Totale complessivo	**90**



Source: National Register of Ethics Committees and Clinical Sites https://www.aifa.gov.it/web/guest/osservatorio-nazionale-sperimentazione-clinica

OsSC: Services

The services that the OsSC makes available to operators in the sector mainly consist of:

◊ *Single portal (with area reserved for Sponsors.CROs, EC, Regions)*

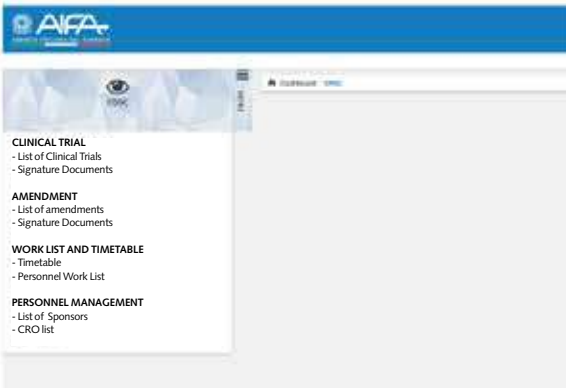
- equipped with secure access of web-based technology;
- with electronic transmission of documentation;
- indispensable for tracking, reporting and data analysis;
- supported by Help-desk.

◊ *Information/Training/ Editorial activities*

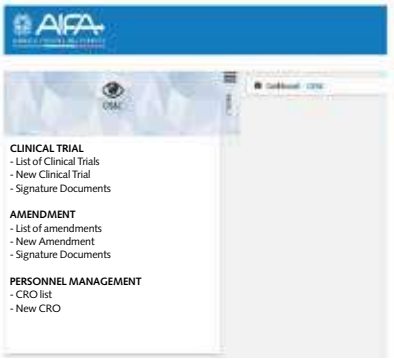
- Information/Training of operators (Manuals, Video-tutorials);
- Editorial activities (National Report on Clinical Trials of Medicines).

Access to OsSC via credentials allows for a different view depending on the user profile.

AIFA display



Applicant display (Sponsor and CRO)



Ethics Committee display

OsSC: training and information

These activities are manifested through:

- publication of an annual national report;
- monitoring and analysis of clinical trials of medicines on the Italian territory;
- implementation of training initiatives for personnel involved in clinical trials of medicines (courses previously and recently video-tutorials);
- operational announcements;
- participation of OsSC staff as speakers at workshops, conferences and university masters.

In particular, as regards the **information of operators,** all the communications of interest, including those relating to the management of clinical trials in Italy during the Covid-19 emergency are all to be found on AIFA's Institutional site in the given area (https://www.aifa.gov.it/web/guest/comunicazioni-aifa-ossc).

OsSC: value of publishing and sharing data

The publication and sharing of data from trials and analyses on relevant indicators constitute benchmarks within which each operator or institution can evaluate their own work and plan initiatives, corrective actions and adaptation to best practices:

- EC (e.g. analysis of evaluation times);
- Investigators (e.g. creation of networks and collaborations);
- Regions (e.g. information dashboard);
- Sponsors (e.g. analysis of substantial amendments);
- AIFA (elaboration of new regulations).

OsSC: editorial activities

The editorial activity connected to the OsSC is represented by the National Report on Clinical Trials of Medicines, which provides a periodic update on the qualitative and quantitative progress of clinical research in Italy (latest edition: Clinical Trials of Medicines in Italy – 19th Report National – Year 2020, https://www.aifa.gov.it/-/19-rapportonazionale-sulla-sperimentazione-clinica-dei-medicinali-in-italia-20-1).

The OsSC has the following functions:

Check

- because it is a working and collaborative tool for AIFA and the EC;
- allows for the verification of compliance to the Standards of Good Clinical Practice (GCP) and the planning of GCP inspections.

Research support

- promoting the harmonization of national procedures through the use of web-based technologies.

European cooperation

- placing itself at the interface with the European database EudraCT and, in the future, with the EU Portal.

OsSC: legal basis

According to the Law no. 189/2012, converting the Law Decree no. 158/2012 cd "Balduzzi", art. 12, paragraph 12, the exclusively electronic management of the authorization process of clinical trials was envisaged through the OsSC e-submission platform, with integration into the AIFA CA and ISS flow for Phase I trials, as well as with the standard forms of the OsSC which updates the one in the Appendix to the Ministerial Decree of 21 December 2007, taking into account the implementation of the CT1 guideline of the European Commission (March 2010) and the AIFA Determination of 7 January 2013.

OsSC: activity

The activities within OsSC pertain to:

- Management of the Clinical Trial Application (CTA) process/Substantial amendment/declaration of conclusion;
- Management of the preliminary check-in (validation) and evaluation (by the relevant EC/AIFA entities) processes;
- Management of the trial status/administrative data for each site;
- Exchange of information between the Applicant, AIFA and EC (Forum).

OsSC: processes

The processes carried out by the **Applicant** concern:

- Parallel submission of a CTA/Amendment request to AIFA and EC coordinator/EC collaborator;
- Request for withdrawal of a trial/amendment;
- Search by trial status;
- Discussion in the Forum.

  Those headed by **AIFA/ISS** and **the Ethics Committee** (EC) concern:
- Validation process;
- Evaluation process, in turn divided into the following activities (with suspension of the terms in the event of a request for integration):
  - Request for additions/changes to core documentation: AIFA and EC coordinator;

- Request for additions/changes to "centre-specific" documentation: EC coordinator/EC collaborator (e.g. Informed Consent);
- Issue of authorization/opinion: AIFA/EC.

- Search by trial status;
- Discussion in the Forum.

Regarding the **Substantive Amendment** (ES), the OsSC allows for:

- the selection of the sites affected by the substantial amendment;
- parallel submission of amendments.

Depending on the type, the amendment is presented to:

- AIFA and EC coordinator;
- AIFA and EC coordinator/collaborators;
- EC (e.g. change of principal investigator).

Finally, as regards the management in the OsSC of **the trial Status (Appendix 10), of the administrative data of the clinical site (Appendix 11), of the declaration of conclusion (Appendix 12):**

- Appendix 10 becomes a dynamic module that the Applicant updates following the status change of the trial (study in the enrolment phase, active study but that is not recruiting, etc.);
- Appendix 11 includes administrative data of the site and is completed to notify the EC of the closure of the study;
- Appendix 12 represents the statement of conclusion of the study "in toto".

Access to OsSC takes place via **user authentication** (user id and password).

The super - user can enable other users of his organization (Applicant/EC) to OsSC access.

OsSC: roles

The roles of the different user profiles in OsSC are as follows:

CA

- Takes charge of the clinical trial and amendments applications
- Manages the validation of them
- Make requests for integration/objections
- Evaluate positively or negatively
- Releases provision

ISS

- Make objection requests
- Expresses opinion

EC

- Takes charge of the clinical trials and amendments application
- Manages the validation of them

- Make requests for integration/objections
- Evaluate positively or negatively
- Expresses opinion

CRO Applicant (delegate)
- Inserts and modifies Trials
- Inserts and modifies Amendment
- Handles requests for additions made by CA, EC

Sponsor
- Inserts and modifies Trials
- Inserts and modifies Amendment
- Handles requests for additions made by CA, EC
- Deliberates/revokes a delegation to CRO for trial management

Region
- Enable ECs

The **information traced by the information system** are those relating to:
- the **Clinical Trial Application or CTA (Applicant)**
  - Initial CTA
  - Substantial amendments
- **AIFA authorization** and the opinion **of the Ethics Committee**
- **monitoring (Applicant)**
  - Start and conclusion by site
  - Declaration of General conclusion
  - Results

The data of the information system is structured in appendices (from the Ministerial Decree of 21 December 2007, as updated in OsSC) and modules:

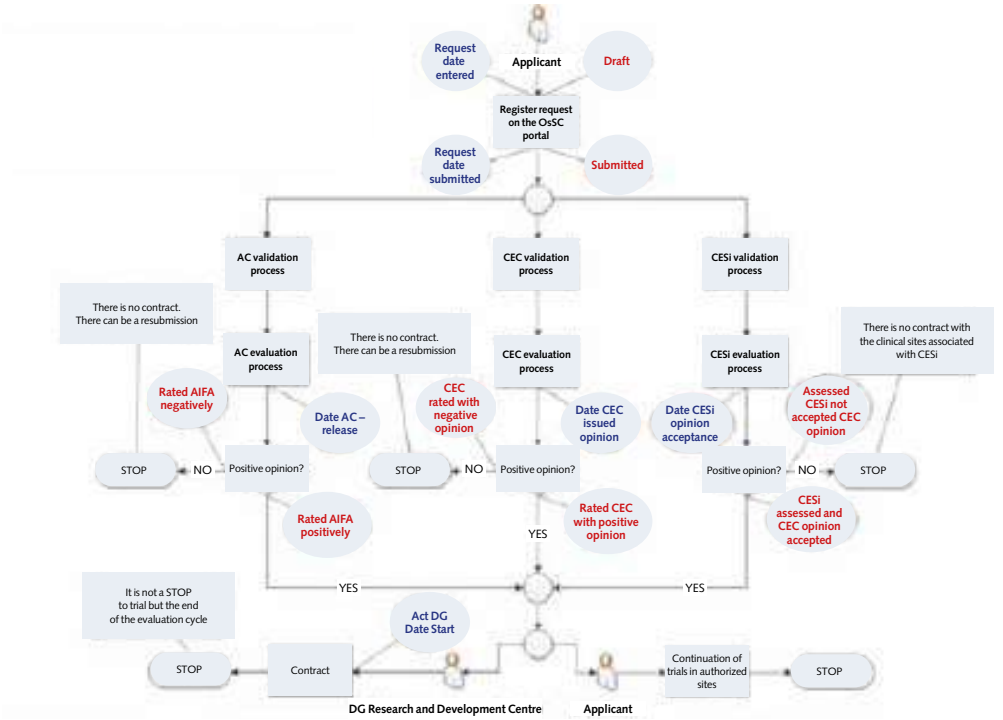
OsSC: appendices
- Appendix 5 (CTA Form) – Clinical trial authorization request (document created and updated based on the data entered by the Sponsor/ CRO during the validation/evaluation phase of the trial or subsequent amendments)
- Appendix 6 – Single Opinion (PU) EC coordinator (CEC) (favourable or unfavourable)
- Appendix 7 – Revocation of PU (where applicable)
- Appendix 8 – Acceptance/refusal/withdrawal by the satellite EC (CES) of the PU CEC (one for each trial site). For the same site there can be two Appendices 8 (e.g. first acceptance and then withdrawal of acceptance)
- Appendix 9 – Request for amendment authorization

- Appendix 10 – Status of the trial in Italy for each clinical site
- Appendix 11 – Conclusion/Withdrawal site
- Appendix 12 – Conclusion of clinical trial in toto

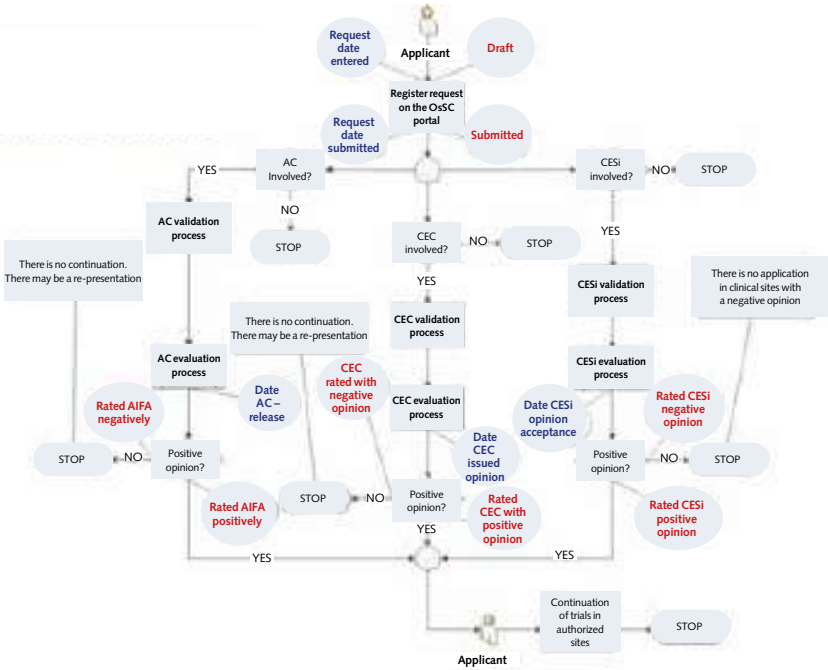
OsSC: modules

- AIFA trial authorization form
- AIFA amendment authorization form
- CEC opinion amendment form
- CES opinion amendment form
- Self-certification form for previous assessments relating to procedures managed extra-OsSC and then brought/reported to the system (previous trial and previous amendment, respectively)
- Revocation form of amendment EC opinion
- Trial/amendment withdrawal formto be sent by the Applicant to AIFA/EC
- AIFA authorization withdrawal form

GENERAL FLOW TRIAL



GENERAL FLOW AMENDMENT



OsSC: the development of the current version of the OsSC compared to the previous one concerns:

- management of the Sponsor-Applicant electronic proxy;
- new Appendix 10;
- closure of flows following Appendix 11 (closure of site) and 12 (closure of clinical trial in toto);
- clinical trial results section;
- digital signature;
- new logic regarding the versioning of the CTA, the progress report, the forum and notifications;
- parallel submission of Substantive Amendments (ES);
- previous ES function (return to the system of a clinical trial submitted in OsSC and then managed extra-system for technical problems).

In particular, where the digital signature is concerned, the **new transversal digital signature method was introduced** (Press release 1 February 2019).

The Transversal Electronic Signature module supports the following signature methods in OsSC:

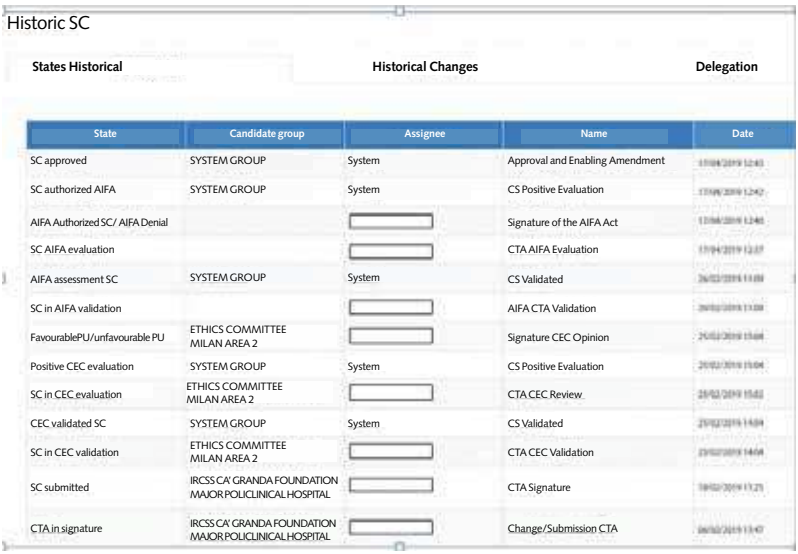
1. Local signature: the local signature, EIDAS compatible, is performed by means of a physical device such as smartcard or USB token.

2. Remote signature: uses the remote signature service of the AIFA supplier (ARUBA SPA). The user in possession of a remote digital signature provided by ARUBA SPA validates the signature operation by entering their ARUBA credentials (username and password) and OTP (one time password) obtained via a physical device or APP.

An active Internet connection is required during digital signature operations.

Furthermore, as regards the **new logics,** these have invested:

- Versioning of the CTA: increase of the sola *minor* unless resubmitted, which instead increases the *major*;
- the Forum: access only from the action button. Messages can only be viewed by the recipients of the message;
- the Progress Report: no longer in graphic format, but a list of actions and changes.



Historic SC

States Historical **Historical Changes** **Delegation**

State	Candidate group	Assignee	Name	Date
SC approved	SYSTEM GROUP	System	Approval and Enabling Amendment	
SC authorized AIFA	SYSTEM GROUP	System	CS Positive Evaluation	
AIFA Authorized SC/ AIFA Denial			Signature of the AIFA Act	
SC AIFA evaluation			CTA AIFA Evaluation	
AIFA assessment SC	SYSTEM GROUP	System	CS Validated	
SC in AIFA validation			AIFA CTA Validation	
FavourablePU/unfavourable PU	ETHICS COMMITTEE MILAN AREA 2		Signature CEC Opinion	
Positive CEC evaluation	SYSTEM GROUP	System	CS Positive Evaluation	
SC in CEC evaluation	ETHICS COMMITTEE MILAN AREA 2		CTA CEC Review	
CEC validated SC	SYSTEM GROUP	System	CS Validated	
SC in CEC validation	ETHICS COMMITTEE MILAN AREA 2		CTA CEC Validation	
SC submitted	IRCSS CA' GRANDA FOUNDATION MAJOR POLICLINICAL HOSPITAL		CTA Signature	
CTA in signature	IRCSS CA' GRANDA FOUNDATION MAJOR POLICLINICAL HOSPITAL		Change/Submission CTA	

Example of progress report: historical status of an approved study (both by AIFA and by EC)

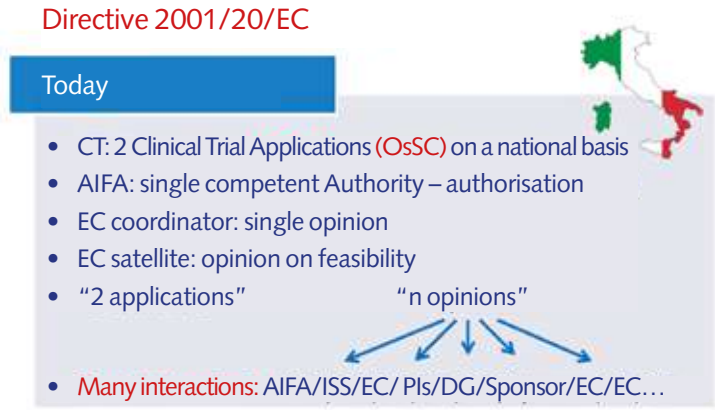
Finally, regarding the **submission of ES in parallel** and the **"previous" ES,** in the current OsSC:

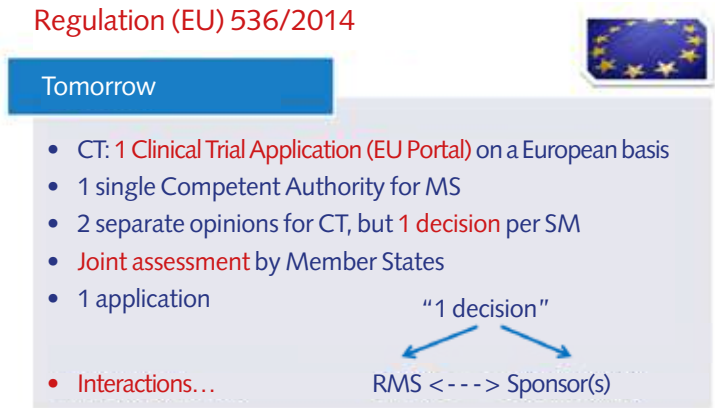
- Different types of ES cannot be submitted in a single application;

- ES can be submitted in parallel when they do not impact on the same documentation;
- "Previous" ES allows to bring back to OsSC a clinical trial that has left the system due to technical problems.

OsSC: potential developments

With the evolution of the regulatory framework from Directive 2001/20/EC to Regulation (EU) no. 536/2014, which provides for the centralized authorization process at European level for clinical trials of medicines, the question arises as to what will be the future national IT systems, i.e. whether it will be based exclusively on **the EU Portal** or if changes/developments of **national IT systems will be planned.**





The Member States are considering the opportunity to have **national IT platforms** to compensate for the functionalities that the **EU Portal** does not guarantee, in particular as regards the CA/EC interaction at national level, while it is essential to develop interoperability between IT systems, this is currently a major challenge. Italy would already have an advantage with the OsSC.

5. The New Regulation (EU) no. 536/2014, the Lorenzin Law no. 3/2018 and the Implementing Decrees: AIFA's point of view

D. Gramaglia, E. De Paola

After a long preparation phase, with the activation of the Clinical Trials Information System – CTIS portal, the Regulation (EU) no. 536/2014 on clinical trials of medicinal products for human use finally became applicable on January 31, 2022.

The transition period of three-years has therefore begun, which will end with the final overhaul of the Clinical Trials Directive no. 2001/20/EC and the national implementing regulations in the Member States (MS) of the EU, which up to now have constituted the reference discipline for clinical trials in Europe.

From January 31, 2022 to January 31, 2023, the sponsors of clinical trials will be able to choose whether to submit an application for authorization to clinical trials (Clinical Trial Application – CTA) pursuant to Directive 2001/20/EC through national procedures or under the Regulation (UE) no. 536/2014 (hereinafter CTR) through the CTIS European Portal.

From 31 January 2023 all new clinical trial applications in the EU and EEA will have to be submitted through the CTIS, under the Clinical Trials Regulation.

From 31 January 2025, the trials approved pursuant to the Directive still in progress will have to be transferred to the CTIS on the basis of the provisions of the Regulation.

With the application of the Regulation, the European Union intended to promote the efficiency of clinical trials, in particular in the case of trials carried out in several Member States, at the same time stimulating innovation and research and limiting duplication of evaluation and repetition of trials without added value.

The European Regulation was created with the aim of creating a favourable environment for the conduct of clinical trials in Europe, by increasing efficiency, through defined timelines, rationalization of resources for the National Competent Authority (hereinafter NCA) and reduction of costs for the sponsors, the harmonization of the rules, the evaluation processes and its supervision, guaranteeing at the same time the highest standards for the safety of the participants and the transparency of information, thanks to the publication of information all concerning the authorization, conduct and results of each trial conducted in Europe.

Italy is ready to accept the new clinical trial applications that will be submitted in the CTIS.

The regulatory framework necessary to apply the new rules will find its find its full implementation at the end of the transition period, during which the current regulatory basis of clinical trials and the Regulation will coexist.

National legislation on clinical trials in Italy:

- Legislative Decree no. 211/2003 (implementing Directive 2001/20/EC)
- Legislative Decree no. 200/2007 (implementing Directive 2005/28/EC)
- Ministerial Decree CTA – Clinical Trial Application 21/12/2007
- Ministerial Decree insurance policies 14/7/2009
- Ministerial Decree CRO 15/11/2011

The implementation of **the Law no. 3/2018**, the so-called Lorenzin Law, and related **Legislative Decree no. 52/2019** began with the Ministerial Decree of 19 April 2018, and subsequent Ministerial Decree 27 May 2021, which established the **National Coordination Centre of Territorial Ethics Committees** for clinical trials on medicines for human use and on medical devices, with coordination, direction and monitoring tasks of the evaluation activities of the ethical aspects entrusted to the Territorial Ethics Committees.

Subsequently, the Ministerial Decree of 30 November 2021, which expressly repealed the Ministerial Decree of 17 December 2004, defined the measures aimed at facilitating and supporting the implementation of **clinical trials of medicines non-commercial** and **observational studies,** and to regulate the transfer of data and results of non-commercial trials for registration purposes.

Finally, the Ministerial Decree of 31 December 2021 established the **measures to adapt the suitability of the facilities where the clinical trial is conducted** to the provisions of Regulation (EU) no. 536/2014.

Lastly, the Ministerial Decree of 1 February 2022 intervened to identify the **three Ethics Committees of national relevance ("CEN")** and the Ministerial Decrees of March 2, 2022 appointed their members:

- National Ethics Committee for Clinical Trials in the Paediatric Field, at the Italian Medicines Agency;
- National Ethics Committee for Clinical Trials relating to Advanced Therapy Medicinal Products (ATMPs), at the Italian Medicines Agency;
- National Ethics Committee for Clinical Trials of Public Research Entities ("EPR") and other national public bodies, at the Italian National Health Institute (ISS).

Evaluation process

Clinical trial sponsors wishing to obtain authorization for a clinical trial in one or more EU Member States and European Economic Area (EEA) countries will no longer have to submit clinical trial applications separately to the national competent authorities, and to the Ethics Committees of each country. A single application form and supporting dossier is required through CTIS.

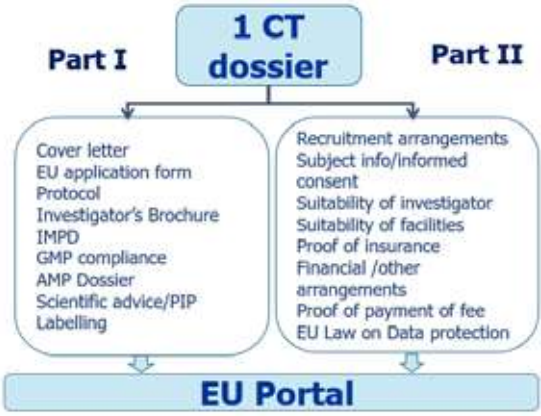


Fig. 1 – Application dossier.

The evaluation process is initiated once the sponsor has submitted one of the following types of CTA: Initial CTA, Substantial Modification (SM) and addition of a Concerned Member State.

The process of evaluating an application includes three main steps: validation, evaluation and decision.

For multinational trials in the first 6 days of the submission of an initial application dossier, in **parallel and independently** of the validation phase, the Reporting Member State (RMS) **selection process takes place,** in line with the art. 5, par. 1, of Regulation (EU) no. 536/2014.

The foreseen **60 calendar day period** to complete the process can be extended **up to a maximum of 46 days** in case – Requests for Information (RFI) – are raised during the validation phase (+15 days) and/or the evaluation phase (+31 days).

In compliance with these deadlines, the **Reporting Member State** and the **Member State Concerned** (MSC) must perform a series of actions called *tasks.* Some tasks are mandatory (*hard task*) and must be performed for the process to go on, while others are not (*soft task – sub task*).

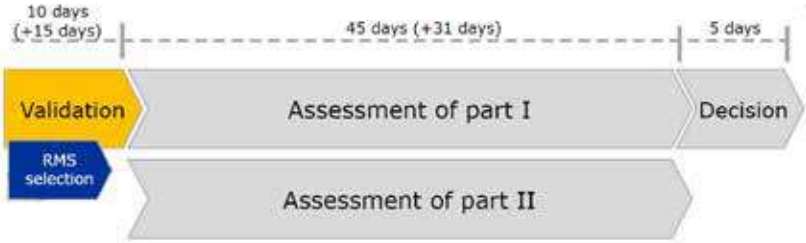


Fig. 2 – Phases and timelines of the evaluation process.

Selection of the Reporting Member State - RMS selection

The main purpose of the Reporting Member State selection process is to identify the Member State that will play a leading role in the evaluation. The RMS guides the evaluation, raises and consolidates the considerations during the validation and evaluation phases of Part I and issues the conclusion on Part I.

There are two main players involved in the RMS selection process in the case of multinational trials:

- Sponsor: proposes a Concerned Member State as an RMS in the application dossier.
- Member State Concerned: expresses willingness/unwillingness to be the RMS.

Although this process runs parallel to the validation phase, an RMS must be selected in order to complete this phase, as the Reporting Member State is responsible for consolidating the considerations (observations on the application dossier) communicated by the Member States Concerned and for submitting the conclusion validation.

In a mono-national trial, the Reporting Member State is assigned to the only Concerned Member State selected by the sponsor in the application.

Validation phase

The validation phase aims to ensure that the clinical trial falls within the scope of the Regulation and that the application dossier is complete in accordance with Annex I (Article 5, Regulation no. 536/2014).

Validation begins when the application dossier is submitted.

In a multinational trial, **validation** represents a joint process of the Member States concerned led by the RMS, which is responsible for sending any requests for additional information, as well as for notifying the outcome.

Evaluation phase

The evaluation phase encompasses two parts: part I and part II. Both parts are similar in terms of workflow and may or may not run simultaneously. The main difference is that Part I consists of a joint assessment of the Member States concerned led by the RMS, which presents the conclusions of Part I, while Part II consists of a separate assessment carried out by each Member State Concerned, which ends with the presentation of an individual conclusion. The evaluation phase can take up to 45 days. In the event that Requests for additional Information are submitted by the Reporting Member State for Part I or by the Member State Concerned for Part II, the deadline of the assessment phase is extended by a maximum period of 31 days. Each evaluation results in the presentation of an individual conclusion.

Part I of the evaluation report mainly includes the evaluation of the following aspects:

a) whether the trial belongs to the category of low-intervention clinical trials, if claimed by the sponsor;

b) compliance with CTR - Title V as regards the assessment of the expected therapeutic and public health benefits (IMP, clinical relevance, data reliability) and risks (IMP, AxMP, comparison with normal clinical practice, safety measures, risks related to the clinical condition) of the trial;

c) risks and inconveniences for the subject;

d) compliance with manufacturing and import requirements for investigational and auxiliary medicinal products (Title IX);

e) compliance with labelling requirements (Title X);

f) completeness and adequacy of the dossier for the investigator.

Part II consists of a **separate assessment carried out by each Member State** Concerned, which in relation to its territory must take into account the following aspects:

a) compliance with the requirements on informed consent;

b) compliance with the remuneration or compensation requirements of the subjects involved and the investigators;

c) compliance of the procedures for recruiting subjects with the requirements established by the regulation;

d) compliance with Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the processing of personal data;

e) compliance with art. 49 of the regulation, concerning the suitability of individuals involved in conducting the clinical trial;

f) compliance with art. 50 of the regulation, concerning the suitability of clinical trial sites;

g) compliance with art. 76 of the regulation, concerning compensation for damages;

h) compliance with applicable rules on the receipt, storage and future use of the biological samples of the subject.

Decision phase

Within 5 days of the submission of the conclusions of Part I and Part II of the evaluation, **each Member State Concerned** shall notify the sponsor if the clinical trial is authorized, authorized subject to conditions or if the authorization is refused in its territory.

In order to submit a decision, a conclusion relating to Part I and Part II must have been previously drawn. The decision phase, therefore, always follows the evaluation phase.

Clinical Trials Information System - CTIS

Harmonization of clinical trial evaluation and supervision processes across the EU is implemented through the Clinical Trials Information System (CTIS), the single entry point for submitting clinical trial information in the EU and in the European Economic Area (EEA).

CTIS supports the daily operational processes of EU Member States and sponsors throughout the life cycle of a clinical trial through collaboration and communication tools between sponsors and Authorities and among Authorities, dealing with workflow, management of documents and reporting. CTIS also supports the transparency of data relating to clinical trials conducted in the EU to the general public through a public website.

The authorization and supervision of clinical trials remain under the responsibility of the Member States, while the European Medicines Agency (EMA) manages the CTIS and the publication of its contents in the public section of the portal.

The European Commission guarantees the correct interpretation and implementation of the regulation on clinical trials, also through the issue of implementing regulations and delegated regulations.

CTIS is structured in **two reserved and protected workspaces,** accessible only to registered users, and **an open website accessible to the public**:

- The **Sponsor Workspace** is accessible to commercial and non-commercial sponsors. It supports the preparation, compilation and submission of clinical trial data for their evaluation by Member States (https://euclinicaltrials.eu/ct-sponsor-services/login).

- The **Authority Workspace** is accessible to NCAs, Ethics Committees, the European Commission and the EMA. It supports the activities of the Member States and the European Commission in the evaluation and supervision of clinical trials (https://euclinicaltrials.eu/ct-authority-services/login).
- The **Public Website** is accessible to patients, healthcare professionals, researchers, clinical research associations, the media and the public. It supports open access to clinical trial data in the European Union, in line with the transparency objective established in Regulation (EU) no. 536/2014 (https://euclinicaltrials.eu/search-for-clinical-trials).

Additionally, all this information can be accessed from the Clinical Trials website: https://euclinicaltrials.eu/home

Categories of data stored in CTIS

CTIS stores different categories of data to support user activities in both work environments. This data includes:

User Self-Filled Data: Data entered into the system when completing or evaluating a clinical trial dossier, as well as documents uploaded as attachments to certain parts of an application or dossier (e.g. cover letter, protocol information, product information such as quality, safety and efficacy, paediatric investigation plan, proof of fee payment, informed consent form, Annual Safety Reports - ASR).

Data retrieved from other databases that interact with CTIS, such as:

- Medicines data extracted from the EudraVigilance Medicines Dictionary: XEVMPD.
- User data (such as first name, last name, e-mail or user ID) extracted from Identity Access Management (IAM). IAM is a central EMA access system that allows access to CTIS and other systems and applications managed by EMA. All users must be registered with IAM before they can access CTIS, i.e. they must have an **EMA account.** Users of other EMA applications (e.g. IRIS, EudraVigilance, EudraCT) who already have an account can use these credentials to log into CTIS.
- Organization data (e.g. name, address) extracted from **Organization Management Services (OMS)**, a central database where information relating to all types of organizations (Sponsors, CROs, investigational sites, Competent Authorities) is collected.

Roles and Permissions in CTIS

CTIS is a role-based system that allows users to perform different actions depending on the *Permissions* associated with *Roles.*

Roles are **a predefined set of actions** that users can perform in CTIS in relation to a clinical trial application or in relation to data and documents submitted during the trial life cycle, in accordance with their responsibilities.

There are multiple roles in CTIS, which allow users to perform different actions in the system, in accordance with their respective responsibilities in relation to a trial. Roles in CTIS have a set of specific "permissions" assigned to them.

Permissions are **predefined levels of actions** that users can perform on data and documents stored in CTIS.

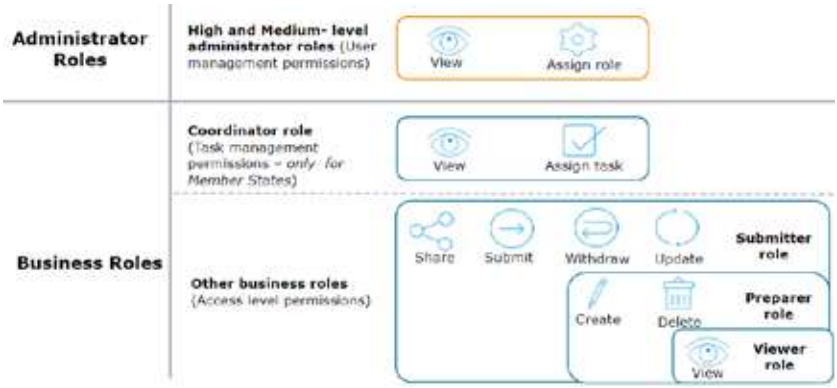


Fig. 3 – Roles and permissions in CTIS.

There are 49 roles capable of allowing users to perform all the necessary activities in the system: 18 roles dedicated to the Sponsor, 31 roles for the competent Authority, of which 25 roles for users of the Member States and 6 roles for users of the European Commission.

A user's profile can be built with a combination of roles within a related workspace that can be revoked at any time.

For the adoption of decisions in the organization of accesses to CTIS in Italy, a pragmatic approach was used aimed at minimizing risks and simplifying activities:

- Minimum number of organizations accessing the system;
- Minimum number of users per organization;
- Limited number of system roles per user;
- Minimum number of activities per process (e.g. limited use of activities and sub-activities).

Fig. 4 – Roles in CTIS.

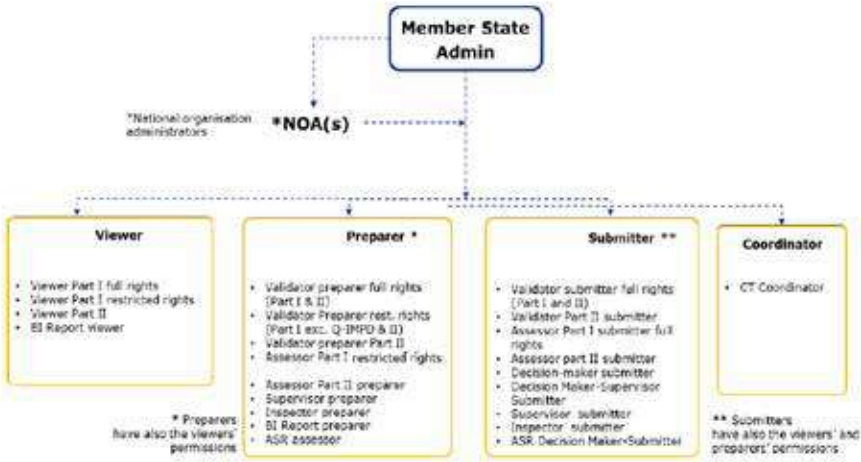


Fig. 5 – Roles for Member State users.

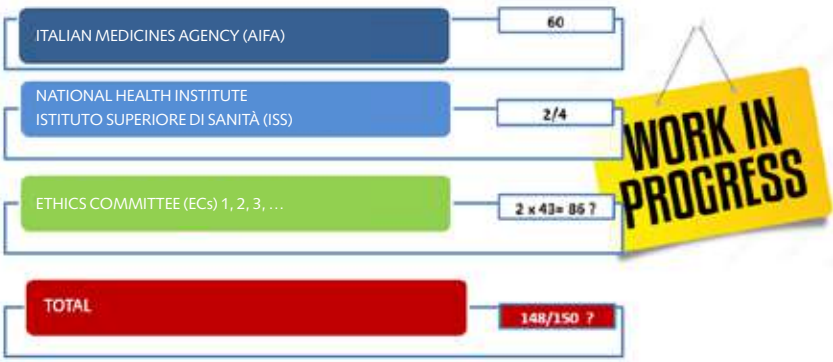


Fig. 6 – Organizations and users accessing the CTIS in Italy.

Role of Ethics Committees

Regulation (EU) no. 536/2014 provides for the mandatory involvement of the Ethics Committees for the evaluation of "Part II" (ethical aspects) of the trial application and the payment of a single fee at national level to cover the evaluation costs of AIFA, the Ethics Committee and the ISS, when applicable.

The review by the Independent Ethics Committee may also include aspects addressed in Part I, in conformity with the legislation of the Member State Concerned, which is responsible for ensuring alignment between the timing and procedures of the review by the Ethics Committee and those of evaluation of the application for authorization.

In each case, for each trial the evaluation is carried out by a single Ethics Committee, which must be independent from the trial centres.

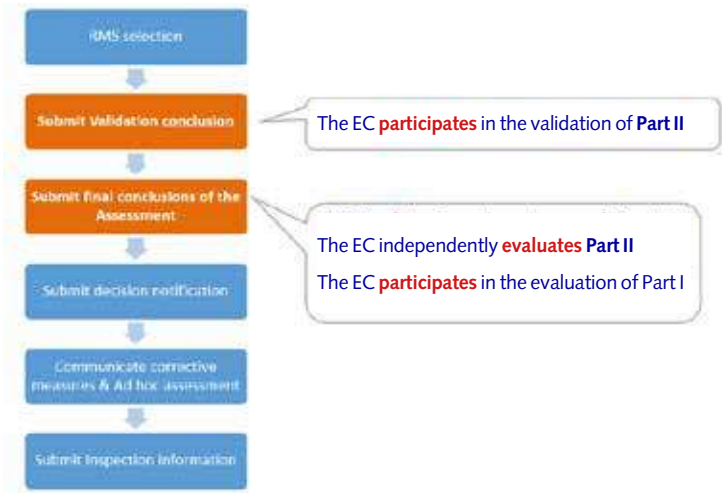


Fig. 7 – The involvement of the EC in Italy.

Pending the entry into force of the Ministerial Decrees for the reorganization of the Ethics Committees, the introduction of the single fee and the decree on the temporary phase, a temporary operating procedure has been put in place and applicable from 31 January 2022.

The Ethics Committee in charge of evaluating the trial, as the single national Ethics Committee, is identified among the ECs of the centres **not** involved in the trial itself. The list of Ethics Committees – identified by the Regions from those currently available to voluntarily evaluate the applications

for trials presented on the European portal – is published on the AIFA portal, in the section "European regulation on clinical trials". If the sponsor does not propose a single Ethics Comittee,, the identification of the Ethics Committee for each clinical trial is carried out by AIFA through the application of an algorithm that allows an adequate rotation with respect to the trial centres and Ethics Committees previously involved.

The current Ethics Committees registered in OsSC, i.e. the National Observatory on Clinical Trials, are already registered in the European portal and, therefore, are also enabled to operate in the system.

Training

EMA offers a modular online training program to help and prepare Sponsors, National Competent Authorities, Ethics Committees, the European Commission and EMA staff to use CTIS.

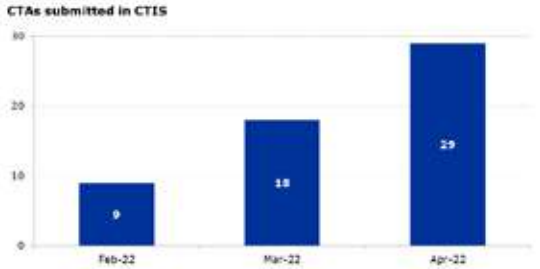
The training program consists of 24 modules, which cover the entire life cycle of the presentation, authorization and supervision of the clinical trial (https://www.ema.europa.eu/en/human-regulatory/research-development/clinical- trials/clinical-trials-information-system-ctis-online-modular-training-program).

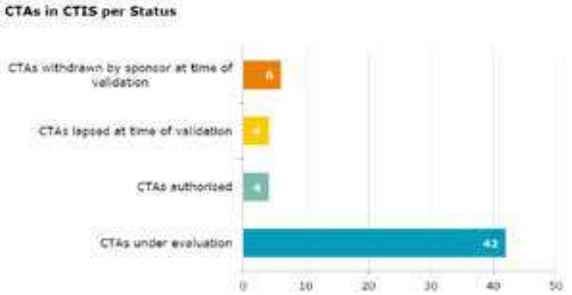
At national level, AIFA has activated specific training sessions for the use of the portal for the representatives of the Ethics Committees in order to allow immediate operation.

First results following the implementation of CTR

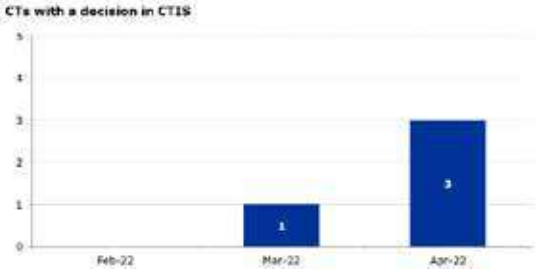
EMA published the first report on the implementation of the Regulation in May 2020. The data presented reflect the status of clinical trial applications in CTIS submitted between January 31, 2022 and April 30, 2022, as of May 2, 2022.

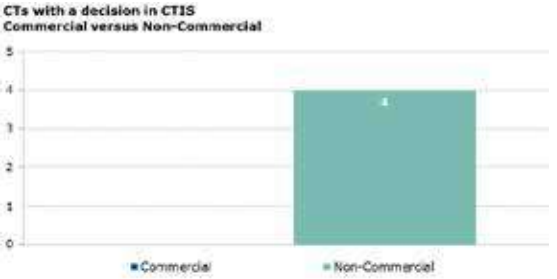
Overall, during the first 3 months from the launch of the system, 56 clinical trial applications were submitted in CTIS, of which 3 are re-submissions, following 2 withdrawn applications and one expired. The applications submitted are all initial clinical trial applications.

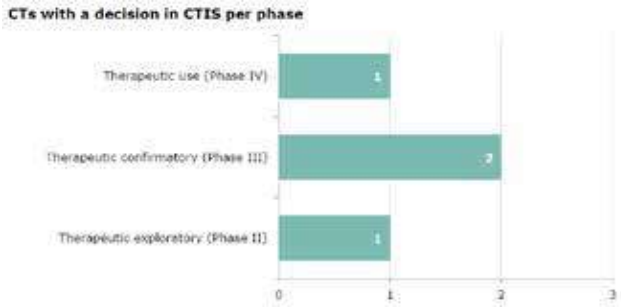




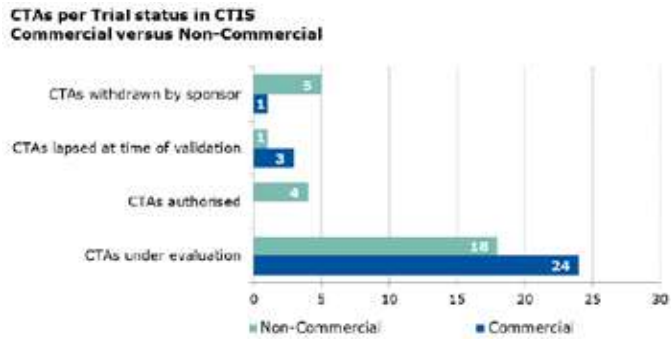
The clinical trials for which a decision has been issued are 4: in all cases the sponsor is non-commercial, 1 is phase IV, 2 are phase III and 1 phase 1.







Below is a graphic in which the 56 initial clinical trial applications in CTIS are broken down by status and by type of sponsor.



In this scenario, Italy ranks fifth among the Member States for the number of clinical trial applications received.

18 May 2022
EMA/246644/2022

Key performance indicators (KPIs) to monitor the European clinical trials environment

Metrics on the Clinical Trials Regulation and Clinical Trials Directive

31 January – 30 April 2022

On the 31 January 2022 the Clinical Trials Regulation (EU) No 536/2014, hereinafter 'CTR', repealing the Clinical Trials Directive 2001/20/EC, hereinafter 'CTD', became applicable and the Clinical Trial Information System (CTIS) was launched. In line with the provisions outlined in Article 97 of the Clinical Trials Regulation, the European Commission shall assess the impact of the Regulation on scientific and technological progress.

This report provides an overview of Key Performance Indicators (KPIs) related to the implementation of the CTR. The Clinical Trials Regulation Metrics report is published on a monthly basis starting in May 2022.

This report is published as part of the business change programme Accelerating Clinical Trials EU (ACT EU), involving the European Commission, the Heads of Medicines Agencies (HMA), Clinical Trial Coordination Group (CTCG) and the Agency.

ACT EU seeks to transform how clinical trials are initiated, designed and run. One of the priority actions of ACT EU focusses on monitoring the implementation of the CTR.

The metrics presented below reflect the status of applications in CTIS and EudraCT[1] as of 2 May 2022 for Clinical Trial applications (CTA) submitted between 31 January 2022 and 30 April 2022[2].

[1] EudraCT is the (European Union Drug Regulating Authorities Clinical Trials Database) European database for all interventional clinical trials on medicinal products authorised in the European Union (EEA) under the Clinical Trial Directive and outside the EU/EEA if they are part of a Paediatric Investigation Plan (PIP)
[2] The two 'smoke test' trials, submitted to CTIS for testing purposes just before the CTIS launch, are not counted.

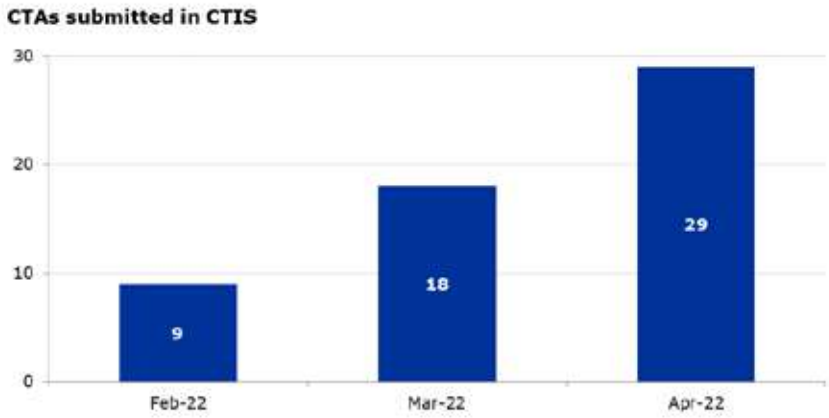
Table of contents

1. Clinical Trial Information System (CTIS) and EudraCT metrics

This report shows the key performance indicators (KPIs) generated from the two databases containing information on clinical trials in the EU/EEA, namely CTIS and EudraCT.

1.1. Number of clinical trial applications (CTAs) submitted under the Clinical Trials Regulation in CTIS

The graph below shows the number of clinical trial applications (equal to the number of the clinical trials during the selected period) that have been submitted to CTIS. The applications submitted are all initial clinical trial applications[3].



Overall, 56 clinical trial applications have been submitted in CTIS during the first 3 months since the launch of the system on 31st January 2022.

Of the submitted applications 3 are re-submissions of previous applications, following 2 withdrawn and 1 lapsed applications.

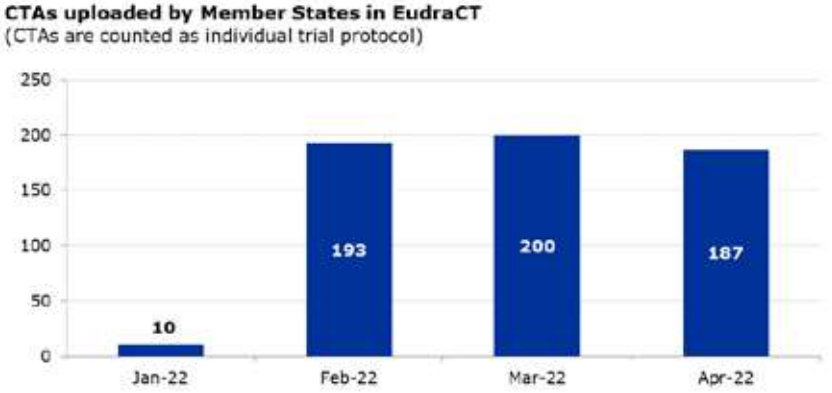
1.2. CTAs under Clinical Trial Directive (CTD) uploaded by Member States (MSs) in EudraCT, counted as individual clinical trial protocol

The graph below shows the number of CTAs uploaded by the Member States in EudraCT as individual clinical trial protocol[4], per month during the selected period[5].

[3] Initial clinical trials applications are those submitted in accordance with the requirements of Article 5 and Article 11, as applicable, of the Clinical Trials Regulation (EU) No 536/2014

[4] The figures presented below are based on distinct counts of CTA, if the same protocol is submitted to more than one MSC is counted once.

[5] The data for January that appear in the graph below refers to CTA uploaded by the Member State on the 31st January only



1.3. Number of ongoing clinical trials (CTs)

CTs under the CTR with at least one positive decision in the EU

The term 'ongoing' refers to clinical trials that have been authorised in at least one Member State Concerned where the recruitment of patients has started at the clinical investigator sites[6].

There were no reported clinical trials ongoing in CTIS as of 2nd May 2022.

CTs under the CTD

In EudraCT there are no fields available to capture recruitment status at the site.

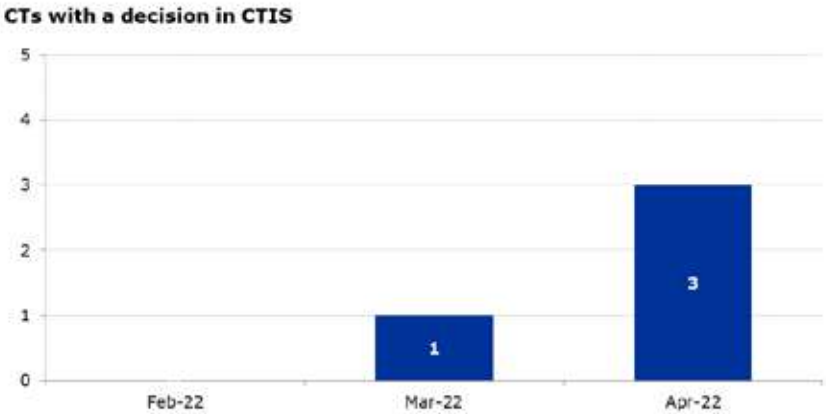
1.4. Number of trials for which a decision has been issued under the CTR with/without deferral7 for the protocol

There were no trials for which a decision has been issued with deferrals[8] of the protocols. All the trials with a decision have published protocols.

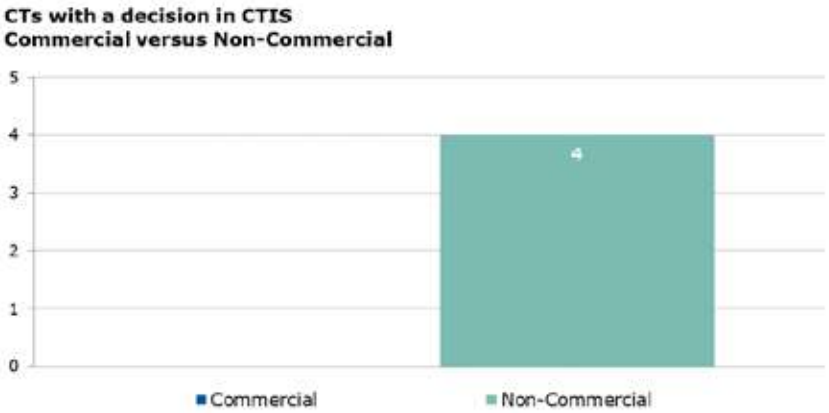
1.5. Number of mononational-multinational trials for which a decision has been issued by the Member States Concerned (MSC) under the Clinical Trials Regulation, broken down per sponsor type (commercial vs. non-commercial) and average number of MSCs[9]

The graph below shows the number of trials for which a decision has been issued in CTIS by the Member State Concerned, per month, since 31 January 2022. The trials reflected in the graph below have all been authorised.

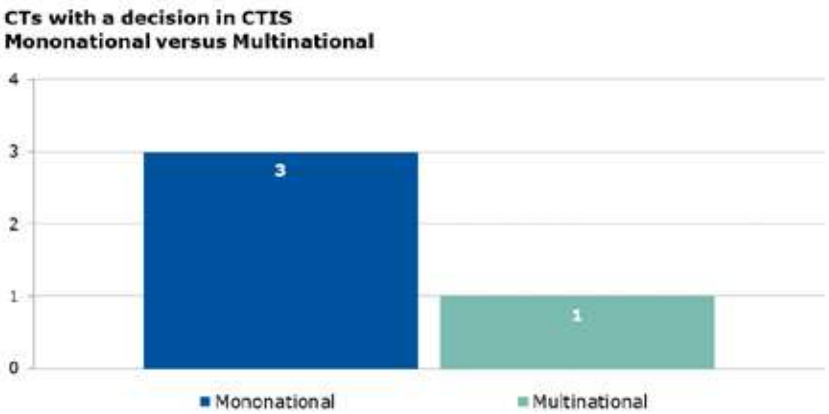
[6] Details on recruitment status are based on the information reported by the trial sponsor in CTIS
[7] The option to defer the protocol is only available in CTIS.
[8] Deferral is a functionality implemented in CTIS that has been introduced to reduce the burden of redaction of commercially confidential information (CCI) in the documents uploaded in CTIS. More information on deferrals can be found in the Appendix on disclosure rules
[9] The information on trial sponsor type: commercial *vs* non-commercial is derived from OMS: Organisation Management Service database, and it is not recorded as such in the clinical trial application form



The graph below shows the number of trials for which a decision has been issued in CTIS by the Member States Concerned, broken down by sponsor type.

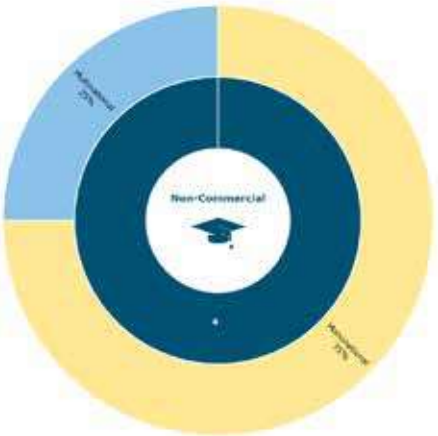


The graph below shows the number of trials for which a decision has been issued in CTIS by the Member States Concerned, broken down whether the trial is a mono- or multinational.



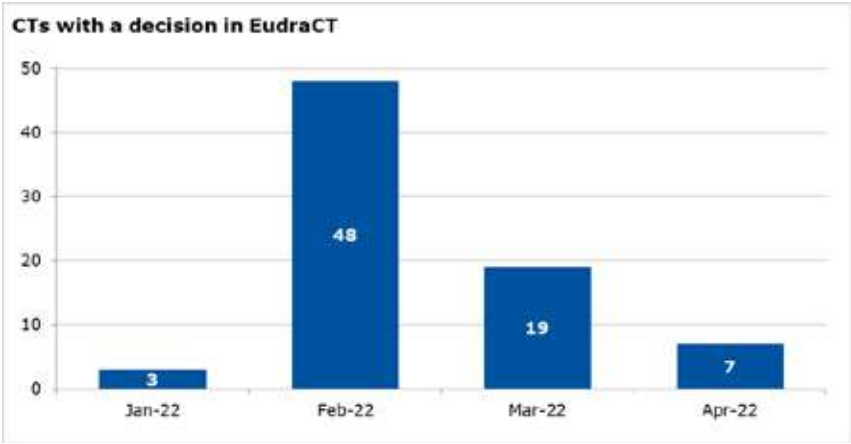
Currently one multinational clinical trial has a decision (authorised) in CTIS with 14 Member States Concerned. An average will be provided in future reports when more than one multinational trial has a decision recorded.

The graph below shows the number of clinical trials for which a decision has been issued, with information whether the trial is a mono- or multinational and in relation to sponsor type.

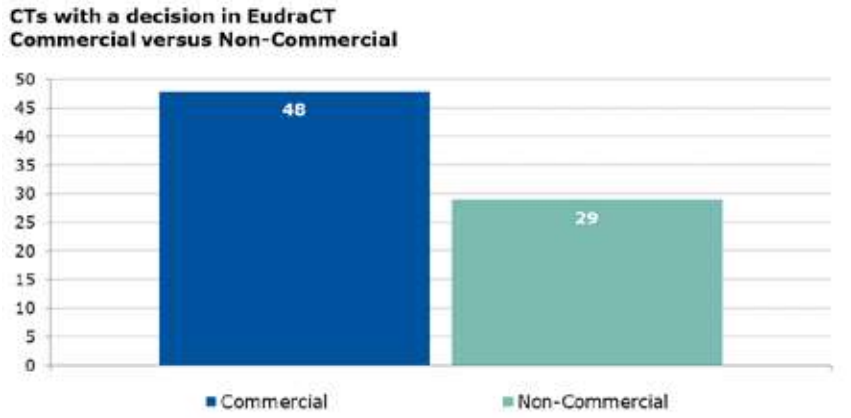


1.6. Number of mononational-multinational trials for which a decision has been issued by the Member States under the Clinical Trials Directive, broken down per sponsor type (commercial vs. non-commercial) and average number of MSs

The graph below shows the number of trials that received a National Competent Authority decision and an Ethics Committee opinion from the Member States, per month, since 31 January 2022. The trials reflected in the graph below have all been authorised[10].

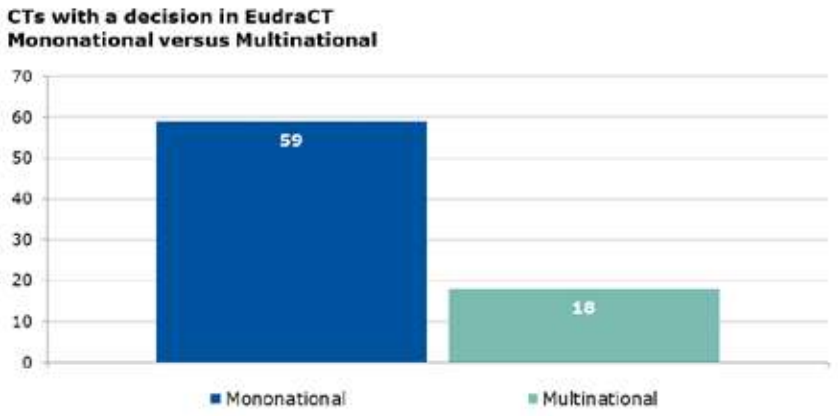


The graph below shows the number of trials for which a decision has been issued by the Member States in EudraCT broken down by sponsor type.



[10] The data for January that appear in the graph below refers to CTA authorised by the Member State on the 31st January only.

The graph below shows the number of trials for which a decision has been issued by the Member States in EudraCT broken down whether the trial is a mononational or multinational trials.

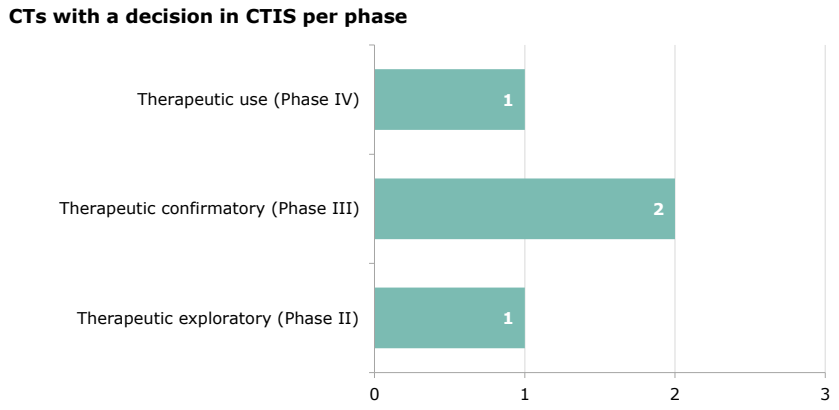


Considering clinical trials for which a decision has been issued, on average 2 Member States are involved in multinational trials.

The graph below shows the number of clinical trials for which a decision has been issued, with information whether the trial is a mono- or multinational and in relation to sponsor type.

1.7. Number of clinical trials for which a decision has been issued per phase (i.e. I, II, III, IV, as well as CT first in human or combined phases early (I and II)) under CTR[11]

The graph below shows the number of clinical trials for which a decision has been issued, broken down per trial phase.

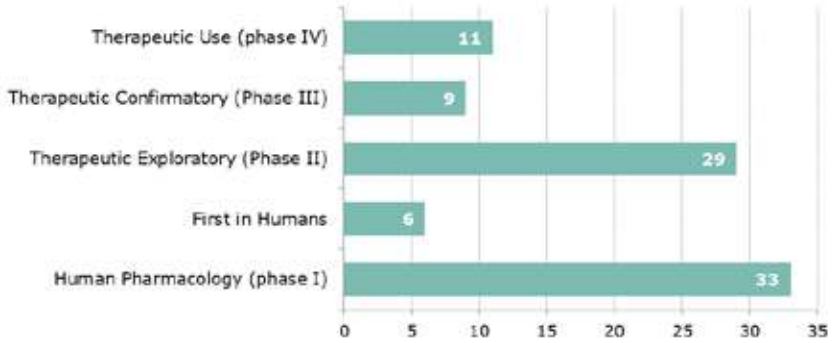


Number of clinical trials for which a decision has been issued per phase (i.e. I, II, III, IV, as well as CT first in human or combined phases early (I and II)) under CTD[12]

The graph below shows the number of clinical trials, as individual clinical trial protocol, for which a decision has been issued by the Member States in EudraCT broken down per trial phase.

[11] More than one trial phase can be selected for a single trial and it is counted in each trial. The graph shows only the applicable trial phases for the authorised trials in the selected period.
[12] More than one trial phase can be selected for a single trial and it is counted in each trial. The graph shows only the applicable trial phases for the authorised trials in the selected period.

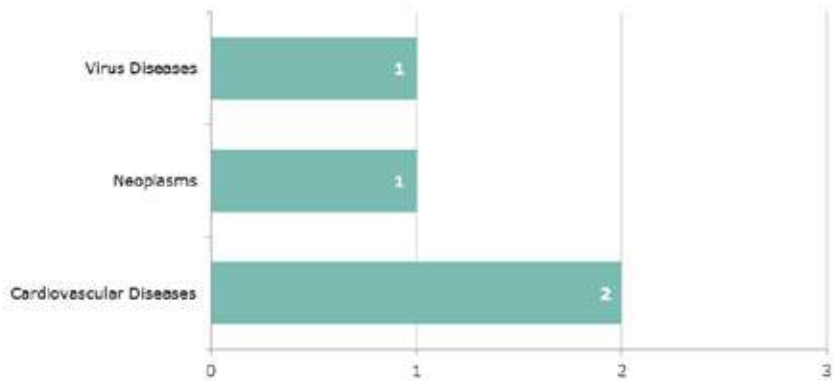
CTs with a decision in EudraCT per phase



1.8. Number of trials for which a decision has been issued under CTR, per therapeutic area[13]

The graph below shows the number of clinical trials for which a decision has been issued in CTIS, broken down per therapeutic area.

CTs with a decision in CTIS per therapeutic area

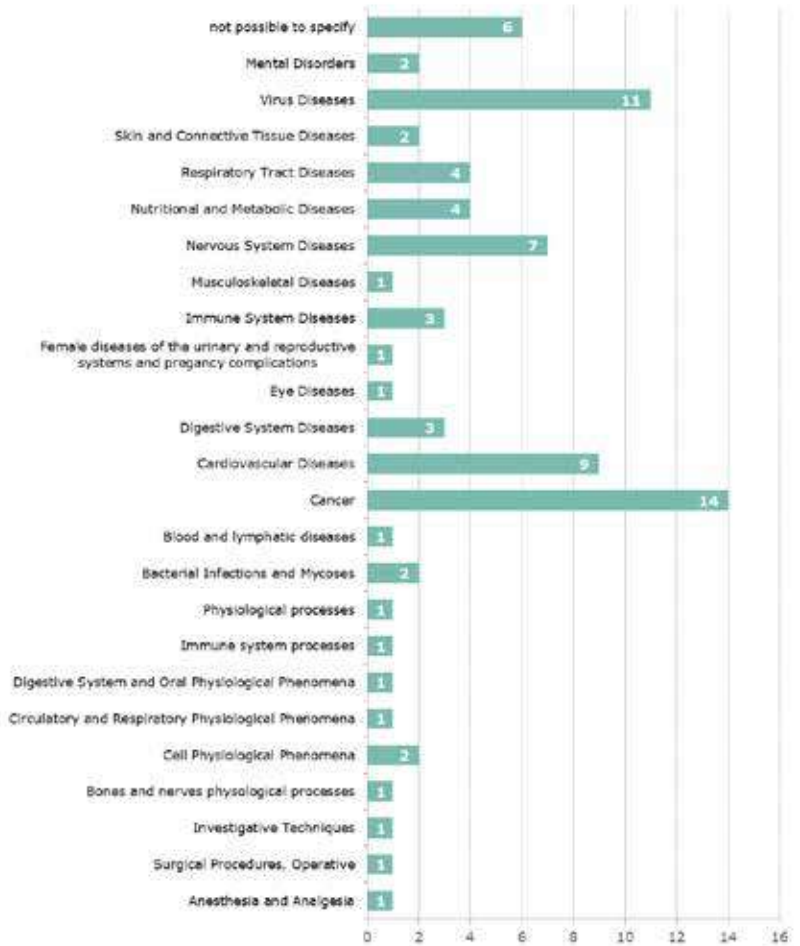


[13] More than one therapeutic area can be selected for a single trial and it is counted in each trial. The graph shows only the applicable therapeutic areas for the authorised trials in the selected period.

1.9. Number of trials for which a decision has been issued under CTD, per therapeutic area[14]

The graph below shows the number of trials, as individual clinical trial protocol, for which a decision has been issued by the Member States in EudraCT broken down per therapeutic area.

CTs with a decision in EudraCT per therapeutic area



1.10. Number of trials for which a decision has been issued on Advanced Therapy Medicinal Products (ATMP) under CTR

None of the clinical trials for which a decision has been issued in CTIS during the selected period includes an Advance Therapy Medicinal Product.

1.11. Number of trials for which a decision has been issued, with ATMP of type "gene therapy", "somatic cell therapy" and "tissue engineered therapy" under CTR

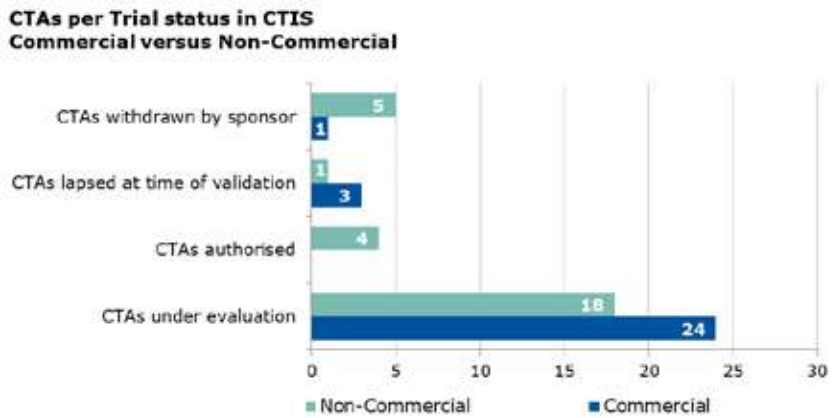
None of the clinical trials for which a decision has been issued in CTIS during the selected period includes an Advance Therapy Medicinal Product of type: gene therapy, somatic cell therapy and tissue engineered therapy.

1.12. Number of trials for which a decision has been issued, with ATMP of type "gene therapy", "somatic cell therapy" and "tissue engineered therapy" under CTD.

There were two clinical trials with a decision (authorised) during the selected period including an advanced therapy medicinal product, both of them on a gene therapy product.

1.13. Number of clinical trial applications under the CTR per applicable trial status during the selected period, broken down per sponsor type: non- commercial/commercial

The graph below shows the number of initial clinical trial applications, per applicable trial status and information of sponsor type.



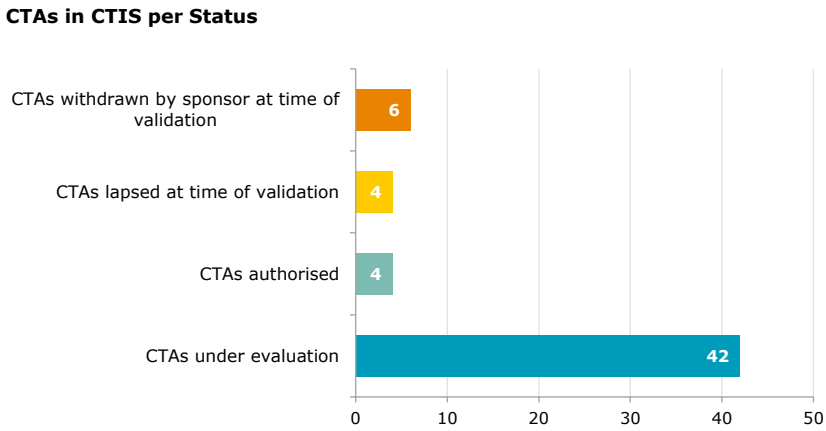
Art 14 applications: (re-)submission, authorisation, rejection, lapsed and withdrawn dossiers

[14] It should be noted that more than one therapeutic area can be selected for a single trial and it is counted in each trial. The graph shows only the applicable therapeutic areas for the authorised trials in the selected period.

There are no applications in CTIS for the addition of a new MSC foreseen under Article 14 of Regulation (EU) No 536/2014.

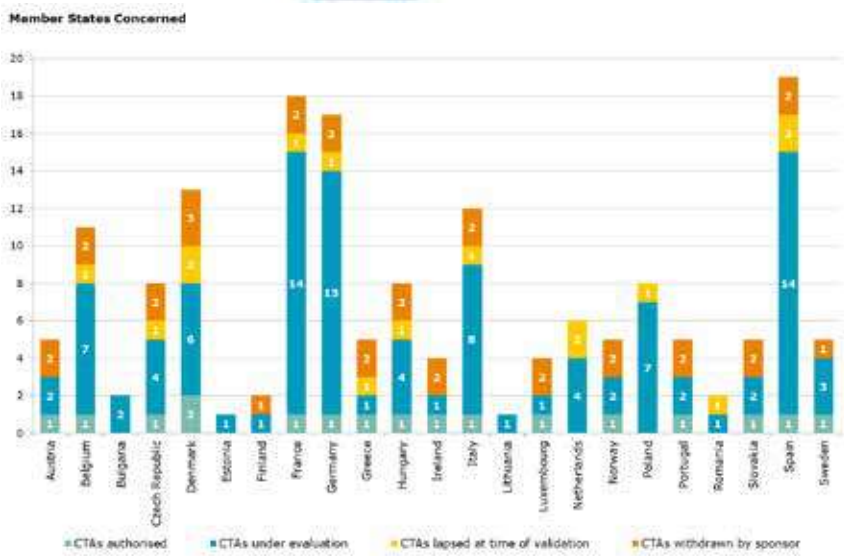
1.14. Number of CTAs Article 5 of CTR [full dossier initial applications] per applicable trial status during the reporting period, at EU, at MS level and with Reporting Member State (RMS) details

The graph below shows the number of initial clinical trial applications with full dossier, submitted in accordance with Article 5 of CTR, per applicable status at EU level.

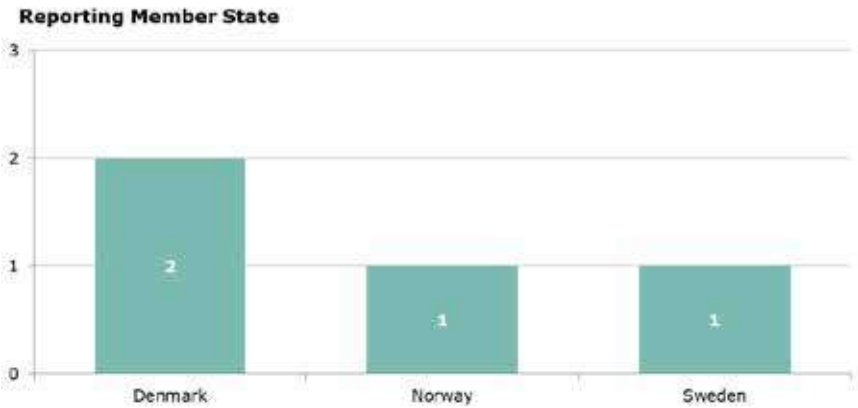


The graph below shows the number of initial clinical trial applications with full dossier, submitted in accordance with Article 5 of CTR, per applicable status at the level of the Member States Concerned[15].

[15] In multinational clinical trials the same application has been submitted to multiple Member State Concerned, and it is counted in the graph in each applicable MSC.



The graph below shows the distribution of appointment of Reporting Member State (RMS)[16], amongst the applicable Member States Concerned, for clinical trial applications on which a decision has been issued.



[16] RMS is the Reporting Member State appointed in line with the requirements of Article 5 of the Clinical Trials Regulation (EU) No 536/2014

1.15. Number of CTAs Article 11 of CTR [partial dossier initial applications with later Part II submission] per applicable trial status during the reporting period, at EU and at MS level

Partial initial applications submitted to CTIS in line with the requirements of Article 11 of the Regulation (EU) No 536/2014 will be considered for future reporting.

1.16. Average time from submission to reporting date[17] (Article 11 and Article 5 of CTR), and to first decision (Article 5 of CTR) for initial applications and Substantial Modifications part I or part I and II

The table below shows the number of calendar days since the submission of the initial clinical trial application to CTIS up to the time of the first decision of the Member States Concerned.

Submission date	Decision date	Days to Decision
9 February 2022	7 April 2022	57
15 February 2022	27 April 2022	71
28 February 2022	28 March 2022	28
15 March 2022	27 April 2022	43

On average it took 50 calendar days from submission to decision for the 4 authorised initial CTAs.

1.17. Number of submitted, validated, authorised, rejected, lapsed and withdrawn Substantial Modification (SM) applications, related to part I / II / I and II, by sponsor type

There are no applications in CTIS related to submission of substantial modification part I only, part II only or part I and part II as foreseen in Chapter II of the Regulation (EU) No 536/2014.

1.18. Number of active substances (ASs) in CTR EU trials (mononational and multinational AS)

KPI on the number of active substances (also linked with KPI 16 on saMS selection) will be considered for future reporting.

1.19. Number of safety assessing Member State (saMS)-ships per MS

The safety assessing Member State Concerned (saMS) will be The safety assessing Member State Concerned (saMS) will be applicable for the multinational clinical trials. No saMS have been appointed during the selected period.

[17] The reporting date is equal to the date of the RMS conclusion on part I assessment

6. The Clinical Trial and the Vigilance Device according to the directives of Regulation (EU) no. 745/2017

6.1 The point of view of the Ministry of Health

a) Office 3 Regulatory

E. Cecere, A. Basilisco

The medical devices sector plays a major role in health care in Europe, contributing to the improvement of the level of health protection through the development of innovative solutions for diagnosis, prevention, treatment and rehabilitation.

Regulation (EU) 2017/745 (from now on in the "regulation" text) amended the rules governing the medical device system, taking into account the developments in the sector over the last twenty years, with the aim of ensuring a robust, sustainable regulatory framework, with transparent procedures and maintaining a high level of safety, while encouraging innovation.

The regulation was published in the *Official Journal of the European Union* on 5 May 2017 and entered into force 20 days after its publication. The date of full application, initially scheduled for 26 May 2020, was postponed to 26 May 2021. In fact, on 23 April 2020, the Council and the Parliament adopted Regulation (EU) 2020/561 which postponed by one year the date of full application of the regulation, in order to relieve pressure on national authorities, notified entities, manufacturers and all other parties involved, so that they could focus on the contrast action and containment of the Covid-19 health emergency caused.

The need to change sector legislation arose from the need to ensure, also through ever greater harmonization, the smooth functioning of the internal market within the European Union, while raising product quality and safety standards in the context of a state of the art, innovation-friendly framework, which places the EU as the guarantor of public health and patient health and safety in the field of medical devices. The regulation represents a significant step forward compared to the past and a strengthening of the existing regulatory system for medical devices in Europe; through a gradual process, which requires national transitional solutions, not incompatible with

European provisions, the Directives 93/42/EEC and 90/385/EC in force for over 20 years will be progressively replaced.

The regulation, directly applicable without the need for transposition through specific national legislation, will allow greater legal certainty and will limit the heterogeneity of content in the adoption of medical devices regulations by the individual European Union Member States.

The regulation contains articulated rules and provides for a subsequent implementation activity through enforcing activities and interpretative guidelines shared with all EU countries.

The subjects most involved are the European Commission and the Medical Device Coordination Group (MDCG) which are called to develop guidelines aimed at guaranteeing an effective and uniform implementation of the regulation, whilst the authorities of the Member States will have to ensure its implementation on the EU territory.

For this reason, the European Commission and the Member States have organized themselves according to a program of activities in progress, which will involve the gradual adaptation to the new legislative framework. The *Implementation Rolling Plan Regulation (EU) 2017/745 and Regulation (EU) 2017/746,* updated on a quarterly basis, reports the list of implementing acts that the Commission has adopted or intends to adopt and the initiatives to be undertaken (the rolling plan updated in April 2022 is available at the following link https://ec.europa.eu/health/system/files/2022-04/md_rolling-plan_en.pdf).

This is a demanding path, in which the commitment of all the players in the medical device system will be required, but it is also a challenge to be faced in the awareness that medical devices is a sector that, thanks to technological innovation, will play an increasingly important role in the process of continuous improvement which is one of the main characteristics of the entire National Health Service.

The regulation, as already mentioned and fully applicable from May 26, 2021, has however allowed in some particular cases, to keep CE marked devices on the market pursuant to the previous directives.

It is in fact possible until 26 May 2024 to place on the market or put into service class I devices as per Directive 93/42/EEC, for which a declaration of conformity was drawn up before 26 May 2021 and for which the procedure conformity assessment in accordance to Regulation (EU) 2017/745 requires the involvement of a notified entity and the devices with a valid certificate issued as per Directive 90/385/EEC or Directive 93/42/EEC. Nonetheless in both cases, two conditions must be met, namely that the devices in question continue to comply with the relevant directive and that no significant

changes have been introduced in the design and intended use. These devices are identified with the term "legacy devices".

For the legacy devices, the requirements of the regulation on post-marketing surveillance, market surveillance, surveillance, registration of economic operators and devices and certification notifications will apply immediately from 26 May 2021, which replace the corresponding provisions of the Directives.

These devices may be made available on the market and put into service until 26 May 2025 (sell off). This means that where a manufacturer has placed a device on the market by May 26, 2021, it is granted to distributors in the supply chain to make it available during a further subsequent year. In October 2021 the MDCG approved the document MDCG 2021-25 *Regulation (EU) 2017/745 – application of MDR requirements to 'legacy devices' and to devices placed on the market prior to 26 May 2021 in accordance with Directives 90/385/EEC or 93/42/EEC* which provides indications for the identification of the regulations applicable to CE marked devices in accordance with the directives.

As mentioned, the regulation has introduced many new features and additional charges, both for economic operators and for the regulatory authorities. Economic operators will have to respond to increased requests aimed at ensuring a high level of protection of public health and patient safety.

As far as the manufacturer is concerned, art. 10 of the regulation has strengthened the role and its tasks, specifically identifying all the obligations and introducing the burden of an insurance to ensure financial coverage of any damage that may arise to the patient or user from the use of the device. Similarly, the role and tasks of the authorised representative, in accordance with the written mandate given by the manufacturer, becomes jointly and severally liable with the manufacturer, in the event of any defective products, have been better defined.

For the distributor and the importer, previously excluded from the sector regulations, a specific discipline has been defined that also binds these subjects to play a role in the compliance of the medical device, with a series of checks and verifications to be foreseen prior to making it available.

For distributors and importers who are configured as parallel traders, art. 16 was responsible for establishing the rules for the provision of re-packaged or re-labelled products. It is in fact foreseen that the subjects who intend to carry out this type of trade (parallel trade) must first contact a notified body that issues a certification relating to the quality system for the activities that these subjects carry out.

All economic operators (see art. 25 of the Regulation) were then required to guarantee the traceability of medical devices, ensuring information on the subjects to whom they have supplied and from whom they have received a device as well as information on health institutions and healthcare professionals to whom they have directly supplied a device.

Identification and traceability will be allowed through the use of two tools: the medical device nomenclature and the Unique Device Identification (UDI) system.

The nomenclature aims to facilitate the functioning of the EUDAMED database and art. 26 of the regulation foresees that it must be internationally recognized and available free of charge.

The Medical Device Coordination Group (MDCG) in the meeting of 14 February 2019 decided to identify the Italian classification, the National Classification of Medical Devices (CND), due to its peculiarities of structure, purpose, usability and updating methodology as a basis for the realization of the EMDN nomenclature.

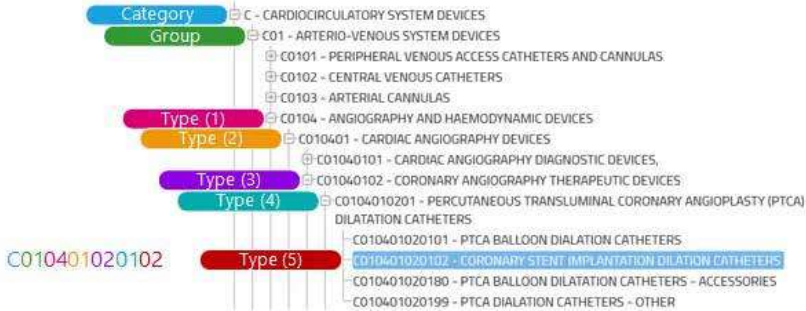
The adoption of the National Classification of Medical Devices as a nomenclature at EU level represents one of the concrete results obtained, with a view to exporting a model that favours the spread of a structured system aimed at guaranteeing the availability and access of medical devices throughout Europe.

UDI, on the other hand, is a unique numeric or alphanumeric code associated with a medical device, which allows specific devices placed on the market to be clearly and unambiguously identified and facilitates their traceability.

The obligation to keep the UDI of the devices is imposed not only on economic operators but also on health institutions that from 26 May 2021 are obliged to register and maintain, preferably by IT, the UDI of the devices they have supplied and received if these devices belong to class III implantable devices (high risk devices).

For other types of medical devices, the regulation leaves the power to Member States to impose the same obligations and recommends the adoption of measures that encourage healthcare institutions to implement traceability systems for all medical devices.

EMDN and UDI nomenclature will also be required data for registration in EUDAMED, the European database of medical devices developed by the European Commission to implement Regulation (EU) 2017/745 on medical devices (MDR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR).



At the time of publication of this text, EUDAMED is unfortunately not yet fully functional. For this reason, in May 2021 with the document MDCG 2021-1 Rev. 1 *Guidance on harmonized administrative practices and alternative technical solutions until EUDAMED is fully functional,* the MDCG provided indications on the administrative practices to be followed in the absence of EUDAMED. In general, the guide indicates to continue to comply with the registration procedures in place in the various Member States; therefore, in the Italian case, the registration obligations provided for by the regulation are deemed to be fulfilled with registration in the national database.

In fact, from 1 December 2021 the national medical devices database, established pursuant to art. 13 of Legislative Decree no. 46/97, has been adapted from a structural point of view to allow manufacturers and their agents to fulfil the registration obligations of CE marked medical devices pursuant to the regulation, until the European database EUDAMED won't be fully operational.

The medical devices sector was based (with directives) and continues to be based (with regulations) on the so-called mechanism of the new approach,

which has changed over the years into a "*new new approach*" and now become "*new legal framework*". These systems are all based on the manufacturer's responsibility for CE marked products placed on the market. However, for devices associated with a higher level of risk, the system provides for the involvement of notified bodies, third parties designated to issue the CE certifications necessary for the manufacturer to place on the market devices other than those of Class I (low risk).

Italy and the whole system of the European Union have put in place considerable efforts to ensure an adequate presence of these entities on the territory of the EU. At the time of drafting this text, seven notified bodies were designated in Italy, authorized to certify the different types of devices, according to the different certification procedures provided for in the regulation (see art. 52).

The designation of the Notified Bodies can be verified in the Nando (New Approach Notified and Designated Organizations) Information System, a database in which it is possible to identify all the notified bodies for the regulation of the specific types of medical devices, identified by the codes listed in the Commission Implementing Regulation (EU) 2017/2185.

The need for a consistent presence of Notified Organisms is also dictated by the multiple situations of up-classification that the regulation has determined, that is to say that for many devices the regulation, with respect to Directive 93/42/EEC, has provided, according to the rules of Annex VIII, higher risk classes.

Some examples. By virtue of rule 3 of the Regulation, all non-invasive devices consisting of a substance or a mixture of substances, intended for use in vitro in direct contact with human cells, tissues or organs removed from the human body or used in vitro with human embryos prior to their implantation or administration they are now classified in class III. These devices were previously classified in class IIa or IIb, depending on the type of contact, by virtue of rule 3 of Directive 93/42/EEC. In fact, there was no *ad hoc* rule for this type of device, rule 3 was non-specific or, worse still, poorly suited to the devices.

Rule 8 regarding implantable devices indicated the highest risk class, class III, for surgical meshes (previously in class IIb); for all joint prostheses, total or partial (Directive 2005/50/EC had reclassified only hip, shoulder and knee prostheses to class III); for disc prostheses or implantable devices, which come into contact with the spine (previously only devices that came into contact with the brain, meninges and spinal cord were classified in class III).

The legislator taking into account the considerable development of Electronic health has had in recent years, in particular e-health, also thanks

to the impetus given to the European digital agenda, introduced for the classification of software the specific rule 11 that classifies the software in a variable class from I to III. In particular, also class III are all those software intended to provide useful information for making decisions for diagnostic or therapeutic purposes, when such decisions have such effects as to cause the death or irreversible deterioration of a person's health conditions. The same type of software could instead be classified in class IIa if one does not operate in a situation of such criticality in relation to the patient's health conditions.

In a third case they would be classified in IIb, when decisions can lead to a serious deterioration of a person's health condition or lead to the need for surgery, but not to an irreversible outcome.

The same method is used for the classification of software intended to be used for monitoring vital physiological parameters: if the nature of the changes in the parameters is such as to create an immediate danger for the patient, it is a class IIb device; unlike a class IIa device. All other software is class I.

In the case of software, up to now classified mainly in class I, the application of the new rules will, in most cases, involve the passage to higher risk classes, effectively leading to the involvement of a notified body in the assessment activities compliance.

Rule 19, on the other hand, concerns devices that contain or consist of nanomaterials. The level of risk for these devices is associated with the potential for internal exposure. The legislator has recognized the situation of scientific uncertainty regarding the risks and benefits of the nanomaterials used for the devices and in order to guarantee a high level of health protection has established for these devices, risk classes for which there are strict conformity assessment procedures. In fact, devices containing nanomaterials are classified according to the level of internal exposure in class III (medium or high level), IIb (low level) or IIa (negligible level). Previously, the classification rules did not take into account the presence of nanomaterials for the definition of the risk class, also in consideration of the fact that the development of the associated technologies was subsequent to the issuance of the 1993 Directive.

Rule 21 is undoubtedly the one that most of all will have a strong impact on the industry that has been active in the sector for years. It concerns devices consisting of substances or combinations of substances intended to be introduced into the human body through an orifice of the body or to be applied to the skin and which are absorbed by the human body or locally dispersed in it. They can come in pharmaceutical-like forms such as capsules, creams, sprays, powders, syrups, tablets and micro-enemas.

All these products can no longer be class I, but must always fall into one of the higher classes, in particular class III if they, or their metabolic products are systemically absorbed by the human body in order to achieve their intended use in the stomach or lower gastrointestinal tract and they, or their metabolic products, are absorbed systemically by the human body. But even if applied on the skin or in the nasal or oral cavity up to the pharynx to achieve their intended use on the said cavities, they will be classified in class IIa.

The possibility that substance-based devices can be classified in class I is therefore definitively excluded. Therefore, the involvement of a notified body will always be envisaged for this type of products.

Finally, even if we cannot speak in the literal sense of up-classification, a novelty introduced by the regulation concerns reusable surgical instruments. These devices so far classified in class I according to Directive 93/42/EEC, will now be identified as a particular type of class I devices, so-called, albeit improperly, class "Ir" (in analogy to what already happens for Class I devices in a sterile state, identified as class "Is" devices). Although, this is not a higher risk class than in the past, it will now be necessary for these devices to be evaluated by a notified body.

Reusable surgical instruments, marketed in a non-sterile state and intended by the manufacturer to be reused, must therefore be subject to evaluation by a notified body as regards the aspects relating to the reuse of the device, in particular cleaning, disinfection, sterilization, maintenance, functional test and related instructions for use. This outlook stems from a research project funded by the European Health Program 2014-2020 in which some competent Authorities, including Italy, participated. The study had in fact highlighted how the quality of the information provided in the printed matter was not fully compliant with the essential requirements reported at the time in Directive 93/42/EEC.

To guide manufacturers and all operators in the sector, the MDCG in October 2021 published the document MDCG 2021-24 *Guidance on Classification of Medical Devices*, which provides a methodology for the classification of medical devices as well as a series of examples for each classification rule provided for in Annex VIII of the regulation. The documents approved by the MDCG group, although not binding from a legal perspective, represent the point of view of the legislator and therefore must be taken into utmost consideration.

The revolution around the medical device sector does not end with the innovations introduced by the regulation. In fact, the Law of 22 April 2021, no. 53, in force from 8 May 2021, laid the foundations for the adaptation of Italian legislation, with the aim of complying with the provisions of the

regulations, while maintaining some national provisions already consolidated and not in contrast with the new European measures.

Pending the adjustment of the national standard, the Directorate General for medical devices and pharmaceutical service has disclosed the circular of 12 November 2021 in which some aspects necessary for the implementation of Regulation (EU) 2017/745 are clarified, in order to guarantee uniform and consistent application until the full functioning of EUDAMED and during the period of validity of the CE markings in accordance with the directives.

b) Office 4 IVD

A. Colliardo, G. Ippoliti, D. Croce

Directive 98/79/EC has always been the reference standard in the field of *in vitro* diagnostic medical devices (IVD), implemented in Italian law with Legislative Decree 8 September 2000, no. 332, which introduced common standard requirements at European level, to standardize the degree of safety, quality and performance of IVDs.

The regulatory framework in the field of in vitro diagnostic medical devices is undergoing a profound revision with the Regulation (EU) 2017/746 (IVDR) of the European Parliament and of the Council, which repeals Directive 98/79/EC and decision 2010/227/EU of the Commission.

It is specified that for "*in vitro diagnostic medical device*", as reported in art. 2 of Regulation (EU) 2017/746 means: "*any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:*
(a) concerning a physiological or pathological process or state;
(b) concerning congenital physical or mental impairments;
(c) concerning the predisposition to a medical condition or a disease;
(d) to determine the safety and compatibility with potential recipients;
(e) to predict treatment response or reactions;
(f) to define or monitoring therapeutic measures.
Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices".

Products intended for general laboratory use or research-use only products, unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for *in vitro* diagnostic examination. In general, in vitro diagnostic medical devices are products intended to be used for the examination of samples originating from the human body, in order to provide analytical indications of chemical-clinical interest. They are generally used in health facilities (laboratories) by professional operators (with the exception of tests for self-diagnostic use, intended for lay users) with adequate training and experience regarding the performance of diagnostic tests and the use of the instruments.

The Regulation represents a significant development and strengthening

of the existing regulatory system. This Regulation, although it entered into force on May 25, 2017, became applicable, with some exceptions, from May 26, 2022.

The IVDR limits the heterogeneity in the adoption of the rules relating to *in vitro* diagnostic medical devices by the individual Member States of the European Union (EU) and provides for a progressive implementation activity through implementing acts and shared interpretative guidelines with the EU. Numerous working groups, of which the Ministry of Health is part with its own representatives, and task forces, have been set up at European level to work jointly on the correct implementation, as well as on the revision of all guidelines and documents in the light of the new Regulation.

For this reason, the European Commission and the Member States have organized themselves according to a program of activities in progress, which will involve the gradual adaptation to the new legislative framework.

The *Implentation Rolling Plan Regulation (EU) 2017/745 and Regulation (EU) 2017/746,* updated on a quarterly basis, reports the list of implementing acts that the Commission has adopted or intends to adopt and the initiatives to be undertaken. The document *Joint implementation and preparedness plan for Regulation (EU) 2017/746 is available specifically for IVDs on in vitro diagnostic medical devices (IVDR),* which proposes a draft common implementation plan for the IVDR, listing priority actions for Member States and Commission services, to be monitored at MDCG (Medical Device Coordination Group) level.

In addition to setting priorities, the plan will serve as a document to monitor their implementation. The status and deadlines of the points will be updated to adapt to the progress of the work.

The impact of the IVDR on IVD safety and performance management is great, thanks to the introduction of many new requirements for all economic operators, laboratories, notified bodies and competent authorities.

The main changes introduced by Regulation (EU) 2017/746 are represented, among other things, by:

- a new classification of devices, which are divided into classes A, B, C and D (Annex VIII), according to the intended use and the risks it entails. For more information on the classification rules, please also refer to the guideline MDCG 2020-16 rev.1 *Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (UE) 2017/746*;
- new conformity assessment procedures (art. 48 and Annexes IX, X, XI);
- the prediction of clinical evidence;
- performance evaluation and performance studies (Articles 56 to 77 and Annexes XIII and XIV);

- new obligations for manufacturers, agents, importers and distributors (respectively articles 10, 11, 13 and 14);
- from the inception of the role of the compliance officer with the legislation (PRRC - Person Responsible for Regulatory Compliance – art. 15); which manufacturers are obliged to have access to;
- from the UDI (Unique Device Identification) system (articles 24-25 and Annex VI), identification of a device;
- the strengthening of supervisory and surveillance activities (Articles 78 to 95);
- by the establishment of reference laboratories of the European Union (art. 100);
- from the European database of medical devices EUDAMED – European Database on Medical Devices (art. 30), developed by the European Commission to implement the Regulation (EU) 2017/745 on medical devices and the Regulation (EU) 2017/746 on medical devices- in vitro diagnostics.

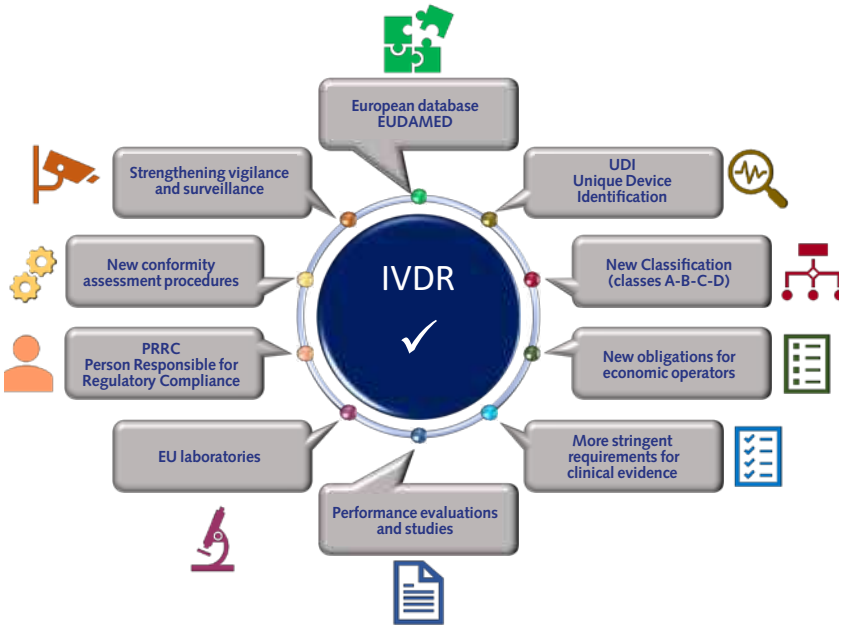


Fig.1 – Some of the main innovations introduced by the IVDR.

Another important change in Regulation (EU) 2017/746 was to increase the involvement of conformity assessment bodies ("notified bodies", when designated by a Member State) in the procedures that precede the availability of many of the devices affected by the Regulation in question. Under Directive 98/79/EC, only a relatively small number of high risk devices are subject to control by notified bodies. Under the Regulation, about 80% of the devices become under their control, most of them for the first time.

On January 28, 2022, Regulation (EU) 2022/112 of the European Parliament and of the Council of January 25, 2022 was published in the *Official Journal of the European Union*, amending Regulation (EU) 2017/746 regarding the transitional provisions for certain in vitro diagnostic medical devices and deferred application of prescriptions for in-house manufactured devices.

Regulation (EU) 2022/112 does not modify the requirements of Regulation (EU) 2017/746 in substance, and does not lower the safety level of products, but modifies its transitional provisions (Article 110).

No changes are envisaged for CE marked devices that do not require the intervention of a notified body pursuant to the Regulation or for "new" devices, i.e. those that have neither a certificate from a notified body nor a declaration of conformity pursuant to the current Directive 98/79/EC. For these types of devices, Regulation (EU) 2017/746 will therefore apply from May 26, 2022 as envisaged.

There is also a deferred application of the requirements for devices manufactured and used within the same healthcare institution ("*in-house devices*"). Regulation (EU) 2017/746 introduced a set of common rules for such devices which include requirements for the justification of their use and rules to ensure their safety and performance, such as an adequate quality management system.

The activities of Office 4 – In Vitro Diagnostic Medical Devices of the Directorate General for Medical Devices and the Pharmaceutical Service are as follows:

- **Completion and implementation of the general discipline of in vitro diagnostic medical devices.**
- **Preliminary activities for the authorization of notified bodies.**

Notified bodies are public or private bodies authorized to carry out certification activities, within the scope of a specific directive or regulation, by the authorities of the countries in which they are based. The bodies are notified by each Member State (in Italy by the Ministry of Economic Development) to the European Commission, which assigns them an identification number. The notified bodies,

based in Italy, which issue the required certification to the manufacturers of in vitro diagnostic medical devices, are authorized by the Ministry of Health. At the moment, 1 notified body is authorized in Italy pursuant to Directive 98/79/EC (Istituto Superiore di Sanità) (National Health Institute).

The Office has the task of carrying out the preliminary activities required for initial authorizations and renewals, as well as for surveillance activities. The Office also draws up the authorization decree.

- **Market surveillance at national and European level and activities resulting from inspections of economic operators in the field of in vitro diagnostic medical devices.**

The surveillance activities, carried out by the Ministry of Health, are aimed at verifying the work of manufacturers, distributors, importers in order to guarantee public health and end-users.

The Office carries out the surveillance activity on in vitro diagnostic medical devices both following reports from national subjects, and following information from other Member States, and on its own initiative, following for example, controls carried out during routine checks (inspections, database of in vitro diagnostic medical devices, issue of free sale certificates, etc.).

- **Registration of manufacturers and in vitro diagnostic medical devices and supply of the European database - Monitoring of consumption of in vitro diagnostic medical devices, purchased directly from the National Health Service.**

Based on the provisions of art. 10, paragraph 2, of Legislative Decree no. 332/2000, manufacturers and authorized representatives established in Italy who place on the market in vitro diagnostic medical devices in their own name are obliged to communicate their data and those identifying their device to the Ministry of Health. It is also required that for some devices (such as those listed in Annex II and self-diagnostic test devices), placed on the market in Italy, the manufacturers and/or authorized representatives, even if not established in Italy, must also send to the Ministry of Health, in addition to the communication of identification data, the labels and instructions for use. From 5 June 2014, with the entry into force of the decree of 23 December 2013, manufacturers and authorized representatives based in Italy or their delegates will comply with the obligations set out in the aforementioned decree, by registering in the Medical Device Directory.

Thanks to the availability of this information, the Office can identify any issues worthy of further study or can carry out checks on the devices present in the Directory.

The governance of the in vitro diagnostic medical devices sector is based on the registration number in the Repertoire, which allows the device to be identified, and in the National Classification of Medical Devices (CND) which groups the devices in a homogeneous classification level.

The CND, together with the Repertoire number, makes it possible to monitor the consumption of the devices and to better manage the supervision and surveillance of the market.

- **Monitoring and surveillance of incidents concerning in vitro diagnostic medical devices and adoption of consequent measures.**

The Ministry of Health has the role, at the national level, of assessing incidents involving in vitro diagnostic medical devices and, within the Community, of guaranteeing a high level of health protection through integrated surveillance systems between the Member States and the European Commission.

Public or private health workers who in the exercise of their activity detect an incident involving an in vitro diagnostic medical device are required to notify the Ministry of Health, with the terms and procedures established by the legislation.

The communication is made directly or through the health facility where the reported incident took place, in compliance with any regional provisions that require the presence of contact persons for the supervision of medical devices. The communication must also be sent to the manufacturer or his authorized representative, also through the supplier of the in vitro diagnostic medical device.

Among the tasks assigned to the health care worker there is also that of communicating to the manufacturer or the authorized representative any other inconvenience which, although not presenting itself with the characteristics of the incident, may allow the adoption of corrective measures to guarantee the protection and health of patients and users.

The legislation establishes the obligations regarding the supervision of incidents with in vitro diagnostic medical devices for the manufacturer or his authorized representative, in particular the immediate communication to the competent Authority of all incidents of which they have become aware and of all corrective actions that have been undertaken to prevent or reduce the risk of death or serious deterioration of the state of health associated with the use of an in vitro diagnostic medical device.

The manufacturer is also responsible for managing all other problems that do not present the conditions to be considered real incidents, but which may require corrective actions.

Specific forms of forms are envisaged for these requirements.

- **Issue of free sale certificates.**

To export in vitro diagnostic medical devices to countries outside the European Union, manufacturers (and/or authorized representatives) with registered office in Italy can request to the Ministry of Health a certificate of free sale (CLV), "certification of marking CE". The Ministry of Health, after checking the documentation submitted by the applicant, issues the certificate (CLV) certifying the CE marking of the product and consequently the free circulation of the same products in the EU countries. Before issuing the aforementioned certification, the competent Authority carries out a verification action on the CE marked device already present on the market, carrying out documentary checks both on the product and on the procedures implemented by the manufacturer in the CE marking process.

- **Authorization for the import and export of human blood and its products for the production of in vitro diagnostic medical devices.**

Companies, based in Italy, that produce in vitro diagnostic medical devices must apply to the Ministry of Health for authorization to import and export human blood and its products for the production of in vitro diagnostic medical devices. This authorization accompanies the batches of human blood in their movements from the entry into Italy, or its exit, up to the production site of the IVD and must be shown by the manufacturer to the border health authority.

- **Evaluation of advertising messages relating to in vitro diagnostic medical devices.**

The Office participates in the authorization procedure for advertising messages on in vitro diagnostic medical devices, providing technical opinions on the contents of the messages themselves.

c) Office 5 Device-Supervision

L. Lispi, D. Minella

Vigilance on medical devices. Introduction

The medical devices sector[1] constitutes, both nationally and in Europe, an aspect of great importance in the diagnostic and therapeutic paths of health care, contributing to the improvement of the level of health protection through the development of innovative solutions for diagnosis, prevention, treatment and rehabilitation. In this context, the protection of public health and safety is achieved through the proper operation of the surveillance and vigilance system, which, acting in conjunction and in a complementary manner, allow the rapid identification of unexpected risks deriving from the use of medical devices.

The Ministry of Health, recognized as a competent authority on medical devices, constantly carries out vigilance and surveillance activities in order to guarantee the circulation and use of products that are safe and of high quality, always taking into account the constant development of scientific know how and technological activities involving the sector.

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[1] Art. 2 def. 1 MDR (EU) no. 745/2017 medical device: any instrument, apparatus, equipment, software, implant, reagent, material or other article, intended by the manufacturer to be used on humans, alone or in combination, for one or more of the following intended uses specific medical:

– diagnosis, prevention, monitoring, prediction, prognosis, treatment or mitigation of diseases,

– diagnosis, monitoring, treatment, alleviation or compensation of an injury or disability,

– study, replacement or modification of the anatomy or of a physiological or pathological process or state,

– provide information through in vitro examination of samples from the human body, including donated blood and tissue,

and which does not exert in or on the human body the main action for which it is intended by pharmacological, immunological or metabolic means, but whose function can be assisted by such means.

The following products are also considered medical devices:

– devices for conception control or conception support,

– products specifically intended for the cleaning, disinfection or sterilization of the devices referred to in art. 1, par. 4, and those referred to in the first paragraph of this point.

The purpose of medical device vigilance is to guarantee a high level of safeguarding and protection of the health and safety of patients, users and all subjects who interact with them for various reasons. This is made possible through the functioning of a **vigilance system** that allows the rapid identification of any problem related to a device, as well as with the identification of any corrective actions aimed at eliminating and/or reducing the problems that occur in the post market phase. The vigilance system operates during the entire life span of the device and is a complex system that provides for the essential involvement and active participation of numerous actors, who take part in it at various institutional levels: central, regional, healthcare facility level, and at national and European contexts.

The **regulatory framework for vigilance**[2], represented for over 20 years by European Directives[3] implemented with the respective legislative decrees, is today facing a profound change, determined by the entry into force for medical devices, of the New European MDR Regulation (EU) no. 745/2017[4], which became fully applicable on May 26, 2021. The new European Regulation, taking into consideration the developments in the sector that have characterized the last twenty years, pursues the objective of guaranteeing a solid, sustainable regulatory framework, with transparent procedures and suitable for maintaining a high level of safety, while favouring technological innovation. The purpose of the vigilance system, while maintaining its fundamentals, will be strengthened in consideration of some requirements that characterize the new legal framework.

Unlike directives, regulations are directly applicable and do not have to be transposed into national law. Through a gradual process, which requires national transitional solutions, the new European regulation will progressively replace the aforementioned European Directives.

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[2] All the standards and guidelines mentioned are available on the portal of the Ministry of Health and the European Commission – medical devices section – at the following links: http://www.salute.gov.it/portale/documentazione/p6_2_6.jsp?lingua=italian&area=13&btnCerca=search/; http://ec.europa.eu/growth/sectors/medical-devices/guidance/index_en.htm/.

[3] Directive 90/385/EEC relating to active implantable medical devices; Directive 93/42/EEC on medical devices; Directive 98/79/EC on in vitro diagnostic medical devices.

[4] New MDR Regulation (EU) no. 745/2017 available at the following link: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02017R0745-20200424/.

At present we are currently in a peculiar situation, characterized by a European Regulation, already fully applicable and by national legislation resulting from the previous Directives. In this transitional period, work is underway for the review of national legislation, Legislative Decree no. 46/97 for medical devices, the Legislative Decree no. 507/92 for active implantable medical devices and Legislative Decree no. 332/2000 for in vitro diagnostic medical devices. The Law of 22 April 2021, no. 53, containing "*Delegation to the Government for the transposition of European directives and the implementation of other European Union acts - European delegation law 2019-2020*", in particular art. 15, paragraph 2, lett. a), in fact, provides for the adaptation and connection of the national provisions in force to the provisions of Regulation (EU) 2017/745, as amended by Regulation (EU) 2020/561, and of Regulation (EU) 2017/746, with specific reference to the procedures for vigilance, market surveillance and control of the safety of devices, the express repeal of incompatible national regulations and the coordination and reorganization of the remaining ones.

In the meantime, with regard to vigilance, the Ministry of Health has deemed it useful to issue a specific circular (ministerial circular of 8 July 2021[5]), bearing "*Indications for the supervision of incidents occurring after their placing on the market, in the light of Articles 87, 88, 89 and 90 of Regulation (EU) no. 745/2017*" aimed precisely at regulating the transitional period. This document intends to provide operational indications to economic operators, health professionals and lay users on the methods and timing of the reports relating to incidents and serious incidents occurring with medical devices, corrective safety actions, as well as reports on trends, as regulated by articles 87, 88, 89 and 90 of the Regulation.

At the same time, work is being done **at European level** to ensure the full functionality of the Regulations through the definition of guidance documents and guidelines. This is made possible through a demanding work, still in progress, which involves the European Commission, the Medical Device Coordination Group (MDCG) and the Authorities of the Member States, which have organized themselves according to a program of activities that will involve the gradual adaptation to the new legislative framework. These implementing acts and guidelines are reported in the Implementation

[5] Ministerial Circular of 8 July 2021 available at the following link: https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2021&codLeg=81733&parte=1%20&serie=null/.

Rolling Plan Regulation (EU) 2017/745 and Regulation (EU) 2017/746, which is updated on a quarterly basis[6].

The development of the New European Regulation MDR (EU) 745/2017 in the field of vigilance

The New European Regulation (EU) no. 745/2017, as mentioned above, arises mainly from the need to modify the sector legislation, characterizing it by a new style capable of keeping up with the times, which is able to ensure, through harmonization, the proper functioning of the medical devices sector within the European Union. In general, the new European regulations maintain all the provisions already present within the European Directives, however emphasizing some aspects with the aim of raising the quality and safety standards of the products.

Post-market vigilance and surveillance, in the new regulation, do not present any novelties from a conceptual point of view, but the importance and rigor with which they must be implemented is also emphasized. The implementation of the surveillance and vigilance system therefore represents one of the most important aspects of the New Regulation, aimed at further supporting its solidity and guaranteeing a high degree of rigor and greater harmonization at the Euro-Union level. In particular, the obligations required by the new European regulation on vigilance are described in Chapter VII, Section 2, and specifically in Articles 87-92. The requirements, already present in the European Directives, are then re-proposed in the regulation in an updated and strengthened key and enriched with more detailed definitions and explanations.

Among the main changes introduced in the new MDR regulation (EU) no. 745/2017 in the field of vigilance on medical device, the following are highlighted (Fig. 2):

- the new definitions for incident and serious incident (art. 2 def. 64 and def. 65 MDR);
- the definition of a serious threat to public health (art. 2 def. 66 MDR);
- clear timelines for reporting serious incident to the competent Authority by the manufacturer/authorized representative (art. 87 MDR);
- trend reports (art. 88 MDR);

[6] https://ec.europa.eu/health/medical-devices-sector/new-regulations_en/.

- the obligation to submit incident reports within the EUDAMED European database (art. 92 MDR);
- greater traceability of devices through the UDI system;
- also on devices that have no medical purpose and are therefore included in Annex XVI of the MDR;
- the identification and standardization of coordination mechanisms between EU countries in the areas of market vigilance and surveillance (art. 89 MDR);
- the establishment of registers and databases of specific types of medical devices (art. 108).

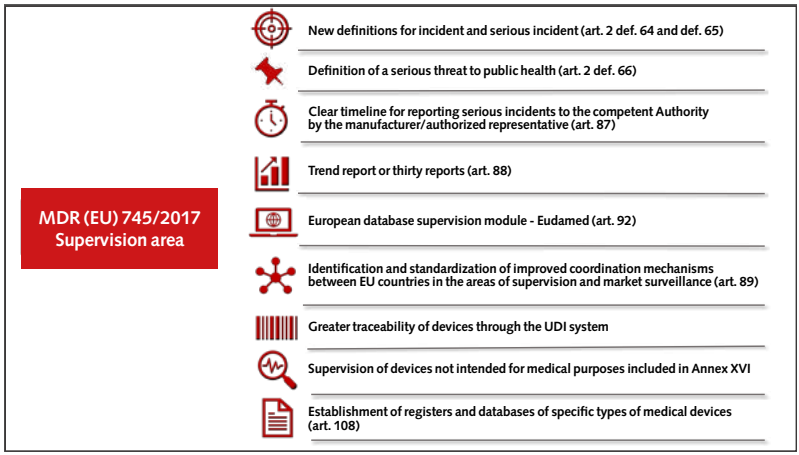

Fig. 2 – Some of the main changes introduced by the new regulation in the field of vigilance of medical devices.

One of the main changes introduced by the new regulation in the field of vigilance is linked to the definitions of incident and serious incident, the distinction of which lies essentially in the concrete and/or potential outcome deriving from the incident connected to a problem with a medical device on the market.

Specifically, as indicated in art. 2 def. 64 and 65 of the new Regulation, we mean by:

- **incident:** any malfunction or alteration of the characteristics or performance of a device made available on the market, including the error of use caused by the ergonomic characteristics, as well as any inadequacy in the information provided by the manufacturer and any undesirable side effect;

- **serious incident:** any incident which, **directly or indirectly, has caused, may have caused or may cause** any of the following consequences:
  a) the death of a patient, user or other person;
  b) the serious deterioration, temporary or permanent, of the health conditions of the patient, the user or another person;
  c) a serious threat to public health.

It is emphasized that the definition of serious incident includes the concept of the potential of the incident, already present in the European directives and taken up in the new Regulation.

The new Regulation defines what is meant by "serious threat to public health" (art. 2 def. 66) or "*an event that could lead to an imminent risk of death, a serious deterioration in the health conditions of a person or a serious illness which may require prompt corrective action and which may cause a significant rate of human morbidity or mortality and which is unusual or unexpected for that particular time and place*".

The change in the definitions of incident and serious incident therefore determines important implications on the correct interpretation of incidents involving medical devices and therefore on what must be reported by economic operators and health professionals and end-users.

The European database EUDAMED: Vigilance module

Another of the main innovations introduced in the new regulation and with a significant impact in the field of vigilance is represented by the European database EUDAMED (European Database on Medical Device)[7] defined in art. 33 of MDR no. 745/2017, developed and managed by the European Commission. This database, made up of 6 interconnected modules, will make it possible to improve the transparency and coordination of information regarding medical devices available on the European market.

Although the date of full operation has been postponed[8], the development and implementation of EUDAMED represent an element of priority

[7] European Commission page on EUDAMED: https://ec.europa.eu/tools/eudamed/#/screen/home/; Ministry of Health page on EUDAMED: https://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=5657&area=dispositiva-medici&menu=registrazione/.

[8] On 30 October 2019 the Commission published a notice in which it concluded that the full functionality of EUDAMED requires the availability and full functioning of

importance for the European Commission. The approach that is being followed is represented by a gradual release of the various modules to be used on a voluntary basis. Failure to start the full functionality of EUDAMED does not affect the date of application of the regulation and the related obligations regarding the registration of economic operators and devices, surveillance, clinical investigations and certification notifications. However, until EUDAMED is not fully operational, the MDR establishes that the corresponding provisions of the directives continue to apply in order to fulfil the obligations established regarding the exchange of information (ref. art. 123 (d) of the MDR (EU) no. 745/2017). In this context, please refer to the document drawn up by the MDCG on the indications relating to harmonized administrative practices and alternative technical solutions to be applied until EUDAMED is not fully functional. This guideline (MDCG 2021-1)[9] is available on the European Commission's website.

As regards the correlation between EUDAMED and the requirements of the new regulation in the vigilance field, please refer first of all to art. 92 of MDR 745/2017, which precisely defines how all information relating to vigilance will be collected and managed. The art. 92 is therefore an explicit reference to what is expected to be contained within the vigilance module of EUDAMED, i.e. the reports of serious incidents, safety notices, periodic summary reports PSR (Periodic Summary Report), trend reports, the PSURs, the information exchanged between the competent authorities or the NCARs (National Competent Authority Reports), and the ways in which this information will be processed and made available to the competent authorities of the Member States, the commission and the notified bodies.

The importance of EUDAMED in addition to the above is certainly also linked to greater transparency and dissemination of information in consideration of the fact that a public interface is envisaged that will allow an adequate level of access by health professionals and the public to information contained in the electronic system (art. 92 par. 3 MDR).

Below are some of the main advantages deriving from the integration of EUDAMED in the vigilance area (Fig. 3):

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all six modules in accordance with the technical specifications and confirmed by an audit pursuant to art. 34 of the MDR.

[9] MDCG 2021-1 "*Guidance on harmonized administrative practices and alternative technical solutions until EUDAMED is fully functional*" available at the following link: https://ec.europa.eu/health/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en/.

- centralization and harmonization of supervisory data collected at European level. EUDAMED will collect and manage all information related to vigilance (reports of serious incidents, field safety corrective actions, periodic summary reports (PSR) summary reports, trend reports, PSURs and information exchanged between the competent authorities (NCAR);
- EUDAMED will provide a vivid picture of the life span of medical devices made available in the European Union;
- EUDAMED will integrate different electronic systems (modules) to collect and process information on medical devices and related companies (e.g. manufacturers). In this way, the aim is to strengthen general transparency, including through access to information for the public and healthcare professionals;
- strengthening coordination between the different EU Member States;
- direct connection between the modules and therefore of the information of the certified medical device, traceability through a link to the UDI database;
- information made available to other competent Authorities, the European Commission and Notified Bodies, leading to greater communication efficiency.

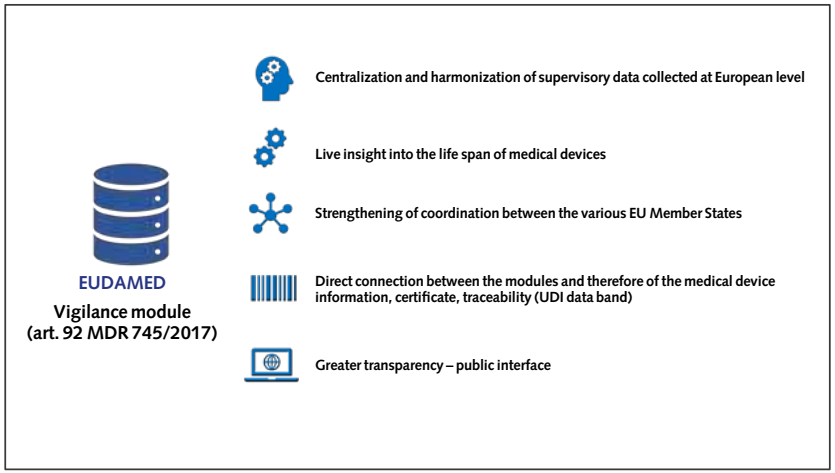

Fig. 3 – EUDAMED advantages in the area of vigilance.

The medical device vigilance system: structure and operational notes

The vigilance of medical devices carried out by the Ministry of Health constitutes an activity of fundamental importance in order to guarantee the circulation in national territory of safe and effective products for patients, users and health professionals.

The Ministry of Health, as competent authority, constantly carries out its vigilance and surveillance activities in order to guarantee products that are safe and of high quality, always taking into consideration the advancement of scientific and technological knowledge involving the medical device sector. These activities therefore have the task of leading to a complete monitoring of the devices in all phases of their life span, starting from the implementation of controls during the marketing phase up to post-marketing controls and identification and evaluation of any incidents involving end users.

The **vigilance** system is a complex system that finds its solidity and completeness in the collaboration of all the actors involved in it for various reasons such as:

- health professionals/users who have obligations regarding the reporting of incidents/serious incidents with medical devices;
- manufacturers who have an obligation to report serious incidents with medical devices as well as trend reports in the event of incidents and expected side effects, and to arrange corrective safety actions if deemed necessary;
- the Ministry of Health which, as competent authority, constantly monitors and evaluates incidents and corrective actions;
- the territorial and regional level also thanks to the establishment of the national vigilance device network;
- the european and international level through the constant exchange of information that takes place between the competent authorities.

Therefore, in addition to the supporting architecture based on the reporting of incidents with medical devices and field safety corrective action, the importance of two other key elements in the vigilance system is emphasized, such as the definition of a national vigilance device network and integration of the national vigilance system with the European and international systems.

The establishment of a national vigilance device network for the vigilance device is intended to ensure a timely and widespread exchange of information between the Ministry of Health, the Regions and Autonomous Provinces and the Health Authorities, relating to serious incidents/incidents

and field safety corrective action that involve the devices and aims primarily at strengthening the vigilance system, at achieving its uniformity throughout the national territory.

Furthermore, it should be noted that the Ministry of Health, in its vigilance activity, carries out its role not only at the national level, through the monitoring and evaluation of incidents involving medical devices, but also at european level through partecipation in vigilance system integrated between the Member States and the European Commission. The coordination, collaboration and constant exchange of information (through specific documents, NCAR and monthly Enquiry and Conference Call Vigilance) between the various competent Authorities of the European Union therefore represent a further cornerstone in the vigilance system in order to ensure an elevated level of protection of the health and safety of patients and users that is effective and consistent in the single European market.

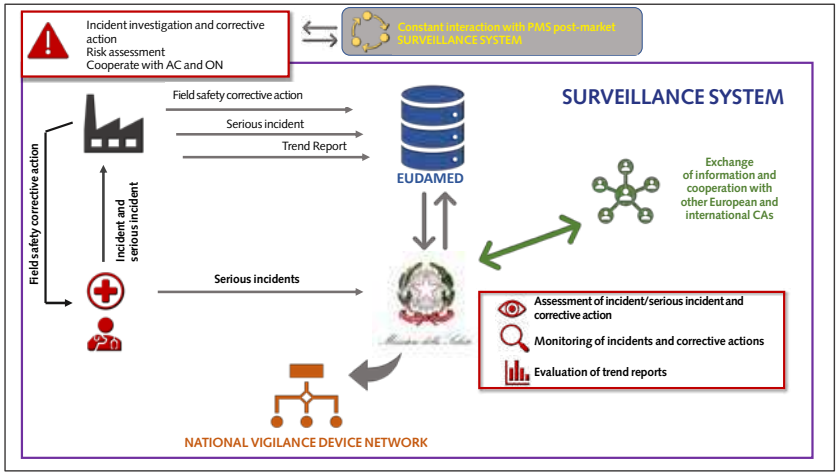

Fig. 4 – Activities and roles of the various actors who are involved in various capacities in the complex supervisory system.

Going into the specifics of reporting serious incidents/incidents, at present the vigilance system is influenced, as mentioned above, by a transitional period, in which, on the one hand, the new MDR Regulation (EU) no. 745/2017 became fully applicable on May 26, 2021, on the other hand, at a national level, it continues to find its basis in the legislative decrees transposing European directives until they are fully adapted to the new European legislation. While waiting for the adaptation of the national legislation to

be completed, the Ministry of Health issued the **circular of 8 July 2021**[10], designed to provide operational indications to economic operators, health professionals and lay users on the methods and timing of the related reports of incidents and serious incidents occurring with medical devices, safety corrective actions, as well as trend reports, as governed by the respective articles in the regulation.

The provisions contained in Legislative Decree no. 46/97 and subsequent amendments, implementing Directive 93/42/EC, in Legislative Decree no. 507/92 and subsequent amendments, implementing Directive 90/385/EC and in Legislative Decree no. 332/2000 and subsequent amendments, implementing Directive 98/79/EC, as well as those contained in Regulations (EU) 2017/745 and 2017/746, entrust the **Ministry of Health,** as the competent Italian authority, the task of recording and analyzing data regarding incidents related or potentially correlated with medical devices. The Ministry of Health has the task of monitoring the investigations carried out by the manufacturer or his authorized representative, to evaluate the corrective actions implemented by the same and to ascertain their effectiveness. If necessary, the Ministry of Health may, at any time, intervene autonomously by carrying out investigations on its own and imposing the corrective measures identified and deemed necessary, always with a view of promoting and protecting health and safety. In the event that the Ministry of Health deems there are risks to public health, it can define restrictions and/or limitations on the trade or commissioning of medical devices and in vitro diagnostic medical devices.

The role of the healthcare operator and the manufacturer/authorized representative in the medical device surveillance system is described below. For further information, please refer to the dedicated page on the institutional website of the Ministry of Health[11].

In the complex system of medical device vigilance, **healthcare professionals** are the first to detect incidents that can occur with the use of a medical device and therefore play a key role in reporting incidents that have occurred. As required by current legislation, public and private health workers, on the basis of the findings in the exercise of their activity, are required to immediately

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[10] Ministerial Circular of 8 July 2021 available at the following link: https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2021&codLeg=81733&parte=1%20&serie=null/.

[11] Ministry of Health page dedicated to the Supervision section on medical devices: https://www.salute.gov.it/portale/temi/p2_5.jsp?lingua=italiano&area=dispositiva-medici&menu=vigilanza/.

any incident involving a device to the Ministry of Health. This communication is made directly or through the health facility where the reported incident occurs, in compliance with any regional provisions that require the presence of contact persons for the vigilance of medical devices using the online form available on the website of the Ministry of Health. At the same time, the health care worker also notifies the manufacturer responsible for the device involved in the event of the incident, thus allowing the latter to begin the investigation aimed at defining the cause of the incident.

Going more specifically, the healthcare professional is referred to in the new European Regulation, in art. 2 (def. 37), when defining the user of a medical device. As regards the reporting of an incident, in art. 87, par. 10, the new regulation leaves it to the competent Authority the task of organizing the most appropriate modality for the registration of serious incidents in a centralized way at national level. The new regulation therefore refers to national legislation the reporting of serious incident by health professionals. With this in mind, the provisions defined in the relevant legislation or Legislative Decree no. 46/97 and the ministerial decree of 15 November 2005.

In the aforementioned circular of 8 July 2021, the ways in which healthcare professional and lay users are called to report a serious incident, even if only suspected, and a different serious incident involving a medical device are reported.

In particular:

- Public and private healthcare professional who in the exercise of their activity detect a **serious incident, even if only suspected,** involving a medical device are required to notify the Ministry of Health in accordance with the procedures set out in the Ministerial Decree of 15 November 2005 and subsequent amendments and additions to the manufacturer, his authorized representative or distributor, including through the supplier of the medical device.
- Public and private healthcare professional who in the exercise of their activity detect an **incident other than a serious one,** involving a medical device, must notify the manufacturer, the authorized representative or the distributor, also through the supplier of the device and may also notify the Ministry of Health.

At present, therefore, the methods of reporting incidents are those provided for by the Ministerial Decree of 15 November 2005 (published in *the Official Gazette - General Series* no. 274 of 24 November 2005).

The communication of serious incidents/incidents is carried out directly or through the health facility where the reported incident occurs, in compliance with any regional provisions that require the presence of contact persons

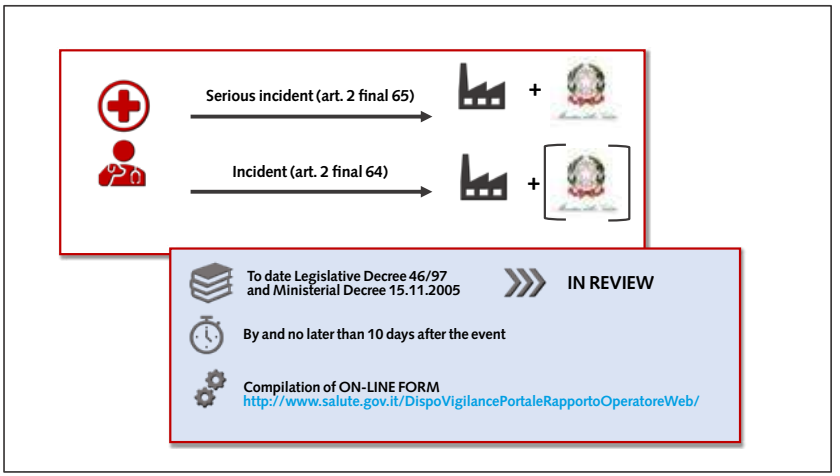

Fig. 5 – Reporting of incidents and serious incidents by health professionals.

for the supervision of medical devices using the online form available on the Ministry of Health website at the following link: http://www.salute.gov.it/DispoVigilancePortaleRapportoOperatoreWeb/.

At the same time, the health care worker also notifies the manufacturer responsible for the device involved in the event of the incident, thus allowing the latter to begin the investigation aimed at defining the cause of the incident.

The **manufacturer/representative,** as the legal responsible person for the medical devices he places on the market, he is required to report serious incidents affecting his device to the Ministry of Health and if he highlights a possible danger or risk associated with the use of his devices., is required to voluntarily undertake preventive and/or corrective actions, commensurate with the severity of the danger, which may lead to the disclosure of new safety information, safety instructions or the withdrawal or recall of the device from the market.

The latter constitute the safety and corrective actions (FSCA, Field Safety Corrective Action) that is all those measures taken by the manufacturer in order to minimize the future risk associated with the use of a device.

This information is communicated to the Ministry of Health and health professionals and determines the preparation of Field Safety Notice (FSN). The manufacturer is required to prepare, for all member countries, safety notices (FSN) for use by users, which describe the reasons for the corrective action, the inadequacies of the devices, the risks associated with their

use, the measures to be to adopt. The manufacturer must ensure that the organizations involved are reached by the transmission of the notices and must require the recipients to be informed all those who may be affected by the notice. The Ministry supports the dissemination of such information by publishing the safety notices on its portal, on a dedicated page within the thematic area relating to medical devices[12].

Specifically, in the New Regulation (EU) no. 745/2017, art. 87 punctually defines obligations, methods and timing of reporting for serious incidents by manufacturers. As defined in art. 87, par. 1, a) and b), the manufacturer is obliged to report to the competent authorities:

(a) any serious incident related to devices made available on the Union market, except expected side effects which are clearly documented in the product information and quantified in the technical documentation and which are the subject of trend reports pursuant to Art. 88;

(b) any field safety corrective action relating to devices made available on the Union market, including field safety corrective actions taken in a third country in relation to a device legitimately made available also on the Union market if the corrective action in question not caused only by the device made available in the third country.

The deadlines that the manufacturer is required to respect in relation to the reporting of serious incidents are clearly defined in art. 87 paragraphs 2 to 5 and are commensurate with the severity of the incidents as shown in Table 1 (2 to 15 days).

Incident reports must be notified by manufacturers/authorized representatives using the MIR Form (Manufacturer Incident Report)[13], available on the European Commission's website and the use of which has become mandatory from 1 January 2020; the forms relating to the safety notices to be used by manufacturers are those attached to the MEDDEV 2.12-1 rev.84 guidelines[14].

A further form of reporting an incident, which can be used by the manufacturer as an alternative to the MIR Form, is represented by the

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[12] Safety notices page of the Ministry of Health website: https://www.salute.gov.it/portale/news/p3_2_1_3_1.jsp?lingua=italiano&menu=notizie&p=avvisi&tipo=dispo/.

[13] Mir Form form available on the website of the Ministry of Health and on that of the European Commission at the following link: https://ec.europa.eu/docsroom/documents/41681/.

[14] European Commission DG Health and consumers (SANCO) MEDDEV 2.12-1 rev. 8 January 2013 Guidelines on a medical devices vigilance system: http://ec.europa.eu/growth/sectors/medical-devices/guidance/index_en.htm/.

Periodic Summary Report (PSR). As indicated in art. 87, par. 9, for similar serious incidents that occur with the same device or type of device and of which the root cause has been identified or which have been the subject of a safety corrective action, or if the incidents are common and well documented, the manufacturer may submit periodic summary reports (PSRs) rather than individual reports on serious incidents, provided that the format, content and frequency have been agreed with the coordinating authority. Although a new model for the submission of periodic summary reports (PSR) is being defined in the specific European task forces, at the present stage and pending implementation of EUDAMED, the model to be used remains the one contained in the current Meddev guidelines. 2.12-1 Rev. 8.

The manufacturer becomes aware of a serious incidents, as indicated in art. 89 of the MDR, is required to carry out without delay all the necessary investigations related to the serious incident and the devices involved, carrying out a careful assessment of the risk and possibly preparing a corrective action aimed at reducing the same. The manufacturer then submits a final report to the competent authority containing the conclusions of the investigation carried out.

In relation to incidents other than serious ones, the new regulation defines in art. 88 relation of trend or trend reports. With these reports, the manufacturer is required to report any statistically significant increase in the frequency or severity of incidents other than serious incidents or expected undesirable side effects that may have a significant impact on the risk and benefit analysis (referred to in Annex I, points 1 and 5, "General safety and performance requirements" of the Regulation) and which have entailed or may entail risks for the health or safety of patients, users or other people, which are considered unacceptable compared to the expected benefits. The manufacturer, as defined in articles 83-86 of the MDR, is required to record incidents and expected side effects in his post-marketing surveillance plan but are notified to the competent Authorities through trend reports only in the event that a statistically significant increase in the frequency and severity occurs that alters the risk-benefit ratio. Also in this case, the new model for the trend report and related guidance documents is being defined within specific European groups. At present, the model to be used continues to be the one present in the Meddev 2.12-1 Rev.8 guidelines.

Subject of the report	Timing for reporting	Method of reporting	Referral links	PEC for reporting
Serious incidents	Immediately and in any case no later than 15 days	MIR 7.2.1	[redacted]	[redacted]
Serious threat to public health	Immediately and in any case no later than 2 days	MIR 7.2.1	[redacted]	[redacted]
Death or unexpected serious deterioration in a person's health condition	Immediately and in any case within 10 days	MIR 7.2.1	[redacted]	[redacted]
PSR	To be agreed with the Unit 5 of DGDFM	MEDDEV 2.12/1 rev. 8	[redacted]	[redacted]

Times and procedures for reporting serious incidents by manufacturers/authorized representatives.

The novelty of the serious incidents reporting form: MIR Form

One of the first changes introduced in view of the full application of the European Regulations in the field of vigilance of medical devices was the preparation of a new model for the reporting of incidents by manufacturers/authorized representatives. The first MIR Form[15] (Manufacturer Incident Report), and the related accompanying documentation, was published in December 2018 on the European Commission's website. The use of the MIR Form, which became mandatory from 1st January 2020, therefore represents the new method of reporting serious incidents by manufacturers/authorized representative and is able to incorporate the innovations introduced by the new regulatory references.

The new MIR Form is not only enriched with the new requirements for reporting incidents envisaged by the new European regulation (EU) 2017/745-746, but also introduces a series of undoubtedly important innovations that will facilitate supervisory and monitoring activities. carried out by the competent authorities.

Fig. 6 – Innovation of MIR Form.

[15] MIR form (Manufacturer Incident Report) (v. 7.2.1) available on the European Commission's website at the page: Manufacturer incident report 2020; Question and Answer document related to the Mir Form available at the link: https://ec.europa.eu/docsroom/documents/41322?locale=en/.

Among these we find:

(i) the fields relating to the univocal identification of the manufacturer and agent through the SRN (Single Registration Number) and of the device through the relative UDI (Unique Device Identification) codes;
(ii) the presence of specific fields for trend data on the number of similar incidents and for marketing data, in the Member State where the incident occurred, in the EU and worldwide;
(iii) the possibility that this Form can be used both in the transitional period (through the.pdf and.xml files) and can be directly loaded into EUDAMED once it is available;
(iv) the presence of a section dedicated to information coming from the health worker or the lay user;
(v) the inclusion and therefore the use of the harmonized nomenclature AER IMDRF Term and Code Terminology for the description of events, their causes and effects on users for incidents involving medical devices. Surely the latter represents one of the most important innovations introduced within the MIR module.

This last aspect represents one of the most important innovations introduced within the MIR module. The IMDRF terminologies for categorized Adverse Event reporting (AER): terms, terminology, structure and codes (IMDRF/AE WG/N 43 Final: 2020 Edition 4) developed by the International Medical Device Regulators Forum (IMDRF)[16], provides a nomenclature harmonized for the reporting of "adverse events" relating to pre and post-market medical devices. The dissemination of a univocal nomenclature and system of terminologies and codes, appropriate for the description of adverse events and harmonized, has the important aim of improving the incident reporting system allowing faster and more accurate communication both for industry and for the competent Authorities, as well as brings about advantages for healthcare professionals by allowing to increase the accuracy, reliability and sharing of information with manufacturers and with the competent Authorities.

The nomenclature includes 4 distinct sets of terminologies and their associated alpha-numeric codes and is made up of 7 Annexes (Annexes A to G).

[16] International Medical Device Regulators Forum: http://www.imdrf.org/.

Conclusions and insights for an increasingly efficient vigilance system

The introduction of the new European regulation has certainly provided a renewed and innovative style to the regulatory framework underlying the vigilance system. However, the improvement of collaboration between all the players involved represents one of the main objectives so that the vigilance system can really and concretely function at its best.

The acquisition of the requisites required by the new regulation, including first and foremost the correct interpretation of the definitions of incident and serious incident, be it among manufacturers or with health workers, represents a key point on which to focus attention. Avoid therefore that there is a different interpretation of the definitions, at the same time increase the sensitivity of healthcare professionals and manufacturers to report and do so correctly, in the manner and timing provided for by the regulations, increase the training and diffusion of the culture of medical device supervision, to prevent the erroneous idea from circulating that the reporting of a serious incident corresponds to malpractice, rather to emphasize how correctly reporting a serious incident involving a medical device represents an essential tool aimed at the protection of patients and end users, are all factors underlying the improvement of the vigilance system.

The harmonization at national level and the uniformity of interpretation of what is required by the regulations in force and of the behaviour of all the subjects involved represent essential elements aimed at the continuous improvement of the vigilance system.

d) Office 6 Clinical Trials

*A.M.R. Bonaventura**

The objective of the new Regulation is to raise the quality and safety standards of the products and at the same time create a sustainable legislative framework, favourable to innovation that places the European Union as the guarantor of global health and the proper functioning of the medical device market.

May 26 is the date from which the full applicability of Regulation 2017/745 begins, however, as foreseen by the same, the failure of EUDAMED to operate, allows the use of transitional solutions by the Member States as regards the registration of devices and economic operators, certification and supervisory notifications of clinical investigations.

The use of this in-depth study will allow the achievement of some objectives such as:

- Understand the role of clinical evaluation and clinical investigations in the life span of medical devices;
- Distinguish the different types of clinical investigations and their regulatory paths;

Analyze the administrative procedures necessary for conducting clinical investigations.

First of all, it is significant to highlight the fundamental legislative requirements: **Regulation (EU) 2017/745 and the considerations** before clarifying the relative details of the clinical investigation with medical devices.

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* The author thanks Eng. Pietro Calamea (Director of Office 6 – Clinical Trials of Medical Devices – General Directorate of Medical Devices and Pharmaceutical Service – Ministry of Health), for having granted the availability, to participate in the drafting of the relevant chapter.

Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 relating to medical devices, amending Directive 2001/83/EC, Regulation (EC) no. 178/2002 and Regulation (EC) no. 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.

Council Directive 90/385/EEC and Council Directive 93/42/EEC constitute the Union regulatory framework for medical devices other than in vitro diagnostic medical devices. However, there is a need for a substantial revision of these directives in order to establish a robust, transparent, predictable and sustainable regulatory framework for medical devices, which ensures a high level of safety and health while supporting innovation.

The value of clinical data for the safety and quality of devices

This Regulation aims to ensure the proper functioning of the internal market in medical devices, taking as a basis a high level of protection of the health of patients and users and taking into account small and medium-sized enterprises active in this sector. At the same time, it sets high standards of quality and safety of medical devices in order to meet the common safety requirements relating to these products. Both objectives are pursued simultaneously and are inextricably linked, without one being secondary to the other. […] This Regulation harmonises the rules for placing medical devices and their accessories on the market and putting them into service on the Union market enabling them to benefit from the principle of free circulation of goods. […] This regulation establishes high quality and safety parameters for medical devices ensuring, among other things, that the data obtained from clinical investigations are reliable and solid and that the safety of the subjects participating in such investigations is protected.

The "key elements" to improve safety and health

In order to improve health and safety, some key elements of the current regulatory approach should be deeply strengthened, such as:

- the control of notified bodies,
- the conformity assessment procedures,
- clinical investigations and clinical evaluation,
- market supervision and surveillance,

and at the same time introducing provisions that guarantee the transparency and traceability of devices.

The relationship between clinical assessment and risk management

The risk management system should be carefully aligned with and reflected in the clinical evaluation of the device, including the clinical risks to be addressed in clinical investigations, clinical evaluation and post-market clinical follow-up.

Risk management and clinical evaluation processes should be interconnected and regularly updated.

Consultations by expert groups

For class III implantable devices and class IIb active devices intended to administer to the body and/or remove a medicinal product from the body, notified bodies should be required, except in certain cases, to request expert groups to monitor their evaluation report on the clinical evaluation.

Consultation of the expert group in relation to clinical evaluation should lead to a harmonized evaluation of high-risk medical devices.

For class III devices and for certain class IIb devices, a manufacturer should be able to voluntarily consult a panel of experts, prior to his clinical evaluation and/or investigation, on his clinical development strategy and proposals for clinical investigations.

Clinical investigations as a basis for evidentiating compliance

To ensure a high level of safety and performance, the demonstration of compliance with the general safety and performance requirements set out in this Regulation should be based on clinical data which, for class III devices and implantable devices, should in principle be obtained, from clinical investigations carried out under the responsibility of a sponsor. The role of the sponsor who assumes the responsibility for the clinical investigation should be able to be performed by both the manufacturer or another individual or legal person.

Global references for clinical investigations in Europe

The rules applicable to clinical investigations should be in line with established international guidelines in the sector, such as the international standard ISO 14155: 2011 "Clinical investigation of medical devices for human subjects - Good clinical practice", in order to facilitate the acceptance outside the Union of the results of clinical investigations conducted in the Union as documentation, as well as acceptance within the Union of the results of clinical investigations conducted outside the Union in accordance with international guidelines.

Furthermore, the rules should be in line with the most recent version of the World Medical Association's (WMA) Helsinki Declaration on Ethical Principles for Medical Research Involving Human Subjects.

Circulation of information on clinical investigations

An electronic system should be established at Union level to enable each clinical investigation to be recorded and communicated in a database, which is also accessible to the public.

To uphold the right to the protection of personal data, stated in Article 8 of the Chart of Fundamental Rights of the European Union ("Chart"), no personal data of subjects participating in a clinical investigation should be recorded in the IT system.

In order to ensure synergies with the clinical trials sector of medicinal products, the IT system for clinical investigations should be interoperable with the future EU database on clinical trials of medicinal products for human use.

Coordinated evaluations between the states of the European Union

Where a clinical investigation is to take place in more than one Member State, the sponsor should have the possibility to submit a single application in order to reduce the administrative burden.

To allow for the sharing of resources and a consistent assessment of the health and safety aspects of the investigated device, as well as of the scientific design of that clinical investigation, the procedure for the assessment of the single application should be coordinated between Member States under the management of a coordinating Member State.

Such coordinated assessment should not address the intrinsically national, local and ethical nature of a clinical investigation, including informed consent.

For an initial period of seven years from the date of application of this Regulation, Member States should be able to participate in the coordinated assessment on a voluntary basis. After this period, all Member States should be required to participate in the coordinated evaluation.

The increase in the legislative provisions on clinical investigations can be summarized with Table 1, so that it is easy to use.

Table 1 – Increase in legislative provisions on clinical investigations.

Legislative Decree no. 46/97 (transposition of the Directive)	**Regulation (EU) 2017/745**
1 article (Article 14 – Clinical investigations)	**22 items** (Chapter VI – Clinical evaluation and clinical investigations, articles 61 to 82)
2 Attachments • Declaration relating to special purpose devices (Annex VIII) • Clinical evaluation (Annex X)	**2 Attachments** • Clinical evaluation and post-marketing clinical follow-up (Annex XIV) • Clinical investigations (Annex XV)
Many of the obligations that in the Directive were defined only in the Annexes, have been integrated into the provisions of the Regulation to facilitate their implementation.	

We collect the articles relating to the clinical trial of medical devices for illustrative purposes by topics, identifying the various types of administrative, clinical, technical and ethical aspects.

Articles on general aspects of clinical evaluation and investigation
Article 61 – Clinical evaluation
Article 62 – General requirements relating to clinical investigations conducted to establish the conformity of devices

Articles on the protection of participating subjects and on ethical aspects
Article 63 – Informed consent
Article 64 – Clinical investigations on incapable subjects
Article 65 – Clinical investigations on minors
Article 66 – Clinical investigations on pregnant and breastfeeding women
Article 67 – Additional national measures
Article 68 – Clinical investigations in emergency situations
Article 69 – Compensation for damages

Procedures articles
Article 70 – Application for clinical investigation
Article 71 – Evaluation by the Member States
Article 72 – Conducting a clinical investigation
Article 73 – IT system for clinical investigations
Article 74 – Clinical investigations relating to devices bearing the CE marking
Article 75 – Substantial changes in a clinical investigation
Article 76 – Corrective measures to be taken by Member States and exchange of information between Member States

Article 77 – Information from the sponsor at the end of a clinical investigation or in the event of a temporary interruption or early conclusion

Articles on coordinated assessment, safety reporting and further regulations
Article 78 – Coordinated evaluation procedure for clinical investigations
Article 79 – Revision of the coordinated evaluation procedure
Article 80 – Recording and reporting of adverse events occurring during clinical investigations
Article 81 – Implementing acts
Article 82 – Requirements relating to other clinical investigations

Definitions

Clinical evaluation

Evaluation is a systematic and planned process to continuously produce, collect, analyze and evaluate clinical data related to a device to verify safety and performance, including clinical benefits, when used as intended by the manufacturer.

Clinical investigation

Any systematic investigation involving one or more human subjects, aimed at evaluating the safety or performance of a device.

Clinical data

Safety or performance information derived from the use of a device and that comes from:

- clinical investigations relating to the device in question;
- clinical investigations or other studies published in the scientific literature relating to a device whose equivalence to the device in question can be demonstrated;
- clinically relevant information from post-marketing surveillance, in particular post-marketing clinical follow-up.

Clinical evidence

Clinical data and clinical evaluation results related to a device, in sufficient quality and quantity to allow a qualified assessment that the device provides the expected clinical benefits and safety when used as intended by the manufacturer.

Clinical performance
The ability of a device, due to direct or indirect medical effects, deriving from its technical or functional characteristics, including diagnostics, to obtain the intended use declared by the manufacturer, thus procuring a clinical benefit for patients, when used as intended by the manufacturer.

Clinical benefit
The positive impact of a device on a person's health, defined in terms of a significant, measurable and relevant clinical outcome for the patient or a positive impact on patient management and on public health.

Clinical evaluation: objectives, responsibilities, tasks

Confirmation of compliance with the relevant general safety and performance requirements under normal conditions of intended use of the device, as well as the assessment of undesirable side effects and the acceptability of the benefit/risk ratio referred to in Annex I, is based on clinical data that provide sufficient clinical evidence.

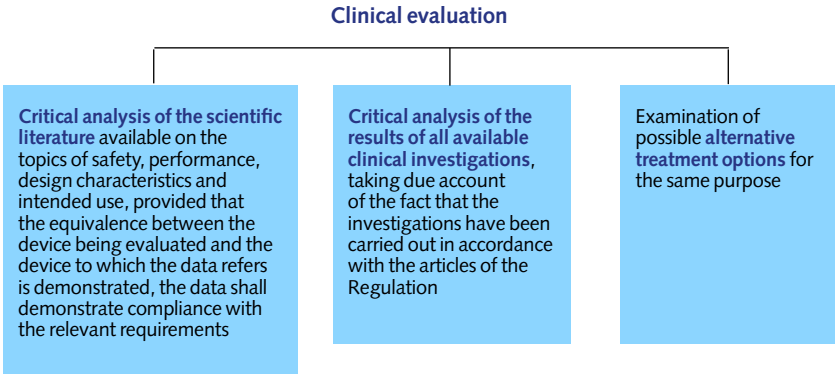


Fig. 1 – Clinical evaluation: foundations.

The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate compliance with the relevant general safety and performance requirements.

This level must be appropriate in consideration of the characteristics of the device and its intended use.

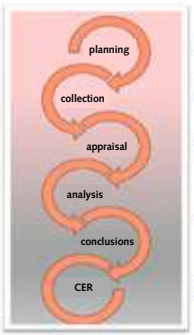
To this end, manufacturers plan, carry out and document the clinical evaluation.

Clinical evaluation, identification of activities

PLAN: Establish and update a Clinical Evaluation Plan.

CONDUCT: Identify (systematic scientific literature review), review and produce new or additional clinical data through properly designed clinical investigations.

RECORD: Analyze relevant clinical data; Demonstrate compliance with clinical safety and performance requirements, and clinical benefits.



- **Planning and definition of the purpose;**
- **Identification and collection of available clinical data;**
- **Appraisal of each data set in terms of relevance, quality and applicability;**
- **Analysis of individual data sets in order to determine for example their robustness and to draw conclusions on the clinical evidence;**
- **Production of the Clinical Evaluation Report (CER)**

Fig. 2 – Clinical evaluation: the phases.

Documentation and updating of the clinical evaluation

The clinical evaluation and related documentation are updated throughout the life span of the device in question with the clinical data obtained following the implementation of the PMCF plan and the manufacturer's post-market surveillance plan.

For class III devices and implantable devices, the PMCF assessment report and, if indicated, the summary relating to safety and clinical performance, **is updated** with this data at least once a year.

The clinical evaluation, the results and the clinical evidence derived from it are documented in a clinical evaluation report, which forms part of the technical documentation concerning the device in question.

Clinical evaluation plan

- Identification of the general safety and performance requirements;
- specification of the intended use of the device;
- specification of target groups with clear indications and contraindications;
- detailed description of the expected clinical benefits;
- specification of the methods to be used for the examination of the qualitative and quantitative aspects of clinical safety (residual risks and side effects);

- indicative list and specification of the parameters to be applied to determine the acceptance of the benefit-risk ratio;
- Indication of how issues relating to the risks and benefits of specific components (pharmaceuticals, non-viable animal or human tissues) should be addressed;
- clinical development plan indicating progression from exploratory investigations (*first-in-man* studies, feasibility studies and pilot studies) to confirmatory investigations, and a PMCF.

The purpose of clinical investigations conducted to demonstrate compliance

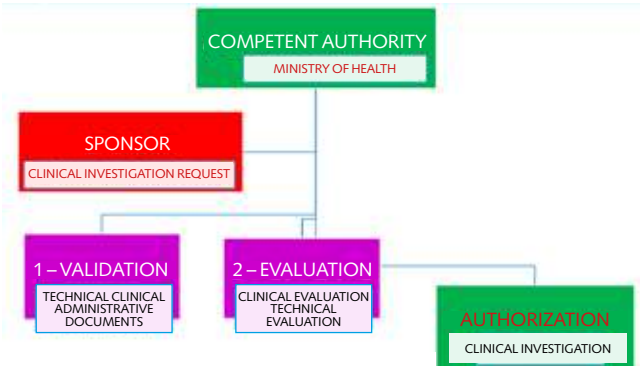
Establish and verify

a) that under normal conditions of use the devices are designed, manufactured and packaged in such a way as to be able to perform one or more medical purposes, and to provide the intended performance specified by the manufacturer;
b) the clinical benefits of a device specified by the manufacturer;
c) the clinical safety of the device and any undesirable side effects under normal conditions of use of the device and assess whether they represent an acceptable risk compared to the benefits achieved by the device.

Safeguards in clinical investigations conducted to demonstrate compliance

Clinical investigations are planned and carried out in such a way that:

- The rights, safety, dignity and well-being of subjects participating in a clinical investigation are protected and prevail over any other interest.
- The clinical data obtained are scientifically valid, reliable and solid.
- Clinical investigations are subject to scientific and ethical review.
- The ethics review is carried out by an Ethics Committee in accordance with national law.



- Member States shall ensure alignment between the procedures for review by the Ethics Committee and the procedures for evaluating the application for authorization of a clinical investigation.

Phase I validation

- Verification of the application and of the subjects contributing to the presentation of the application;
- Verification of the device (or devices) under investigation;
- Investigator's Brochure and related technical documents;
- Clinical Protocol (CIP);
- Centres involved in the clinical investigation and reference Ethics Committees;
- Verification of the nature of the study and of the clinical protocol;
- Other documentation.

Phase II evaluation

Clinical evaluation:

- Clinical protocol study;
- Resident clinical doctors;
- External experts.

Technical evaluation:

- Investigator Brochure, Risk Analysis, Essential Requirements;
- Quality requirements and good practice standards in the production process;
- Verification of the presence of substances and evaluation;
- Biomedical Engineers, In-house Pharmacists;
- External experts.

The clinical context in clinical investigations conducted to demonstrate compliance

Investigators

The investigator is a person whose profession is recognized by the Member State concerned as qualifying for the role of investigator, given the need of scientific knowledge and experience in the field of patient care.

Other staff members participating in the execution of a clinical investigation are suitably qualified, in terms of education, training or experience, in the relevant medical field and clinical research methodology to perform their duties.

Facilities

The facilities in which the clinical investigation is to take place are suitable for

the investigation itself and are similar to those in which the device is intended to be used.

The participants of clinical investigations

The competent authority

The clinical investigation is subject to an authorization issued by the Member State (s) in which the clinical investigation is to take place, unless otherwise specified.

The Directives spoke of Notification to the competent Authority, which could express a contrary decision

The competent Authority, currently with the 2017/745 Regulation, provides for:

- Validation of clinical investigation requests;
- Evaluation of requests relating to clinical investigations on unmarked devices and subsequent notifications of substantial changes;
- Authorization of clinical investigations on non-labelled devices of the higher risk classes;
- Adoption of measures when the provisions of the Regulation are not respected;
- Acquisition of notifications relating to PMCF investigations;
- Acquisition of communications relating to temporary interruptions, early conclusions and end of investigation.

The Ethics Committee

An Ethics Committee is an independent body set up in a State in accordance with the law of that Member State, with consultative powers, taking into account the views of non-professionals, in particular patients or their organizations.

The clinical investigation can be carried out if an Ethics Committee, set up in accordance with national law, has not issued a negative opinion in relation to the clinical investigation, which is valid throughout the Member State.

The Directives spoke of the expression of a favorable opinion by the competent Ethics Committees as a condition for launching an investigation and not for conducting it in the absence of a negative opinion valid throughout the Member State.

The Sponsor

The sponsor is the person, company, institution or organization that takes responsibility for initiating, managing and funding the clinical investigation.

The sponsor of a clinical investigation submits an application, accompanied

by the documentation referred to in Annex XV, Chapter II, in the Member State or States where the clinical investigation will be carried out. A declaration signed by the natural or legal person responsible for manufacturing the device under investigation is attached to the application.

If the sponsor of a clinical investigation is not established in the Union, it ensures that a natural or legal person is established there as its legal representative in the European Union, responsible for ensuring compliance with the obligations of the sponsor and recipient of all communications.

The Directives spoke only of Manufacturers or agents.

Role of the competent authorities of the Member States

The competent authorities of the Member States:

- carry out the scientific review of clinical investigations;
- assess whether, after risk minimization, the potential residual risks are justifiable taking into account the expected clinical benefits;
- issue the authorization to carry out the clinical investigation, unless:
  a) the application file remains incomplete;
  b) the device or documents presented do not correspond to the state of scientific knowledge;
  c) the general requirements on clinical evaluation are not met.
- they guarantee the absence of conflicts of interest, independence and the absence of conditioning for the evaluators;
- ensure that evaluators collectively possess the necessary qualifications and experience.

The Directive talked about starting the investigation after a predefined time unless otherwise decided for public health reasons.

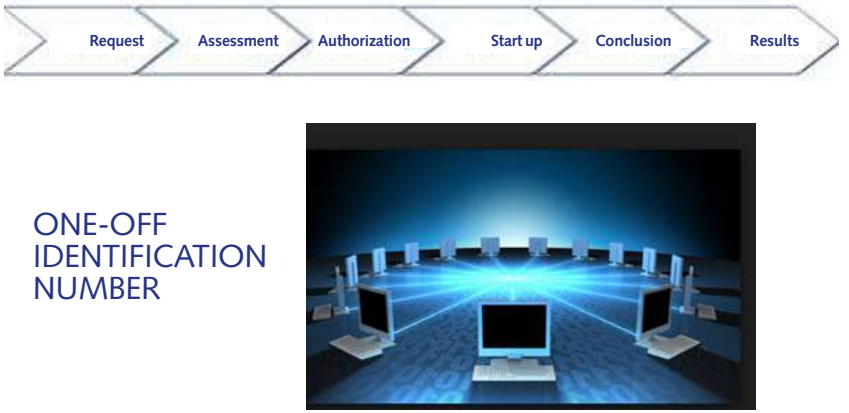


Fig. 3 – New IT system for clinical investigations and administrative procedures.

The IT system, managed by the Commission, constitutes:

- single access point for submitting all applications and for all other data transmissions;
- platform for the exchange of information between Member States and between them and the Commission;
- collection point for reports of serious adverse events (SAE) and device defects (SADE).

The information in the IT system is also accessible to the public, unless there are reasons for:

- protection of personal data in accordance with Regulation (EC) no. 45/2001;
- protection of commercially confidential information;
- effective surveillance of the execution of the clinical investigation.

The application for clinical investigation

The sponsor of a clinical investigation shall submit an application, accompanied by the documentation referred to in Annex XV, Chapter II, in the Member State or States where the clinical investigation will be carried out.

The application is submitted through the IT system which generates a single Union-wide unique identification number for the clinical investigation, which is used for all communications relating to that clinical investigation.

Following any change in relation to the information referred to in Annex XV, Chapter II, the sponsor updates, within one week, the relevant data in the IT system so that the change in the documentation is clearly identifiable.

Table 2 – Conditions for initiating a clinical investigation on a non-CE marked device.

	Verification of the completeness of the application	Technical-scientific evaluation	Ethical evaluation
Directives		Absence of a contrary decision by the competent authority	Positive opinion of each competent Ethics Committee
Regulation	Validation of the application by the competent authority	Authorization by the competent authority	Non-negative opinion valid throughout the member state of an Ethics Committee

The Competent Authority notifies the Sponsor of the authorization within a period of 45 days from the validation date, which may be extended by 20 days in the event that the Competent Authority makes use of expert consultation.

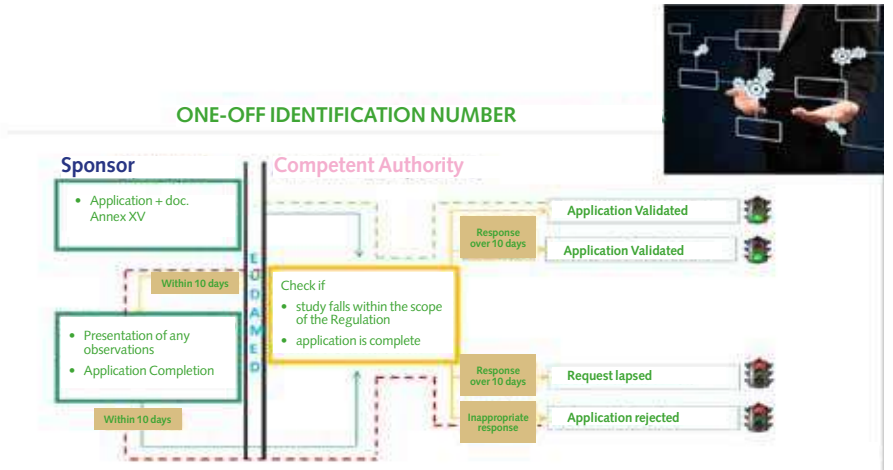


Fig. 4 – Validation of the request for clinical investigation.

Evaluation of the clinical investigation request

Member States shall assess whether the clinical investigation is designed in such a way that the potential remaining risks, after risk minimization, are justifiable taking into account the expected clinical benefits.

The Common Specifications and the applicable harmonized standards allow an in-depth and detailed examination of:

a) the demonstration of compliance with the applicable general safety and performance requirements, with the exception of the aspects that are the subject of the clinical investigation and, for the latter, if all precautions have been taken to protect the health and safety of the subjects;
b) if the risk minimization solutions employed by the sponsor are described in the harmonized standards and, in cases where the sponsor does not use harmonized standards, if the risk minimization solutions provide a level of protection;
c) whether the measures envisaged for the safe installation, commissioning and maintenance of the device under investigation are adequate;
d) the reliability and reliability of the data obtained from the clinical investigation, taking into account statistical approaches, investigation plans and methodological aspects, including sample size, comparator and endpoints;
e) if the requirements of Annex XV are met.

Substantial changes to clinical investigations

A sponsor shall notify the Member State in which the clinical investigation is ongoing or is to be conducted within one week of changes it intends to make to a clinical investigation that are likely to have a significant impact:

- on the safety, health or rights of the subjects participating in it;
- on the solidity and reliability of the clinical data obtained from the survey.

The sponsor may implement the changes no earlier than 38 days from the date of the notification unless:

a) the Member State has not communicated to the sponsor its refusal based on the reasons referred to in art. 71 or on considerations of public health, safety or health of subjects and users
b) an Ethics Committee of that State has issued a negative opinion in relation to the substantial change which, under national law, is valid throughout the Member State.

Corrective measures that Member States can take

If a Member State in which a clinical investigation is conducted has reason to believe that the requirements set out in this Regulation are no longer complied with, it may take at least the following measures for its territory:

Fig. 5 – Provisions on PMCF investigations.

PMCF investigations (Post Market Clinical Follow-up)

Clinical investigations aimed at further evaluating, as part of its intended use, a device that already bears the CE marking.

The provisions PMCF relating to art. 62, par. 4, letters b) to k) and m), of arts. 75, 76, 77 and art. 80, par. 5, as well as the relevant provisions of Annex XV.

It should be noted that in Annex XV, provisions that are not relevant to the PMCF investigations are not expressly indicated, only provisions that have different implications are dealt with depending on whether the device is marked or not.

PMCF investigations with invasive or harsh supplementary procedures
The sponsor informs the Member States concerned at least 30 days before the start.

The sponsor shall include the information set out in Annex XV, Chapter II, as part of the notification.

The extension of the clinical evaluation to the entire life span of the device
Post Market Clinical Follow-up (PMCF) is an ongoing process that updates the clinical assessment and is addressed in the manufacturer's post-market surveillance plan.

In implementing the PMCF, the manufacturer proactively collects and evaluates clinical data relating to the use in or on humans of a device bearing the CE marking, in order to:

- confirm safety and performance throughout the expected life of the device;
- ensure the unchanged acceptability of the identified risks;
- detect emerging risks on the basis of factual elements.

The objectives of a PMCF plan
The PMCF is carried out according to a documented method, established in a PMCF plan.

The PMCF plan specifies the methods and procedures to proactively collect and evaluate clinical data in order to:

- Confirm the safety and performance of the device for its entire period of validity;
- Identify previously unknown side effects and check those already identified and counter arguments;
- Identify and analyze emerging risks on the basis of factual elements;
- Guarantee the unchanged acceptability of the risk/benefit ratio;
- Identify any misuse or systematic off-label uses of the device in order to verify the correctness of the destination.

Outcomes of a PMCF plan
The manufacturer:

- analyzes the results of the PMCF;
- documents the results in a PMCF assessment report which becomes part of the clinical assessment report and technical documentation.

The conclusions of the PMCF assessment report are taken into account for clinical assessment and risk management.

If the PMCF has identified the need for preventive and/or corrective measures, the manufacturer must implement them.

Fig. 6 – Provisions on PMCF investigations.

The objective of the circular of 25 May 2021 is to clarify the application of Regulation (EU) 2017/745 of the European Parliament and of the Council, of 5 April 2017, in the field of clinical investigations relating to medical devices.

It also identifies the provisions applicable after May 26, 2021 to:

- clinical investigations on devices not bearing the CE marking;
- clinical investigations on devices bearing the CE marking;
- substantial changes in clinical investigations;
- information to be provided by the Sponsor after a clinical investigation is initiated;
- digitization and simplification of information exchanges;
- participation of Ethics Committees;
- ascertaining the suitability of the facilities at which a clinical investigation should take place;
- payment of clinical investigation fees for which notification was submitted before May 26, 2021.

Provisions applicable to investigations on non-CE marked devices

As of May 26, 2021, do not apply to the clinical investigations which there has yet been presented a notification the provisions of Legislative Decree no. 46/97 and of Legislative Decree no. 507/92 relating to the methods of presentation and handling of notifications, including their Annexes, as the provisions of the Regulation on

- legitimated subjects (art. 62, par. 2);
- nature and form of the procedure (art. 62, par. 4);
- accompanying documentation (Annex XV).

As from May 26, 2021, however, to the extent permitted by the lack of full operation of the EUDAMED database, the provisions of the Regulation are applied on

- request for clinical investigation (art. 70);
- accompanying documentation (Annex XV, Chapter II).

Provisions applicable to the validation of the clinical investigation request

- The application model defined at European level is used (to make the administrative treatment homogeneous with that of the other Member States and to reduce the costs for sponsors who promote multicentre clinical investigations in several States);
- the application validation process ends with the formal notification of the validation decision by the Ministry of Health (to give certainty to the deadlines, excluding tacit rejection and tacit validation);
- the validation cannot be concluded in the absence of an opinion formulated by an Ethics Committee who expresses an opinion that can be considered valid throughout the national territory (for the purposes of the authorization procedure, the ruling on the ethical review is mandatory and potentially prohibitive).

Provisions applicable to investigations on CE marked devices

Starting from the date of May 26, 2021, the provision, in addition to the previous provisions, which requires the prior notification, with an advance of 30 days, of the start of the PMCF clinical investigations (or carried out on devices bearing the CE marking, in order to further evaluate them in the context of their intended use) when they submit the subjects to additional invasive or severe procedures compared to those performed under normal conditions of use of the device. The requested model defined at European level is used for the exchange of information.

For the other PMCF surveys, also considering that the provisions of the Regulations on communications relating to them are not explicitly and unambiguously expressed, the provisions of Legislative Decree no. 46/97 and of Legislative Decree no. 507/92 as regards the communication of the opening of the investigation. The methods for the exchange information remain those of the pre-existing national procedure, available on the website of the Ministry of Health.

Provisions Applicable to Substantial Changes to Clinical Investigations

Starting from the date of May 26, 2021, the provisions of art. 75 of the Regulation are applied, in order to be able to evaluate the substantial changes

to a clinical investigation, for which the treatment is not subject to specific provisions of the Directives and Legislative Decrees implementing it.

The provisions of the Decree of the Minister of Health of 2 August 2005 no longer apply to the amendments that have not already been communicated, as they are not compatible with the provisions of the Regulation.

The request model defined at European level is used.

The notification must be accompanied by an opinion formulated by an Ethics Committee which expresses an opinion that can be considered valid throughout the national territory.

The evaluation process concludes itself with the formal notification of the outcome by the Ministry of Health (to provide certainty to the deadlines, excluding tacit acceptance).

Provisions applicable to information to be provided after the investigation has started

Starting from the date of May 26, 2021, the provisions of art. 77 of the Regulations, which broaden and better specify what is provided for by the Legislative Decrees implementing the Directives regarding the communications that the sponsor must provide at the end of a clinical investigation or in the event of temporary interruption or anticipated conclusion of the same.

Starting from the date of May 26, 2021 it is applied for an ongoing investigation, the provisions of art. 80 of the Regulation, for the recording and reporting of adverse events that occur during clinical investigations.

To facilitate the transition and give sponsors time to update the Clinical Investigation Plan and procedures, a sponsor may continue to report all serious adverse events until the EUDAMED reporting system is mandatory.

Provisions for digitization and simplification

The submission of applications and notifications, as well as the declarations accompanying them, and still the exchange of information and documents, must take place exclusively using information and communication technologies.

The signing of applications and notifications, as well as declarations, sent electronically, takes place in the manner provided for by the Digital Administration Code.

The people who are entitled to form or submit applications or notifications, as well as the declarations accompanying them, and who have their registered office in Italy or in one of the countries of the European Union, can certify their qualities by means of self-certification deed of notoriety.

Provisions applicable to the participation of Ethics Committees

The identification of the Ethics Committee that can formulate a valid opinion at national level is based on art. 5 of the Ministerial Decree of 8 February 2013 (Criteria for the composition and functioning of the Ethics Committees) and consequently on the Legislative Decree no. 211/2003.

The provisions of art. 7 of Legislative Decree no. 211/2003, on the single opinion in the case of multicentre clinical investigations, constitute the reference for the identification of the Ethics Committee that can express a valid opinion at national level, identifiable in the Ethics Committee competent for the Italian trial centre to which the investigator coordinator for Italy belongs.

In the case of monocentric clinical investigations, or in any case initiated as such, the opinion expressed by the competent Ethics Committee for the trial centre to which the principal investigator belongs can be considered valid at national level.

The opinion of the Ethics Committee which can express valid opinion at national level must be formulated before the adoption of the ministerial decision, due to

- its advisory nature;
- of its mandatory nature;
- of its potential disqualifying effects.

For applications for authorization and notifications of substantial changes not accompanied by the opinion of the Ethics Committee, the Ministry of Health requests the acquisition of the opinion within the deadline set for the adoption of the ministerial decision.

In cases of silence or interlocutory pronouncements, the Ministry of Health requests the formal pronouncement, informing the National Coordination Centre of the Ethics Committees.

In the case of a conditional positive opinion, the conditional clause will be considered as an interim ruling if it is not resolved upon expiry of binding time limits.

Applicable provisions for ascertaining the suitability of structures

Even after May 26, 2021, the legislative provisions relating to the structures where the use of devices not bearing the CE marking that are subject to clinical investigation is allowed remain in force.

- paragraph 5 of Legislative Decree no. 46/97 and paragraph 6 of Legislative Decree no. 502/97
- Ministerial Decree 12 March 2013 and Ministerial Decree 25 June 2014

The forecasts relating to expenses refer to the sponsor, in continuity with the provision for the exemption of health facilities from the expenses deriving from the use of the devices themselves, and in accordance with the nature of the sponsor, who among his responsibilities also assumes that of looking after the financing of the company.

Applicable provisions for the payment of tariffs

Ministerial Decree of 26 January 2005 "Determination of the tariffs for the activities carried out by the Ministry of Health, aimed at authorizing the conduct of clinical investigations".

Applies:

- the procedures for the authorization of clinical investigations (validity of the legislative requirements and continuation of the type of activity that originates the tariff).

Does not apply:

- the procedures for the communication of the initiation of the PMCF investigations (lack of authorization);
- proceedings initiated with notification for the assessment of substantial changes (lack of specific provisions).

Conclusions

This will be a period of intense commitment due to the regulatory innovations which are reflected in the representation indicated below. These innovations will involve both the people we have listed so far, but also the hospital pharmacist whose work too often is overshadowed, but who is regularly engaged in the front line to give feedback on all innovative activities.

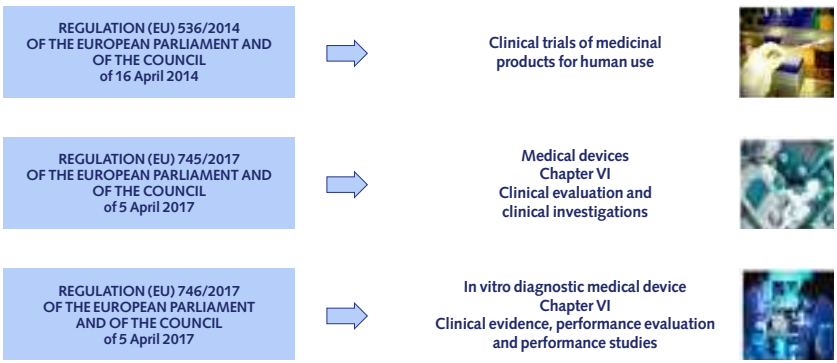


Fig. 7 – A period of regulatory innovations.

Regulation (EU) 2017/745 significantly renews the discipline of medical devices, and clinical investigations are one of the areas in which changes are most felt, due to their close connection to the needs of technological innovation and health protection and security.

The regulations will allow for greater legal certainty and will limit the content heterogeneity of the adoption of regulations relating to medical devices by the individual Member States of the European Union.

It is certainly a very demanding path, in which the commitment of all the players in the medical device system is necessary, but **it is** also a challenge to be faced in the awareness that medical devices is a sector that, thanks to innovation, technological, will play an ever increasingly important role in the process of continuous improvement which is one of the main characteristics of the entire National Health Service.

The pharmacist assumes a considerable and significant role in dealing with all the activities of the case on a daily basis, committing himself as:

- Clinical pharmacist;
- Research Pharmacist;
- Pharmacist expert in pharmacoeconomics;
- Investigating pharmacist;
- Bioethicist Pharmacist – Ethics Committee – Scientific Secretariat for Clinical Trials;
- Pharmacist expert in clinical risk management – pharmacovigilance and device-surveillance.

Bibliography/webgraphy

- Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 relating to medical devices, amending Directive 2001/83/EC, Regulation (EC) no. 178/2002 and Regulation (EC) no. 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.
- Circular May 25, 2021 of the Ministry of Health, Directorate General for Medical Devices and Pharmaceutical Service "Application of Regulation (EU) 2017/745 of the European Parliament and of the Council, of April 5, 2017, in the field of clinical investigations relating to medical devices".
- https://www.salute.gov.it/portale/temi/p2_5.jsp?lingua=italiano&area=dispositiva-medici&menu=sperimentation.

6.2. The point of view of the Hospital Pharmacist: examples and insights according to the directives of Regulation (EU) no. 745/2017

a) The Pharmacist in the New European Regulation of Devices between Innovation and Safety

V. Cola

The Medical Devices (MD) sector plays a primary role in European clinical and health care, contributing to the improvement and protection of health through the development of innovative solutions for diagnosis, prevention, monitoring, treatment, care and rehabilitation of sick people.

Considering the developments in the biomedical sector in the last twenty years, the entry into force of Regulation (EU) 2017/745 and Regulation (EU) 2017/746 has changed the rules governing the system of MDs and medical-diagnostic devices in vitro (IVD), with the primary objective both to ensure a solid, sustainable, transparent and internationally recognized regulatory framework and to improve clinical safety, while fostering innovation and creating fair access to the market for manufacturers.

The need to implement the MD legislation arises from the need to ensure, thanks also to increasing harmonization, the correct functioning of the internal market in the European Union, while improving the quality and safety standards of the MD in a pioneering legislative framework, in support of innovation, which places the EU as the guarantor of public health and patient safety.

The regulations are made up of articulated rules and provide for the possibility of subsequent implementations through implementing acts and interpretative guidelines shared with the EU, thanks to the activity carried out by the Medical Device Coordination Group (MDCG) in collaboration with the European Commission for development of guidelines aimed at ensuring an effective and uniform implementation of the regulation, and with the authorities of the Member States who will have to guarantee its implementation on the territory of the EU.

So, the new MD regulation represents a challenge to be faced in the awareness that MD is a clinical area in continuous and rapid development thanks to a significant technological innovation, which will have an increasingly important role in the healthcare processes of the NHS.

The innovations introduced by the new Regulation (EU) 2017/745 mainly concern the following aspects of the MD:

- Expansion of the application field;
- Identification by the manufacturer of a qualified person responsible for the aspects concerning compliance with the general safety and performance requirements (RGSP);
- EMDN nomenclature for the registration of medical devices in the EUDAMED database (European Database on Medical Devices);
- Unique identification of devices (UDI) with unique numeric or alphanumeric code so as to identify and trace the MDs placed on the market in a clear and unambiguous way;
- Summary relating to safety and clinical performance (SSCP) compiled by Manufacturers and Notified Bodies with updated summary on clinical data and other relevant information on safety and clinical performance of the device;
- Safety and Performance Summary (SSP), prepared by the manufacturer to be submitted to the notified body;
- Strict post-marketing surveillance, in particular, to identify options for improving the usability, performance and security of the MD;
- Reclassification of devices based on risk, duration of contact and invasiveness;
- More rigorous experimental clinical investigations for class III and implantable medical devices;
- Systematic clinical evaluation of medical devices.

From this list of the main innovations of the new Regulation it is clear that the main objective of the regulatory bodies is to have an efficient and updated traceability system of the path of the MD in all areas from clinical trials to marketing. To achieve this goal, the introduction of a European nomenclature of MD was indispensable, so much so that in the meeting of 14 February 2019 the MDCG decided to recognize the National Classification of Medical Devices (CND), conceived by the Italian Ministry of Health as a basis for the creation of the EMDN nomenclature for its peculiarities of facility, purpose, usability and updating methodology. The CND was the starting point for the definition of the European Medical Device Nomenclature, as defined in the Regulations (EU) 2017/745 (art. 26) and 2017/746 (art. 23). The use of the CND allows to have an in-depth knowledge of a sector consisting of numerous highly heterogeneous products, through their homogeneous grouping in specific sectors, according to criteria that allow a comparison between MD, belonging to the same classification segment, even from an economic point of view. It also makes it possible to monitor both the consumption and the use of MDs more effectively and rapidly with

an efficient assessment of incidents comparatively for individual types in the context of supervision. The CND approved with the decree of 22 September 2005 was created by the pharmacists of the NHS. Its continuous updating is still ensured by the Technical Health Committee (section for medical devices, https://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=4446&area=dispositiva-medici&menu=vuoto), there are also pharmacists of the NHS among its members, who carried out the last revision of the CND with the ministerial decree of 10 November 2021. Taking into account all these aspects we can, therefore, highlight the primary role of the NHS Pharmacist in the implementation and management of the EUDAMED database, of the surveillance device as well as in the participation in the meetings of the Ethics Committees, as a MD expert, and in the execution of clinical trials of medical devices. Considering the manufacturer's need to carry out more rigorous clinical studies for class III and implantable MD, the activity of the hospital pharmacist has acquired further relevance especially in the clinical evaluation of the MD which in the coming years will undergo an increase in the number of clinical studies carried out before and after being placed on the market the latter being of particular importance for the evaluation of its performance during the use phase in real world conditions.

b) Regulation (MDR) (EU) 745/2017 and the network of the Medical device vigilance system: the Tuscany Region

A. Garna, S. Asaro, J. Monzillo

Current situation of the Medical device vigilance activity at regional level

In the Tuscany Region, the Medical device vigilance activities are attributed to the Drug Policies and Devices sector within the higher-level structure of the Health, Welfare and Social Cohesion Department. The regulatory reference is constituted by the Directorate for Health, Welfare and Social Cohesion DGRT 790/2016 (*Approval of the Surveillance System on drugs, vaccines and medical devices of the Tuscany Region and allocation of resources*) modified by the DRGT 956/2016, to which reference should be made for the definition of the structure and tasks of the System aforementioned. In this complex and evolving framework, the implementation of the new Regulation (EU) no. 745/2017, which at the European and national level partially modifies the obligations envisaged for the subjects involved in the Vigilance activities, makes it necessary to create a shared information asset that allows to:

- adequately and promptly disseminate information on events that have occurred in the regional context to the Health Authorities;
- support the adoption of appropriate and congruent measures by the regional contracting authority, ESTAR.

The subjects making up the device-vigilance network of the Tuscany region are the following:

- Regional Manager (Responsabile Regionale della Vigilanza – RRV): Vigilance supervisor, appointed by the Region;
- Regional contact person (Referente Regionale – RR): Vigilance contact person, appointed by the Region;
- Local Health Authority-Hospital manager (Responsabile Aziendale-Territoriale – RAV): Territorial-Hospital Manager, appointed by the General Manager;
- Company Representatives (Referenti Aziendali - RA): Company Representatives of the Vigilance of the Hospital or Healthcare Facility to which they belong, appointed by the company Health Director (HD);
- Healthcare Operator (Operatore Sanitario – OS): the person who in the exercise of his functions detects an event related to a MD;
- ESTAR: Regional contracting authority.

Activity of transmission of supervisory information

By the *Drug and Device Policies sector, all safety information and alerts* received by the Regional Health Service from the Ministry of Health are currently being divulged to the Health Authorities. This activity foresees that the Health Authorities concerned are able to certify to the competent Authority and the Manufacturer both the carrying out corrective actions that involve the recall of patients and the acknowledgment of safety communications regarding the use and management of the MD.

The CRFT (Regional Centre for Territorial Pharmacovigilance) interacts with the health structures in order to verify the adequacy and completeness of the reports and prepares a specific report on the Vigilance system reports (adverse events and complaints). The production of the aforementioned information, in addition to responding to regulatory requirements, also has the purpose of supporting ESTAR and users, respectively in the management of contracts and in the appropriate use of the devices.

Structure and meaning of the reports

ESTAR receives complaints from the Health Authorities through the *Help Desk application.* This allows the CRFT to view the reports entered on *Dispovigilance* and the complaints present in the *Help Desk* (ESTAR) application and process the reports that it periodically sends to the Health Authorities and the RRV of the Drug and Device Policies Sector. The aforementioned reports also serve as a verification of completeness (qualitative/quantitative) of the notifications.

Incident reporting activities

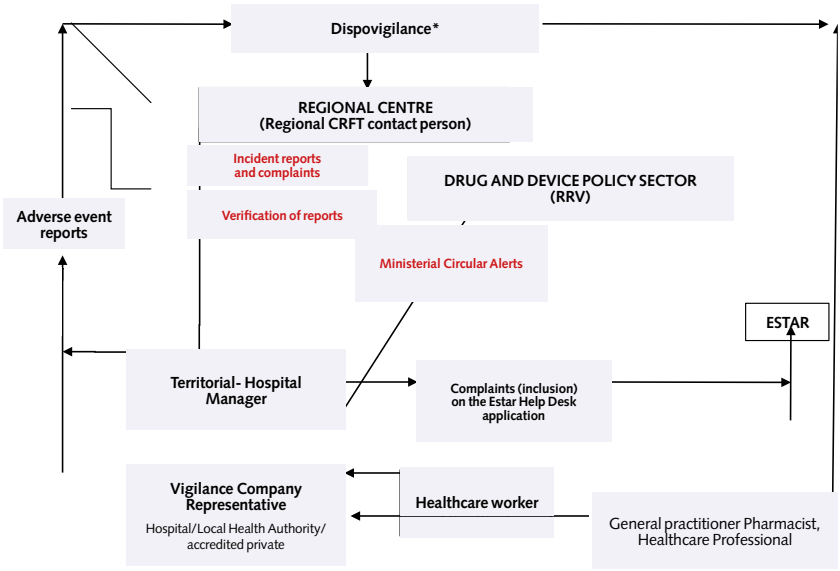
The OS, on the occasion of every incident, even potential, has the task of transmitting the report (operator report) to the Ministry of Health (MdS) through the Dispovigilance application. The RAV takes charge of the report received from the OS and evaluates the adequacy of the data, checks its completeness and correctness. The table below shows the schematic representation of the stakeholders with the various roles.

Table 1

WHO REPORTS IT	WHOM TO REPORT TO
Healthcare worker operating in a hospital/USL/ IRCCS/accredited private facility	RADV of the Hospital/Local Health Authority/ accredited private anzichè Hospital/USL/IRCCS/ accredited private facility that notifies the territorially competent RADV
General Practitioner (MMG – Medico di Medicina Generale) or Free Choice Paediatrician (PLS – Pediatra di Libera Scelta)	It reports autonomously to the Ministry of Health by notifying the RADV with territorial jurisdiction
Public or private pharmacist	
Healthcare professional not employed or contracted (authorized Private Structures)	

Flow chart of the Tuscan regional device-vigilance system

The flow diagram schematically represents the dissemination of the information flows of the device vigilance within the Tuscany Region, as structured in this document.



* Information system for the management of adverse events involving Class and IVD Medical Devices and for the generation of XML files to be sent to the European databank EUDAMED.

The ministerial decree and the Tuscan situation

With regard to the subjects involved in the vigilance-device network identified by the Ministerial Decree (0091486-21/12/2021-DGDMF-MDS-A), the Tuscany Region makes use of Local Vigilance Managers (RLV) stratified on two levels. In fact, the RLV of the area of competence belongs to the Local Health Authority or Hospital, of the single structure or hospital unit (RA) or of the Local Health Authority (RAV) for the Tuscan territorial organization of Local Health Units of AV. The Local Health Authorities in fact include several centres located within the three vast areas: Centre, North West, and South East. Exceptions are the University-Hospitals in which the two figures (RA and RAV) coincide.

The Decree also provides for automatic notification to RLV and RRV by the Ministry of Health, which allows for confirmation of receipt of the validated report, thus allowing this passage to be traced. In a network in which all the passages are known and traced, it is auspicious to further enhance the interaction with the Ministry of Health, to obtain full utility of the information assets deriving from the content of the archived reports, through access to information relating to the whole territory national and not only regional, with anonymity where the law requires it. In essence, it would be a question of making the information on the events that have occurred also accessible to individual health authorities, therefore by means of a different profiling and an expansion of ministerial users to all Tuscan health authorities.

Finally, having acknowledged the complexity of the processes described above, and their progressive implementation, the Drug and Device Policies Sector has activated an e-mail box (e-mail: dm@regione.toscana.it) reserved for all healthcare professionals who intend to ask questions on the methods of application in the Health Authorities of the new Regulation (MDR) (EU) 2017/745, with particular regard to the scope of the device vigilance system.

c) Examples and developments in Pharmacy with MDS: RIAP - Italian Registry of Arthroprosthesis

D. Mamone, R. Sure

Medical Device Registers

The new Regulation (EU) no. 745/2017 concerning Medical Devices (MD) contains a specific article dedicated to Registers (art. 108), which urges Member States to encourage the establishment of Registers and Data Banks on MDs, in order to favour the independent evaluation of safety and the long-term performance of the MDs and to guarantee the traceability of the implantable MDs.

Through the MD registers it is therefore possible:

- Measure the effectiveness of MDs in terms of survival and promptly recall patients in the event of an adverse event being reported;
- Guide surgeons to choose the best performing MDs, thus improving clinical practices;
- Supporting the decisions of administrators, clinicians and patients by providing data on long-term outcomes and cost-effectiveness;
- Having indications about early failures and potential harm to patients;
- Avoid unnecessary and potentially harmful interventions for patients and economically burdensome for health care.

Implantable Medical Device Registers: the Italian Arthroprosthesis Registry - RIAP

The MDs for which the creation of a register acquires greater importance are the MDs belonging to the highest risk classes and, in general, the implantable MDs.

The number of arthroprosthesis implants in Italy in the 2001-2019 period grew steadily, with an average annual increase of 4.2%. In 2019 alone, 220,447 arthroplasty operations were performed. This number, already high in itself, corresponding to an operation every 2.4 minutes, is destined to grow further in consideration of the increase in life expectancy and an ever better quality of life required by patients. It is based on these two considerations that in 2006, the Ministry of Health (MdS), through the Istituto Superiore di Sanità (ISS) (National Health Institute, NHI), started

work on the development of the first national register, the Italian Register of Arthroplasty (RIAP), with the steps shown in Figure 1.

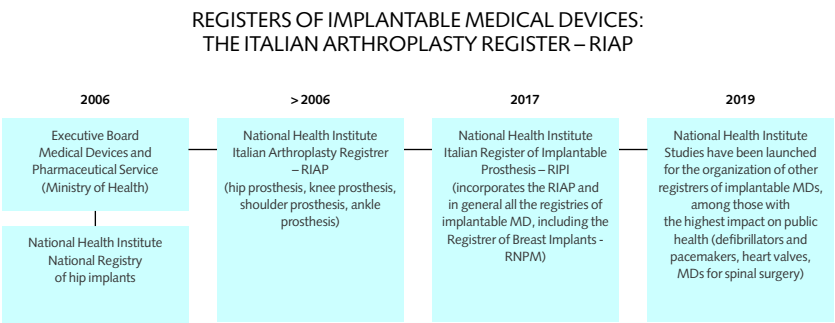


Fig. 1 – Schematic representation of the development of implantable MD Registers over the years from 2006 to 2019.

Initially, the RIAP envisaged to trace exclusively the MD used in the context of hip prosthesis implants. Subsequent implementations have also made it possible to trace the MDs relating to knee prosthetics and, in recent years, also to shoulder and ankle implants.

The growing need to guarantee the traceability of MD and the publication of Regulation (EU) no. 745/2017, in 2017, then favoured the establishment of the Italian Register of Implantable Prostheses (RIPI), which incorporated the RIAP and the other registers dedicated to implantable MDs already active, such as the Register of Breast Prostheses (RNPM), and which will also include all the registers to be implemented soon. In this regard, starting from 2019, the ISS (NHI) has started work on the organization of new registers regarding defibrillators and pacemakers, heart valves and medullary neurostimulators for the treatment of chronic pain (Fig. 1).

RIAP: Pillars

The RIAP is based on the following 3 pillars:

1) Structure as a federation of regional registers that have their own autonomy, but are coordinated at national level by the ISS (NHI), which makes use of an *ad hoc* Scientific Committee (CS) for technical-scientific activities;
2) Data collection based on the use of some information taken from current flows (Hospital Discharge Forms, SDO) supplemented by some additional information;
3) Organization of the Riap-MD Dictionary, a database that contains the

information necessary for the identification and characterization of the implanted MD, fed by the MD database.
(http://www.dati.salute.gov.it/dati/dettaglioDataset.jsp?menu=data&idPag=16).

RIAP: composition of the CS-RIAP

The CS-RIAP is responsible for carrying out the technical-scientific activities of the RIAP project and is made up as follows:

- Representatives of the National Health Institute;
- Representatives of the Ministry of Health;
- Representatives of the Regions;
- Representatives of the Italian Society of Orthopaedics and Traumatology (SIOT);
- Representatives of the Italian Society of Hospital Pharmacy and of the pharmaceutical services of healthcare companies (SIFO);
- Representatives of manufacturers;
- Patient Representatives;
- Secretariat.

RIAP: objectives

The objectives of the RIAP are as follows:

- Keep the use of prosthetic implants under constant control through a timely evaluation of their performance (post-marketing surveillance);
- Protect the safety of patients, promptly tracing those who have been implanted with a medical device subject to recall from the market;
- Interact with the registries already active in other countries.

The Metal on Metal Prosthesis Case (MoM)

In particular, in relation to the second objective abovementioned, the establishment of the register can facilitate the activities carried out by the hospital pharmacist and other professional figures involved in the paths concerning the device surveillance. The case of MoM prostheses can be considered as an example of a situation in which the presence of a dedicated register could have facilitated operations related to a supervisory action. In August 2010 the communication of the voluntary withdrawal by the supplier of the ASR™ Hip System, a hip prosthesis in chromium alloy-cobalt, was announced. The reasons for the withdrawal appear to be detachment of the components due to dislocation, sensitization to the metals released by the prostheses or due to the appearance of pain or periarticular swelling in prosthesis wearers who also have difficulty in walking.

In 2011, the MdS Recommendation (Fig. 2) was released, which draws the attention of all health professionals, executors of the implants, to the importance of inviting patients to undergo specific follow-up programs, in line with what is indicated in the protocol previously suggested by the British Medicines and Health Products Regulatory Agency (MHRA). At the time, the presence of a properly powered national registry, such as the RIAP, would certainly have favoured the tracing and recall operations of the patients involved.

The Prostheses Poly Implant Prosthesis Case (Pip)

Another similar case, which developed a few years later, is that of PIP breast implants. Following an inspection at the production plant of the French manufacturer, it emerges that most of the breast implants produced are filled with a different silicone gel from that described in the technical

MOTIVO DELLA COMUNICAZIONE

RACCOMANDAZIONI DELLA DIREZIONE GENERALE DEI DISPOSITIVI MEDICI, DEL SERVIZIO FARMACEUTICO E DELLA SICUREZZA DELLE CURE

NOTE CONCLUSIVE

Fig. 2 – Communication from the Ministry of Health dated 25 November 2011 on the importance of inviting all subjects with MoM prostheses to participate in follow-up programs to monitor the safety of the implanted MD.

file. In 2010 the supplier decides to declare the suspension of use and the withdrawal of the prostheses. Healthcare professionals are therefore invited by the MdS to quarantine the MDs and report any related incidents. Subsequently, the census of all the PIP prosthesis implants performed since 2001 is required, then the accounting of the implanted patients with the dates of the explantation of the PIPs and the reimplantation of new breast prosthesis.

Data collection was carried out by manually filling in the forms issued by the MdS with the Ordinance of 29 December 2011 (Fig. 3). In this case too, it is evident that the presence of the RNPM register would have facilitated the performance of the analyzes requested by the MdS, guaranteeing a more effective transmission of the data provided.

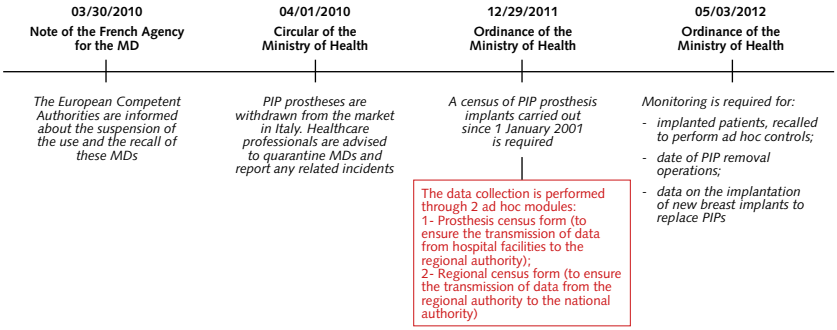


Fig. 3. – Schematic representation of the actions taken by the regulatory authorities to track all patients with PIP prostheses.

The Allergan Prosthesis Case

A few years later, the PIP case is flanked by the case of the Allergan prostheses, which follows a procedure that can be superimposed on that already described above.

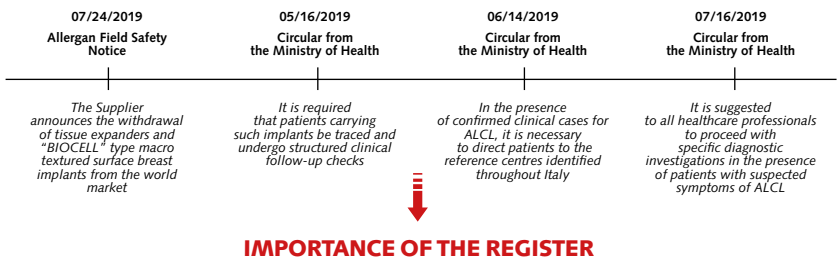


Fig. 4 – Schematic representation of the actions taken by the regulatory authorities to trace all patients with Allergan prostheses and any adverse events.

In fact, in 2019, the CE mark of tissue expanders and breast implants with a macro-textured surface such as "BIOCELL" from the supplier Allergan is not renewed. The reason for this provision is attributable to the possible association between MD implantation and the development of anaplastic large cell lymphoma, a rare form of non-Hodgkin's lymphoma (Fig. 4).

Register of Breast Implants - RNPM

It is in this context that the need for the establishment of a Register of Breast Implants is strengthened which, through the constant archiving of patient data and related implanted MDs, ensures the traceability of MDs and enhances patient safety. Data collection in the RNPM was actually started in March 2019, despite the establishment of the register dating back to an earlier period.

Deliberations

A register, potentially, allows to carry out accurate analyzes concerning the demographic characteristics of the patients, the data relating to clinical practice, the characteristics of the MD. The indispensable condition, for these analyzes to be consolidated, lies in the need to manage registers in full operation, implemented by all the operators involved in a constant and continuous manner. Only in this way can the data deriving from the registers become important tools for all stakeholders.

d) Clinical Trials and the Device Vigilance: the point of view and role of the Pharmacist in the light of the new regulation on MD

F. Vecchione

The world of medical devices (MD) is vast and complex and while the drug has a very long life cycle, that of MDs is, on the contrary, much shorter as technological innovation moves very quickly. It was therefore necessary to update the previous regulations that dated back to the 90s and it was possible to issue this Regulation (EU) no. 745/2017, the application of which, initially scheduled for May 26, 2020, due to the Covid-19 pandemic, was postponed for one year and set for May 26, 2021.

The regulation therefore represents a substantial revision of the previous directives taking into account the developments in the sector over the last twenty years. The aim was to guarantee a solid, transparent, predictable and sustainable regulatory framework for MDs, suitable for maintaining a high level of safety and health, while at the same time encouraging innovation.

The new regulation is much broader, more complex and complete than the previous directives based on the new approach, namely 93/42 on medical devices and 90/385 on active implantable MDs. In fact, it has embraced a whole series of fields that were not regulated before as many MDs did not exist, for example just think of technological innovation in the field of nanomaterials or 3D printing or medical software or they simply needed more stringent legislation.

Furthermore, the European legislator has considered it appropriate to strengthen and expand some key elements, such as the supervision of notified bodies, conformity assessment procedures, clinical investigations and evaluation, surveillance and market supervision. At the same time, it also introduced new provisions that better guarantee the traceability of medical devices. The new regulation is aimed at various stakeholders such as: Member States, competent authorities, notified bodies, economic operators, but it almost never addresses healthcare professionals and healthcare companies, nor does it directly outline the tasks that the latter must perform. Rather, from the tasks and duties assigned to the main stakeholders we can deduce the role and the activities that the health professionals will have to carry out. By health worker we mean any person who carries out health activities and specifically uses MD in the clinical field, in other words professional figures such as the doctor or nurse, and also the pharmacist.

Managing the MD within health facilities (in terms of purchase,

acceptance, dispensing, supervision and experimentation) is not simple as the world of MD has specificities and criticalities that make it difficult to govern, such as product heterogeneity, rapid obsolescence, technological complexity and variability of clinical uses. Precisely because of the complexity of the subject, within the health facilities, it is therefore necessary to set up a multidisciplinary group, made up of different professionals who contribute, each one for their own skills, to the correct management of the MD. This group must include the Company Strategic Management, the user doctor, the nurse, the administrator, the clinical risk manager, the clinical engineer, other professionals, certainly including the pharmacist.

In fact, in this context, the pharmacist, with his competence and knowledge of the subject, must take on a decisive role and, to do so, he must know all the legislation on MD, including the regulation, know how to apply it and always keep himself adequately updated. In particular, we will analyze the importance of the pharmacist in the experimentation of MD and in the vigilance device.

One of the innovations of Regulation (EU) no. 745/2017 is Chapter VI, "*Clinical evaluation and clinical investigations*", because for the first time everything concerning the experimentation of MDs is collected in a single chapter. Previously, there was no univocal legislation on clinical trials but it was very fragmented and from time to time new legislative decrees or new ministerial circulars were issued. Furthermore, in some cases the legislation was not even well defined, so much so that where there was no specific rule, it was referred to the legislation on drugs. In fact, while the legislation on the trials of a new drug has always been very complete, the same could not be said for the regulatory aspects of MD. Therefore, the new regulation has introduced substantial changes by regulating a previously very deficient field. The pharmacist in this area can make his significant contribution. First of all, it would be desirable, precisely due to the peculiarity of the MDs and the complexity of the legislation, the presence of a pharmacist expert in MD both in the Secretariat of Ethics Committees and in the composition of the Ethics Committee itself. In fact, the new legislation on the experimentation of MDs, while closely following that of the drug, differs precisely due to the peculiarities and characteristics of the MD. First of all, these belong to different risk classes for which the type of experimentation is varied. Furthermore, we are not talking about phases, but about pre- and post-marketing experimentation. In addition, other concepts are applicable for MDs, including the principle of equivalence which allows, under certain conditions, not to carry out the clinical trial but to be able to make use of the experimentation carried out on MDs considered "equivalent". Therefore it is essential to know the legislation

on MD and know how to apply it and in this field the pharmacist must assert his own culture and experience.

We must not forget that the first innovation in the experimentation of MDs is represented by the Decree of 8 February 2013 ("*Criteria for the function and composition of Ethics Committees*" - *Official Gazette* no. 96 of 24 April 2013), where for the first time they were included in the composition of the Ethics Committees, two figures who deal purely with MD: an expert in medical devices and a clinical engineer or another qualified professional figure (Article 2 paragraph 5, letter n-o). But the figure of "MD expert" has not been defined, so much so that in many Ethics Committees this role is played by health directors, engineers or clinicians, but also by hospital pharmacists. It is therefore beneficial that in the not too distant future the entry "MD expert" can be changed to "MD expert pharmacist".

Another important chapter of the new Regulation is represented by Chapter VII: "Post-marketing surveillance, vigilance and market surveillance". This chapter is divided into three sections: articles from 83 to 86 are addressed exclusively to the manufacturer, those from 87 to 92 are addressed simultaneously to the manufacturer and the competent Authorities, and finally, articles from 93 to 100 concern only the competent Authorities. Even if not expressly aimed at the figure of the health care worker, everything that must be carried out by the stakeholders in terms of supervision and surveillance of the market and therefore indirectly also by health professionals is illustrated.

The Law of 22 April 2021, no. 53, delegates to the Government the transposition of European directives and the adaptation of national laws to the new Regulations. In fact, important for the purposes of the surveillance device is the Circular of 8 July 2021 in which the Ministry of Health recognizes the key role that health professionals have in the complex surveillance system for the purposes of reporting incidents, and outlines and defines the tasks and the actions to be carried out. But the "surveillance" system consists in the monitoring of the MD in all phases of its life span and is not limited only to the strict reporting of the incident but rather to a series of activities that serve to prevent the incident, avoid that, if has already happened, the same is repeated, and aims to improve the level of protection and safety of patients, users and other figures involved. This objective is achievable through the commitment and collaboration of all the actors. Also in this case the figure of the pharmacist must be central and it is important that he knows the regulations in such a way that he becomes a sponsor, so that within the health company, a series of activities are adopted to ensure that the device is managed in the best way.

First of all, the MDs must be purchased according to the needs of the users and to do this it is necessary to carry out a correct drafting of the technical specifications. It is then necessary to carry out proper supervision during the technical evaluation and acceptance of the products. Finally, it is essential to carry out training so that the MDs are applied according to the instructions for use and the instructions provided by the manufacturer, as well as being installed and maintained correctly.

Therefore, a correct and valid supervisory device is implemented through adequate **training and information** for personnel, because only in this way can **prevention be achieved** which leads to risk reduction. An important role in this whole series of activities is that of the contact person for the device surveillance, a figure introduced by the Ministerial Circular of 2004, but also in this case the professional figure who should perform this function is not defined, even if the circular states "preferably the same person in charge identified for pharmacovigilance ". Certainly, given the peculiarity and heterogeneity of medical devices, this role can and must certainly also be covered by a pharmacist expert in MD, working in collaboration with other stakeholders.

In conclusion, it can be said that the pharmacist has skills, knowledge and experience in the field of MD. However, remembering the words of *Socrates "There is only one good, knowledge, and only one evil, ignorance"*, training and continuous updating to study in this sector is fundamental. However, more must be done so that the hospital pharmacist is recognized, at all levels, the value and skills in terms of knowledge and clinical-regulatory and economic management of MD. In this field, SIFO (Italian Society of Hospital Pharmacy) is very active. In fact, it has set up various scientific and cultural areas, including those dedicated to MD, to the device surveillance, to clinical trials, to legislation, to clinical risk; it also promotes refresher, training and scientific research activities, organizes meetings and congresses; it encourages and initiates collaborations with the Ministry of Health, the Regions, the Health Authorities and other public health bodies and institutions; collaborates in the study of rules useful for improving the professional and legal position of the hospital pharmacist in all fields, including that of MDs.

e) Examples of clinical trials with MD evaluated by the Marche Regional Ethics Committee: possible fundamental role of the NHS Pharmacist

V. Cola

In recent years, several studies with MD have been evaluated by the Marche Regional Ethics Committee (CERM), in which the hospital pharmacist was involved, as a component who played a primary role in improving the design of experimental studies. The synopsis of examples of clinical trials with MD, shown below, are a simple demonstration of the potential essential role of the pharmacist in clinical trials with MD also under the European Regulations 2017/745 and 2017/746.

1) Synopsis of the study "Medical Device Surveillance Register" (PSR) Version 9.0 of 19 May 2020

The study is based on the use of an active, patient-cantered post-marketing registry with an extensible design that allows for the addition of medical devices (MDs) after their release on the market. Patients are enrolled and followed up according to the standard clinical practice of their care centre.

Study Procedures and Evaluations

The PSR is an observational registry platform intended to collect data associated with routine clinical practice, such as demographics, medical history, procedure information, patient status, adverse events, outcome measures, device anomalies.

The evaluation of this study was entrusted to some members of the Ethics Committee, including the pharmacist, as an expert in MD, who led to the suspension of the study since he expressed the following observations to be requested from the Sponsor:

- indicate the types of MD of the supplier company that will be identified for inclusion in the registers (indicate company code/references);
- check if the MD is used at the hospital (temporary deposit account), **an aspect that is the responsibility of the pharmacist**;
- check, if necessary, the involvement of the pharmacy in entering the personal data of the MD (control of the MD used), **an aspect that is the responsibility of the pharmacist**;
- indicate which data and indicators will be reported in the register (technical competence of the pharmacist expert in MD), **an aspect of competence of the pharmacist**;

- indicate the incident reporting procedure and whether periodic safety reports can be sent to the Ministry of Health.

The objectives of the study indicated by the Sponsor are safety and efficacy and post-marketing surveillance of the MD, creating a certain difficulty in its evaluation.

In fact, considering the following objectives:

- Provide a continuous evaluation and periodic reports on the safety and efficacy of the MD released on the market and used according to their indication of use;
- Obtain "real world" performance and safety information from a global network of hospitals, clinics and clinicians intended to represent the range of clinical environments in which MDs are used;
- Conduct post-market surveillance and post-approval studies that are regulated by local governments, or that are conducted to comply with the requirements of government and/or regulatory authorities;
- Obtain clinical evidence to guide the development and improvement of medical devices, therapies, device guidelines, and patient services/ solutions;
- Provide clinical data to support research on health economics and clinical outcomes;
- Identify device failures, adverse event trends/or adverse event.

Further objectives to consider are that the registry can act as a continuous source of data regarding product performance, patient safety and clinical outcomes associated with the use of medical devices already on the market, and allow to:

- Identify device failures, trends in adverse events/or adverse event;
- Characterize patient outcomes;
- Characterize the methods of use of the MD;
- Characterize predictive indicators of performance and effectiveness;
- Identify potential signs of performance problems.

The CERM approved the study, however, highlighting that the PSR-APV is a registry for the collection of data on the use of MD in use in clinical practice regardless of the adoption of the PSR by the structures but it is important to underline that the PSR-APV does not provide safety and efficacy results of MD in clinical practice, but represents only a source of data for conducting appropriate clinical "safety and efficacy" studies on MD.

2) Synopsis of the study "Randomized Clinical Investigation of Non-Inferiority of CRT-DX Systems compared to CRT-D Systems"

Resting heart rate is strongly associated with episodes of worsening heart failure and mortality. Current cardiac resynchronization devices (CRT-Ds) normally provide atrioventricular sequential pacing modes during resynchronization, but the best pacing programming strategy is unclear. On the one hand, a basal rate of 50 to 70 bpm (possibly with a rate response function) could be considered for increasing the dose of therapy, particularly for beta-blockers; on the other hand, increasing the stimulation frequency could partially reduce the benefits deriving from resynchronization, reducing the filling times and contractile reserve. The Pegasus survey is the only large randomized study comparing DDD with baseline rate at 70 bpm with DDD (R) at 40 bpm. The results showed no differences in survey endpoints, including mortality and hospitalization from heart failure. These results would support the use of a device that implements both a CRT function and a single right ventricular catheter with a dipoloatrial (CRT-DX system). This system can monitor ventricular pacing and resynchronization after atrial detection, although it cannot provide atrial pacing support. Therefore, it would be important to assess whether this limitation is counterbalanced by benefits such as a reduced number of catheters required with the consequent simplification of implant procedures and a lower risk of complications. The aim of the investigation is therefore to determine whether atrial pacing support is really needed in the subgroup of patients with CRT-D indication and no evidence of sinus dysfunction under optimal therapy. The investigation proposes to evaluate the hypothesis that a CRT-DX system is not inferior to a conventional CRT-D system in this class of subjects. The study was presented as a prospective interventional multicenter of non-inferiority *Non-Profit.* The criticalities found in this study, approved by CERM, were the presentation of incomplete technical documentation, the need to verify the number of plants envisaged in the study with the number awarded in the tender but above all to consider whether to accept this study as a *Non-Profit.* The conduct of the study did not in any way provide for the involvement of the pharmacist who could instead be a third element for correct and transparent monitoring.

3) Synopsis of the study "Vaporized Ablation for Tumor Lesions Localized in the Lung: Multicentre Prospective Clinical Feasibility Study of Definitive Treatment (Vaporized)"

The treatment of choice for early stage lung cancer is surgery. However, many patients have significant comorbidity that result inoperable. In addition, many patients are at high risk for surgery, such as multifocal, recurrent disease, malignant ground glass opacities, and often the presence of lung metastases. Although these patients may benefit from a circumscribed resection, they are prevented from doing this for various reasons.

Stereotaxic body radiotherapy (SBRT) is considered a possible alternative for some inoperable patients. In some patients, SBRT causes significant toxic side effects and involves a high time commitment, due to the preparation and division of the different fractions over several days. Furthermore, the SBRT requires a significant economic investment for the purchase of equipment and the training of staff, which is prohibitive for many hospitals. Bronchoscopic steam ablation could be a safe and effective tool for ablation of lung lesions using a quick, simple and cost-effective procedure. This bronchoscopic treatment has minimal impact on the patient and may be the treatment of choice for patients with inoperable, recurrent or multifocal disease, such as lung cancer, or with emphysema. The product, in the application foreseen by the indications of use for the treatment of emphysema, received the CE mark from BSI (CE 661757) in March 2017. This technology is now used in the ablation of lung lesions. The preclinical and clinical feasibility analysis seems to indicate this method as a safe and efficient solution for the removal of lung lesions by bronchoscopy, so much so as to suggest the execution of further clinical evaluations and for this reason this study was submitted to the CERM Ethics Committee.

The MD object of the study is the BTVA-C SYSTEM which consists of three main elements BTVA-C generator, BTVA-C water line kit and BTVA-C catheter, supplied by the sponsor who has ascertained the compatibility of these only in a couple of videobroncospi olympus. Unfortunately, the pharmacist was not involved in the logistical and traceability management and it is a pity because he could have offered active support in the execution of the study and in the follow-up of patients in terms of the onset of adverse and side effects.

f) Examples of training activities in the Veneto Region: from the ECM to the post-graduate university course

V. Lolli, MC Giron

In 2021 the Veneto Regional Secretariat - SIFO took charge of the requests presented by some members regarding the need for training on the innovations introduced by the entry into force in May of the new European Regulation on Medical Devices (MD). The articulation of the various chapters and the complexity of the topics covered by the legislation was very difficult to interpret in relation to the vast categories of MD, even for professionals. The application of the new regulation in the drafting of the tender specifications or in the evaluation of the related documentation or in the management of applications for clinical studies led to various interpretative doubts and the rise of a wide variety of questions concerning the correct application of the text to which often an easy applicative answer was found, such as, for example, with regard to classification, traceability and conformity assessment.

By way of example, an in-depth study of the following topics or questions was proposed:

1) *Definitions* (art. 2): what are the most important changes introduced in the definitions. Classification of Devices and Classification rules: what changes (Annex VIII).
2) *Traceability of MDs* by using the mandatory unique identification number (UDI). Deadlines for application of the UDI on the label for the different classes of MD (class III, class IIb, IIa, I). Checks to be carried out by the Health Authorities. Healthcare professionals must register the UDI code upon entry. Operational management of MDs with UDI code (e.g. for class III and implantable). UDI database accessible by healthcare professionals?
3) How do the conformity *assessment procedures* applicable for each risk class of medical devices change pursuant to art. 52 of the MDR (Annex IV and Annex V)?
4) The technical documentation during the tender to be requested by the purchasing Administrations: what to ask for "new" in the tender specifications? For example, following the increased production of clinical evidence (Articles 61-82), what can manufacturers expect for evaluations during the tender?
5) Again, the new regulation introduces a new figure for the Manufacturer responsible for compliance with the legislation (Article 15). Do the tender

specifications starting from May 27, 2021 have to take into account compliance with the legislation?
6) Strengthening of the supervisory and post-marketing surveillance system. What changes for health workers in the field of surveillance. New definitions of incident and serious incident. How to report? New forms? What changes for manufacturers, agents and importers?
7) The transition period and application dates. How to consider the transitional provisions (Article 120)?

Starting from these ideas, with the unconditional contribution of two Venetian companies, Santex and Clinilab, we managed not without difficulty, to put together a group of colleagues plus expert and competent consultants in order to illustrate the new regulatory legislation and seek answers to the expressed training needs, organizing an ECM webinar course, under the patronage of SIFO, with the following interventions.

- Alessia Lazzaro, Vincenzo Lolli, *Introduction*
- Antonella Garna, *General introduction: the new regulation*
- Filomena Vecchione, *Clinical experimentation*
- Daniela Minella, *Supervision of medical devices*
- Roberta Marcoaldi, *Notified Bodies*
- Cecilia Giron, *The new European regulation of MD: innovation and therapeutic safety*
- Mauro Crosato, *Manufacturers and economic operators between rules, competition and the market*
- Riccardo Dainese, *Mandatory and regulatory aspects in the supply chain. Identification and traceability, vigilance and market surveillance*

In particular, the registration of the reports, made by the managers of the regulatory bodies of the Ministry of Health and the National Health Institute, were made available on request to SIFO members enrolled in the webinar. Furthermore, the presence and availability of a social forum in the reserved area of the Sifoweb site was disclosed, created by the working group of the MD - SIFO area in past years, as a useful communication, information and discussion tool that should be re-launched by referring colleagues both for proper management but above all to stimulate profitable interactions between all the professionally interested members. This would allow us to collect useful elements for the in-depth study and understanding of the topics covered in the new European Regulation which can only find a correct and complete meaning and framework only with application in the field and work experience.

Another important updating activity is carried out at the Department of Pharmaceutical Sciences of the University of Padua, with the **Post-graduate**

Advanced Training Course in Medical Devices, established in 2010, usually every two years, and coordinated by Prof. Maria Cecilia. Giron, in collaboration with Dr. Giovanna Scroccaro and Dr. Rita Mottola (Pharmaceutical, prosthetic, medical devices Department - Veneto Region), Dr. Angelo Palozzo (IOV), Dr. Francesca Venturini (Padua Hospital), Dr. Roberta Rampazzo (ULSS 5 Polesana, Veneto Region) Prof. Nicola Realdon (University of Padua) and many other colleagues involved in the management, supervision and experimentation of MD throughout Italy.

The course has been designed in order to provide specific knowledge in the field of general and specialist MDs to pharmacists, doctors and graduates in health or biomedical, or economic-regulatory disciplines involved in the management of MDs in hospitals or in the world of industry.

The operational tools that the course aims to offer to those who work in the medical devices sector are aimed at their correct evaluation, selection, information and use in compliance with current legislation and the clinical needs of patients. Learners who enrol in the Course have the opportunity to acquire the basic concepts of the legislation relating to the entire MD sector (definitions, risk classes, technical standards and compliance of MDs with essential requirements, notified bodies, certifications, methods of clinical trials etc.), and to investigate the evolution of the legislation.

The course provides general concepts relating to the risks associated with the use of MDs (risk analysis, supervisory activities at national level with regional and local applications), clinical evaluation, classification of MDs and the classification system of MDs (software management and its use) as well as the Health Technology Assessment activity with particular reference to the role of the Hospital, Wide Area and Regional Commissions). The in-depth of these topics allows to acquire the necessary tools for the drafting of the tender specifications, the hospital management, the monitoring of consumption and the procurement and storage process of the MD. Ample space is also dedicated to the in-depth study of the characteristics and use of specialist MDs, thanks to exploration sessions with clinical health professionals. The main topics that are addressed during the course related to the world of MD thanks to the teachings held by university professors and experts in the sector are:

- *Current legislation in light of the new European Regulation*
- *Clinical Risk and Device-vigilance*
- *Health Technology Assessment*
- *Clinical trials, compassionate use and off-label use*
- *Logistic management and MD procurement*
- *Innovative MDs*

- *Focus on some categories of MD used in anaesthesia and resuscitation, orthopaedics, cardiology, cardiac surgery, general and laparoscopic surgery, neurosurgery, ENT, tumour pathologies, clinical diagnostics and in specific medications.*

Lessons are held once a month in presence (and, only in case of health emergency, online on the zoom platform), from Thursday afternoon to Saturday morning by university professors, experts and managers of National and Regional Regulatory Bodies, Scientific Societies and Industries of the Sector. Attendance of at least 70% of the lessons of the course is required to be admitted to the final exam which consists in the preparation and presentation of a Power Point presentation aimed at exploring topics addressed during the course or regulatory, managerial, economic, or clinical aspects therapeutic treatment of one or more MDs.

Passing the final exam assigns 10 university training credits (CFU). Under the Continuing Medical Education Program, course participants are exempt from acquiring ECM training credits for the calendar year in which the course was attended. Furthermore, the course constitutes a qualification that can be evaluated in the competitions and admission tests (e.g. Masters, Postgraduate Courses, Specialization Schools, etc.).

Up to now, five editions of the Course have been carried out and have achieved great success in terms of the number of subscribers which has an impact on the workplace for the participants. At the moment, the preparation of the new edition is underway, the announcement of which will be advertised next autumn 2022.

7. Clinical Trials with Galenics and Radiopharmaceuticals and Regulation (EU) no. 536/2014: prospects and findings compared

P. Minghetti, M. Santimaria

1. Alternative therapeutic strategies: the use of medicines without marketing authorization

All medicinal products need a marketing authorization (MA) to assure quality, efficacy, and safety. Marketing authorizations can be granted under a centralised procedure if the drug fulfils Regulation (EU) No. 726/2004[1] criteria, a decentralised procedure, mutual recognition, or a national procedure whether it is comprised by Directive 2001/83/EC[2]. After an evaluation procedure by the EMA or national agencies, marketing authorization is granted. MA is a safeguard for public health; clinicians are meant to prescribe medicinal products within medical indications approved at the time of authorization and listed in the summary of product characteristics and patient leaflet.

However, if the medical doctor believes that medicaments with MA are not the best option for his patient, he can use various strategies (Fig. 1).

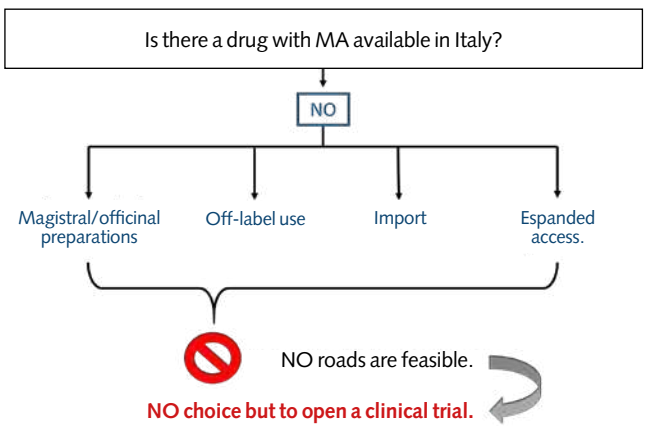


Fig. 1 – Therapeutic strategies available to the clinician.

Magistral and officinal preparations are available strategies, as defined by the EU Directive of 2001, transposed into Italian domestic law by Legislative Decree No. 219/2006[3]. Magistral preparations are defined: "Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient" (art. 3, LD 219/06). In Italy, magistral preparations are governed by the 1934 Consolidated Text of Health Laws (Royal Decree No. 1265 of July 27, 1934) and the appropriate regulation established by Royal Decree No. 1706 of September 30, 1938, as well as Article 5 of Law No. 94/98 (the so-called Di Bella Law)[4]. Doctors are allowed to prescribe, and therefore pharmacists are allowed to prepare, active substances described in the *pharmacopoeias* of EU countries or contained in industrial medicinal products with a European MA or active substances contained in revoked drugs wherein the reason for said revoke is not linked to the product's safety. Magistral preparations of orally administered drugs can include non-pharmaceutical products legally available on the European market (such as supplements). Prescriptions of magistral preparations for external use may include active ingredients contained in cosmetic products regularly marketed in EU countries.

Before starting therapy, physicians' assumption of liability and patients' informed consent acquisition are mandatory when drugs are prescribed outside of approved indications.

Officinal products are medicaments prepared in pharmacies following Pharmacopoeia, whether national or European; a medical prescription is not required for their preparation. Pharmacists prepare magistral or officinal products in compliance with the Good compounding practice (Norme di Buona Preparazione-NBP) described in the current edition of the Official Italian Pharmacopoeia (FU, XII ed.). Radiopharmaceuticals are regulated by specific NBP in nuclear medicine, where the nuclear physician is identified as the responsible person for production, and radiopharmaceuticals are managed by the nuclear medicine facility and not by the pharmacy[6].

Products that cannot be prepared in hospitals as magistral preparations can be industrially produced under Article 5 of Legislative Decree No. 219/2006 also without a marketing authorization. In this case doctors need to file a written application for every single patient with a liability assumption. The permitted active substances are regulated by the above-mentioned laws (Article 5 of Law No. 94/98). Drug quality is assured by the manufacturing authorization issued by a competent authority. Manufacturing authorization certifies that industrial production follows GMP standards. Safety and efficacy are the prescribing doctor's responsibilities.

Another strategy is the off-label prescription of industrial drugs when there

are no approved treatments for a given patient. Physicians' prescriptions are limited to the indication, dosage, and administration route approved in the marketing authorization by the competent authority. However, they can modify the indication, dosage, or administration route for a single patient with a liability assumption and informed consent acquisition. This practice is viable when the doctor believes, on a documented basis, that the treatments approved for that indication, route, or dosage would not be beneficial for the patient. There must be evidence that the proposed off-label use is known and consistent with studies published in internationally recognised scientific journals (Article 3, Law 94/98). However, it is prohibited for the prescribing clinician to use an industrial medicinal product for a therapeutic indication other than the authorised one if favourable phase II clinical trial data for that indication are not available (Article 2, paragraph 348, Law No. 244 of December 24, 2007[7]).

If the right medicinal product is marketed in another country with regular authorization, a physician can import it in accordance with Ministerial Decree 11.2.1997[8], as revised by Ministerial Decree 31.1.2006[9]. Importation is possible if there is no alternative treatment available and should cover a period of less than 90 days. Informed consent acquisition and liability assumption are required.

Medicinal products under clinical trial can be requested from the manufacturer for patients suffering from rare or life-threatening diseases under the Ministerial Decree of 7 September 2017[10], on the basis of a protocol approved by the Ethics Committee and notified to the Ministry of Health. The authorization for use of the medicinal product is granted when the trial data are adequate to form a positive opinion and the medicinal product is the subject, for the same therapeutic indication, of ongoing or completed phase 3 experimental studies (exceptionally for rare diseases phase 2 is accepted), and it has GMP manufacturing certification.

A clinical trial must be undertaken if no legal tactics allow the doctor to obtain a medicine suitable for his patient.

It is defined as a 'clinical trial' when a clinical study fulfils precise conditions, such as the decision to prescribe the investigational medicinal products (IMP) is taken together with the decision to include the subject in the clinical study (Regulation (EU) No 536/2014).

Clinical trials can use:

- investigational medicinal products authorised under Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC;
- unauthorised investigational medicinal products;

- radiopharmaceuticals;
- auxiliary medicinal products needed for the clinical trial, according to the study protocol.

Furthermore, the new Regulation specifies the possibility of conducting clinical studies with pharmaceutical products prepared in hospitals.

2. Regulations for magistral preparation used in Clinical Studies

Before Regulation (EU) No 536/2014's enactment, clinical trials were governed by Chapter III of Legislative Decree No 200 of November 6, 2007[11], which transposed Directive 2005/28/EC[12]. Generally, a manufacturing authorization was required even for partial production of investigational medicinal products. Pharmacies operating in public hospitals or in private scientific care institutions were authorised to prepare investigational medicinal products. Medicinal products for gene therapy, cell therapy, or containing genetically modified organisms and radiopharmaceuticals were excluded (Article 15).

Regulation (EU) No 536/2014 of April 16, 2014, on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC[13], was agreed to reduce differences in regulatory approaches between Member States and enhance international scientific cooperation.

While waiting for the implementing decrees necessary to clarify the Regulation, some preliminary considerations can be made.

As stated in Chapter IX, the manufacturing and import of investigational medicinal products in the European Union shall be subject to the holding of an authorization, and the applicant shall meet the requirements listed in Article 61. Notwithstanding this provision, no manufacturing authorization is required for the following operations: re-labelling or re-packaging, preparation of radiopharmaceuticals used as diagnostic investigational medicinal products, preparation of magistral and officinal products used as IMP (points (1) and (2) of Article 3 of Directive 2001/83/EC) where those processes are carried out in hospitals, health centers or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such processes, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centers or clinics taking part in the same clinical trial in the same Member State (paragraph 5 art. 61).

Member States are responsible to identify appropriate and proportionate requirements to ensure subject safety, reliability, and robustness of the data generated in the clinical trial. They will subject the processes to regular inspections.

In general, investigational medicinal products are manufactured by adopting 'good manufacturing practice' (GMP), however, this does not apply to the above-mentioned operations (Art.63), therefore, in Italy, the Good Compounding Practice (Norme di Buona Preparazione- NBP) for magistral and officinal preparations and the Good Manufacturing Practice (GMP) will continue to apply if the products are prepared by industrial process pursuant to Art.5 of Legislative Decree No. 219/2006.

Although the regulation does not explicitly and precisely define the use of magistral and officinal preparations in clinical trials, it can be inferred that they fall under those products defined as 'unauthorised investigational medicinal products', as they do not meet the standards of either Regulation (EC) No 726/2004 or Directive 2001/83/EC. Article 66 establishes that for the re-labelling of the outer packaging of unauthorised investigational medicinal products and unauthorised auxiliary medicinal products, the following information shall appear:

a) information to identify contact persons or persons involved in the clinical trial;
b) information to identify the clinical trial;
c) information to identify the medicinal product;
d) information related to the use of the medicinal product.

This information shall ensure the patient's safety and the reliability and robustness of the data generated in the clinical trial. Annex 6 lists the information that is to appear on the outer packaging and immediate packaging, including the possibility of limited labelling under certain conditions.

3. Clinical Trials with radiopharmaceuticals

3.1. Future perspectives

In recent years, the amount of innovation in nuclear medicine and the significant contribution of therapeutic application with radiopharmaceuticals has awakened interest in these peculiar drugs and increased their role in the patient's care pathway. Unlike other imaging modalities such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Ultrasonography (US), Nuclear Medicine procedures are capable of mapping physiological function and metabolic activity and thereby giving more specific information about the organ function and dysfunction suggesting indications of physiology, early diagnosis of disease, and treatment response[14].

Recently, but gradually increasing, their application as biomarkers for drug

design (from target identification, pharmacokinetics, pharmacodynamics studies and therapy monitoring), especially for oncology medicines[15].

The identification of new targets, thanks to genetic and molecular biology findings, creates new opportunities for imaging and targeted radionuclide therapies, providing an efficacious approach against cancer[16].

Radiopharmaceuticals production involves handling large quantities of radioactive substances and this makes their management more complicated than conventional medicines, so requiring their production to take place close to the patient use that is immediately before administration to the patient or within a time appropriate to the physical half-life of the radionuclide constituting them. Although numerous radiopharmaceuticals are supplied in a *ready-to-use* form by industrial manufacturers to be used as such for patient administration or where minimal manipulations are required (e.g. decreasing the dosage by expressing off excess volume, diluting the dose), about 70-80% of radiopharmaceuticals used in Nuclear Medicine, are marketed in the form of radionuclide precursors, generators and kits that need to be assembled prior to administration to the patient in a hospital setting[17] depending upon the clinical complexity of the service provision, which is not necessarily dependent on the size or nature of the hospital.

The current routine in nuclear medicine is still mainly driven by "in-house" radiolabelling kits, where radionuclides are added in a nuclear pharmacy to prepare the final radiopharmaceuticals[18] but extemporaneously prepared radiopharmaceuticals are also prepared based on specific clinical need. Activities can therefore range from labelling licensed kits with the eluate of a licensed technetium-99m generator or licensed precursor radionuclide to extemporaneous radiopharmaceuticals, synthesized on site in several steps starting from raw materials and cyclotron produced radionuclides (most radiopharmaceuticals for Positron Emission Tomography (PET) or radiolabelled patient's autologous blood cells).

Due to the widespread application of PET technology, more facilities have been equipped with cyclotrons to produce PET radionuclides and radiopharmaceuticals that typically include radionuclides with half-lives ranging from 2 to 110 minutes, e.g., ^{18}F-Fluorodeoxyglucose or ^{18}F-FDG[19].

In particular for PET radiopharmaceuticals, the current trend for innovative radiopharmaceuticals development often involves manufacturing in hospital radiopharmacy units. Thus, novel radiopharmaceuticals are to a great extent developed at universities and hospitals and are prepared on a *small scale* in a non-industrial setting. This is due to their relatively short shelf life, which typically requires preparation on an extemporaneous basis for individual patients.

In Europe most PET radiopharmaceuticals were developed by independent research groups or university hospitals, that is academic centers without commercial distribution. New radiopharmaceuticals were rapidly implemented in clinical practice in many countries, based on exemptions from the need for a marketing authorization as stated in Arts. 2 and 3 of Directive 2001/83, allowing the 'extemporaneous' preparation of medicinal products (in this case radiopharmaceuticals) based on a prescription for a single patient ("magistral approach")[20].

Despite Nuclear Medicine shown the high potential of novel radiopharmaceuticals in clinical and establishing novel targeted therapies in oncology, the regulatory framework for clinical trials (Directive 2001/20/EC transposed in Italy with Legislative Decree No. 211/2003[21] and Directive 2005/28/EC transposed with Legislative Decree No. 200/2007[11]) have hampered to execute studies with radiopharmaceuticals: the imposition of highly demanding and expensive regulatory requirements (these products have to comply not only with the rules on medicinal products but also with the directions on radiation protection), management, and costs, has made difficult for academia or *no-profit* organization to carry out their own studies and stimulated institutions to face the difficulties raised by scientific societies in the field, especially for *non-profit* studies.

Directive 2001/20/EC applies to every clinical trial on medicinal products (*Investigational Medicinal Products - IMP*), whether sponsored by industry, research organizations or university and contains no exemptions or special provisions for radiopharmaceuticals. It defines the requirement of authorization for manufacturing an IMP, lays down standards for conducting a clinical trial and provides that the manufacture and testing of drugs used in clinical trials must accomplished according with Good Manufacturing Practice (GMP).

However, the transposition of the Directive to the national legislation in the different EU member states, has resulted in many legal variations within Europe and in big differences regarding its application at national level. In particular for the required compliance with the principles of GMP there has been variation between EU member states and there are still differences between countries so making very challenging the use of radiopharmaceuticals within clinical trials across Europe.

To make an example, in Italy, GMP requirements depend on the purpose of the trial, i.e. whether it is commercial or not, and this also holds true for therapeutic radiopharmaceuticals.

The restrictions and limits imposed by Directive 2001/20/EC, firstly the necessity of applying GMP to the manufacturing of radiopharmaceuticals,

have been a major obstacle to the participation of Italian centres to studies promoted by pharmaceutical companies: hospitals don't have industrial status and the health agency can't give this status to healthcare establishment. Thus, for radiopharmaceutical clinical trials involving healthcare establishment for the preparation, control, and release of radiopharmaceuticals, whether or not the final radiopharmaceutical is prepared starting from of a GMP-produced kit and a GMP-produced radionuclide precursor for radiolabeling at the site of administration, Italian legislation does not allow preparation operations to be carried out in a hospital or in academic setting for industrial multicentric clinical trials for registration purposes[22].

In only a few countries have regulatory authorities released documents, addressing the specific nature of these radiopharmaceutical preparations. In Italy, the Nuclear Medicine community recognized need for standards for radiopharmaceutical preparations and a dedicated chapter on radiopharmaceutical preparations in the Italian Pharmacopeia was implemented, the Norme di Buona Preparazione dei Radiofarmaci per Medicina Nucleare (NBPRMN)[23], a set of rules, GMP-like, governing the preparation of radiopharmaceuticals in hospital to be applied also to preparation of radiopharmaceuticals for *no-profit* clinical trials use in centers bound to the National Public Health System both as diagnostics and therapeutics.

To this regard, is noteworthy to underline that Italy, in transposing Directive 2005/28/EC, has inserted in Legislative Decree No. 200/2007 exemption by full GMP application for the preparation and use of radiopharmaceutical IMPs in radiopharmacy units linked to the National Health System with *non-profit* use. Notably, Article 16 allows laboratories – *that manufacture radiopharmaceuticals for nuclear medicine operating in hospital facilities or equivalent to them* […] – to produce medicinal products even in the absence of the provisions of art. 13 paragraph 2 of Legislative Decree no. 211/2003, which requires a Qualified Person being responsible for release of investigational radiopharmaceuticals according to Directive 2001/83 and in compliance with the national standards (namely NBPRMN)[24].

Despite national efforts in the implementation of clinical trials with radiopharmaceuticals, the academic and public worlds have been facing many difficulties, which have resulted in a reduction of research activities in this area, particularly as far as Italy is concerned.

With the intention of overcoming the general negative effects that derived from the old Directive 2001/20 concerning clinical trials, on 27 May 2014 the European Commission issued a New Regulation (No. 536/2014) (Official Journal of European Union, 2014).

The new Regulation on Clinical Trials 536/2014 introduces very substantial changes in the overall authorization procedure for clinical trials and offers new opportunities for radiopharmaceuticals, recognising for the first time that they are peculiar medicines, which is a great step forward compared to the current legislation and will hopefully overcome some of the challenges created by 2001/20/EC.

These changes are:

1. no manufacturing and import authorisation are required to prepare or import radiopharmaceuticals used as diagnostic investigational medicinal products (IMPs) (Art. 61.1);
2. no need to operate in accordance with Good Manufacturing Practice (GMP) to produce diagnostic radiopharmaceuticals for investigational use (Art. 61.5);
3. simplified labelling is permitted for radiopharmaceuticals used as diagnostic investigational medicinal products (IMP) or as diagnostic auxiliary medicinal products (AMP) (Art. 68).

The Regulation established important differences between therapeutic and diagnostic radiopharmaceuticals.

While therapeutic radiopharmaceuticals have no special treatment and are considered in the same way as any other medicinal product used in a clinical trial, the new Regulation introduces some very important exceptions in the field of diagnostic radiopharmaceuticals, exempting hospitals by marketing authorization and by complying with GMP in the case of "*preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State*" (Art. 61.5.b).

Meanwhile, it is clearly stated that the requirement to hold an authorisation for the manufacture or import of investigational medicinal products should not apply to the preparation of investigational radiopharmaceuticals which are prepared to start from licensed products (radionuclide generators, labelling kits and radionuclides precursor) according with the manufacturer's instructions for use in hospitals, health centres, or clinics taking part in the same clinical trial in the same Member State (part 56 of the premises).

The simplification process also includes exemptions in terms of labelling (Art. 68), provided that "*radiopharmaceuticals used as diagnostic investigational medicinal products or as diagnostic auxiliary medicinal*

products shall be labelled appropriately in order to ensure the safety of the subject and the reliability and robustness of data generated in the clinical trial".

The exemption from manufacturing authorization does not apply instead to therapeutic radiopharmaceuticals. For these products, the investigational product(s) should be prepared under official EU GMP standards according to the rules already defined from Directive 2001/83/EC, affecting also small-scale preparations used for research within spontaneous, no-profit programs for hospital facilities and academics as well.

Basically, the new Regulation does not discriminate between *profit* and *non-profit* studies but differentiates between diagnostic and therapeutic radiopharmaceuticals, establishing that hospital facilities are not required to request a manufacture authorisation and to carry out activities in accordance with GMP when production concerns diagnostic radiopharmaceuticals regardless of whether the trial is for registration purposes or promoted by a public or *non-profit* research organization.

All these changes indicate that Regulation in recognizing the unique and special nature of radiopharmaceuticals also considers the real risk for the subjects involved in a clinical trial – where the number of patients and the length of study is limited –, so adapting the regulation burden in relation to the risk posed.

This is true for diagnostic radiopharmaceutical only.

Regulation (EU) No 536/2014 is the first regulatory document of Community value bypassing compliance with Good Manufacturing Practices for diagnostic radiopharmaceuticals prepared and used in hospitals also in the case of trials for registration purposes. However, it also remarks that Member States should ensure equal patient access to effective, safe and high-quality of the radiopharmaceutical used in the clinical trial, as detailed in the following extract of the Art. 61.6: "*Member States shall make the processes set out in paragraph 5 subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial. They shall subject the processes to regular inspections*". It will be in the hand of the national competent authority to tailor the requirements to be applied to ensure the quality of diagnostic investigational radiopharmaceuticals prepared in hospitals, health centres or clinics and this would depend on national legislation.

Therefore, in order to prevent further lack of harmonization, it remains an important task for Nuclear Medicine community in the future to provide a clear position and guidance on this topic and to support the community with a common understanding of the extent of the quality framework for diagnostic IMPs being affected by the exclusion of Art. 61(5)[25].

Both the Regulation and additional documents recently released or in a draft format, such as the guideline on the non-clinical requirements for radiopharmaceuticals published by the European Medicines Agency[26], have recognized the need for a more specific approach for radiopharmaceuticals and for a specific set of rules to be safely prepared, without overproportioned legislation that obstacles the development of new diagnostic molecules for the benefit of the patients[27].

Finally, art. 61.5.b does not exclude the use of prepared IMPs in a different centre than in which they are prepared (whenever it is a hospital, health centre or clinic) with the only condition that they will be in the same Member State. This could facilitate multicenter clinical trials with diagnostic radiopharmaceuticals for which the production of radiopharmaceuticals represents a crucial activity and it is particularly true for radiopharmaceuticals with short half-lives (e.g. ≤ 2 h) that are suitable for use with positron emission tomography scanners.

To clarify some perplexities, the European Commission detailed a document including a series of Q&A on the implementation of the Regulation, which contains specific information related to radiopharmaceuticals and particularly confirms the exemption from GMP compliance for hospital production destined for diagnostic trials[28].

3.2. Critical issues

The EU regulation 536/2014 introduces some important measures that should hopefully contribute to increasing clinical research in Europe and be of benefit for the nuclear medicine community, allowing the use of radiopharmaceuticals in clinical trials in a way that is easier than before. In the field of radiopharmaceuticals, new regulation aims to facilitate the experimental use of diagnostic radiopharmaceuticals, particularly regarding GMP requirements and whether they are trials for registration purposes or *no-profit* use. This certainly will allow the development and availability of new radiopharmaceuticals, including those prepared in nuclear pharmacies of public or academic centres.

However, national authorities are required to work towards full application of the new regulation, in particular concerning the requirements and standards for the production of diagnostic radiopharmaceuticals in clinical trials.

In this framework, in the case of Italy, all indications to implement this new regulation, as well as to regulate the requirements for diagnostic IMPs being affected by the exclusion of art. 61(5) are not yet have been provided at the regulatory level and some issues remain to be solved. To make an example,

the standards and facility adjustments applicable to these preparations when obtained in a nuclear pharmacy, have not yet been completed clarified. Recently, the matter was issued in the Italian Parliament by the Social Affairs Commission[29].

Regarding trials with therapeutic radiopharmaceuticals, the scientific community is also facing with some potential possibilities offered by the Regulation. For example, specific therapeutic radiopharmaceuticals could be considered as magistral or officinal preparations according to the national legislation of the corresponding EU country. In this case, the exception 61.5.c would be applicable, which specifically refers to "*medicinal products referred to in points (1) and (2) of Article 3 of Directive 2001/ 83/EC*" (this paragraph defines magistral and officinal preparations). In addition, the text talks about "preparation", and not "manufacturing" thus acknowledging a risk proportionate approach for a rational and safe advance of nuclear medicine[25].

Therapeutics radiopharmaceuticals that are prepared in accordance with approved regulations and meet approved quality requirements (e.g. as described in a monograph of a pharmacopoeia), could be prepared as magistral or officinal preparation. There are monographs in the European Pharmacopoeia dedicated to therapeutic radiopharmaceuticals that would justify the preparation of the corresponding products as magistral or officinal. Such an interpretation could be fruitful to ensure not only the supply of radiopharmaceuticals but also their clinical applicability and needs an evaluation by the regulatory authorities.

Besides recognising the peculiarities of these medicines, on the other hand it should be stated that the regulation does not reduce the request for *non-profit* sponsors in terms of submission and authorization, documentation to be produced (see the Annexes to the Regulation), pharmacovigilance, insurance aspects, monitoring, except in deserving to *non-profit* sponsors the "low-intervention clinical trials" where additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice. They are subject to less stringent rules as regards monitoring, insurance, and informed consent.

In conclusion, although the new Regulation have recognized, at least at the European level, awareness is grown about the fact that radiopharmaceuticals are really a peculiar group of medicines by seeking to overcome some of the hurdles posed from the previous legislative framework, difficulties still remain in carrying out clinical trials with these drugs, especially in the field of public research. Correct implementation of Regulation 536/2014 could partially overcome this difficulty, at least for diagnostic radiopharmaceuticals to be employed in clinical trials.

To this purpose Faivre-Chauvet et al. wrote: "*The position of hospital radiopharmacy and the "in-house" preparation of radiopharmaceuticals is an important and very specific point and deserves a debate with the worldwide regulators to homogenate the guidelines and thus facilitate the hospital/industry interface. The key to future radiopharmacy success strongly depends on successful harmonization to provide fast development, financial attractiveness, safety, and effective radiopharmaceuticals by "in-house" hospital radiopharmacy units for industrial or institutional multicentric clinical trials. This success, for the benefit of our patients, can only be achieved with the involvement of the different contributors involved at every level in the radiopharmaceutical clinical trials from manufacturing to regulatory approval*"[18].

To allow the Clinical Trials Regulation to become a true opportunity for radiopharmaceuticals development, leading to challenges in patient access to investigational radiopharmaceuticals, it is necessary to engage in a dialogue with authorities and decision-makers in order to constantly point out the difficulties and promote a proportionate approach to risk to ensure the progress towards novel medicines in the coming years. The speed of innovation and high number of developments of ever more radionuclides and radiopharmaceuticals suitable for theragnostic applications, need to increase the mutual understanding of issues in regulatory development of radiopharmaceuticals, so as to be able to guarantee access to patients to increasingly targeted and effective and personalized treatment options.

Taking back to Italy and the impact of NBPMN in the preparation of radiopharmaceuticals for hospitals or academia, it could be of great importance to start a review process, e.g. alignment to the European Pharmacopoeia monograph 5.19 "Extemporaneous preparation of radiopharmaceutical preparations" to come at a more harmonized and rational approaches to provide novel radiopharmaceuticals for patients need.

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8. Law no. 648/1996 and off-label drugs, Law no. 326/2003, art. 48, National Fund for Orphan Drugs and Rare Diseases and Ministerial Decree of 7 September 2017 on "compassionate use"

S. Petraglia

The growing innovation in the pharmaceutical field has led in recent years to an increase in therapeutic options for the treatment of clinical conditions characterized by high clinical unmet need. However, this was accompanied by a parallel increase in the costs incurred by the NHS for accessing new therapies, as well as leaving many conditions without authorized therapeutic options. At the same time, the available evidence on the potential use of drugs already on the market and now of little commercial interest are not applicable to authorize new indications for these drugs in the absence of initiatives in this sense by the companies owning the drug.

In this scenario, early access to innovative drugs and off-label use remain the two options available to respond as quickly as possible to the needs for treatment for conditions without authorized therapeutic alternatives, but also to ensure the sustainability of the SSN (NHS).

Italian legislation addresses these issues with different options, each focused on different approaches, issued over a long period of time and which can be integrated with each other, which create one of the most complete regulatory scenarios in Europe: in strictly chronological order, Law no. 648/96, Law no. 94/98, Law no. 326/2003 (AIFA National Fund), the Ministerial Decree of 15 January 2015 (non-repetitive uses of advanced therapies) and the Ministerial Decree of 7 September 2017 (so-called compassionate use), The optimal integration of the current regulatory provisions can therefore allow a wide range of responses aimed at covering the different situations and clinical conditions and the fragmentation between several regulatory instruments can allow greater adaptability to the specific context for the various clinical situations.

Law no. 94/1998 on the off-label use of authorized drugs

A brief introduction to this regulation is necessary, because it is the mandatory reference for all off-label uses not reimbursed by the NHS, even in the presence of authorized therapeutic alternatives. This is in fact

the standard that defines the criteria and requirements for prescribers of off-label drugs, criteria and requirements therefore also applied for all other methods of early and off-label access charged to the NHS.

The two key elements are the decision and direct responsibility of the clinician (or hospital) in prescribing and using the drug off-label, and the obligation to have available and published evidence from at least Phase II studies. These are usually accompanied, for all accesses on a nominal basis, by the need to acquire informed consent and, where necessary, a favourable opinion from the relevant Ethics Committee.

Law no. 648/1996: use of (non) authorized drugs reimbursed by the NHS

Law no. 648/96 is perhaps the main tool applied in Italy for access to therapeutic options supported by sufficient evidence, in the absence of drugs authorized for the same indication, but also one of the main tools for governing pharmaceutical expenditure, when applied on the basis of to the principles of appropriateness and cost-effectiveness, as per the update introduced with Law no. 79/2014.

This standard allows general access to off-label indications with reimbursement by the NHS, provided that these indications are supported by adequate evidence (at least sufficient data from published phase II studies are required) and a favourable assessment of the relative cost impact. The indications that have access to this method of reimbursement through the SSN (NHS) are included in special lists, published (and regularly updated) on the AIFA institutional portal. The drugs that can be reimbursed through this tool can still be both experimental and commercially available drugs; in this second case, on the market exclusively abroad as well as on the market in Italy, but for other indications or populations. Indications reimbursed through Law no. 648/96, despite having a positive evaluation by the regulatory agency as regards the supporting evidence, remain off-label, therefore they are not included among the indications authorized in point 4.1 of the Summary of product characteristics.

The request for inclusion in the lists pursuant to Law no. 648/96 can be presented by a doctor, a hospital, a scientific society or a Region. The evaluation of the requests is carried out by AIFA, with a mandatory opinion from its Technical Scientific Commission (CTS); subsequently, in the event of a favourable opinion from the CTS, the document relating to the inclusion criteria and clinical monitoring is prepared, together with an impact on the expenditure. In fact, inclusion in the lists pursuant to Law no. 648/96 also provides for the obligation of clinical monitoring and costs, the latter borne by the Regions, which are required to send AIFA a quarterly report. The

monitoring obligation ceases only in the case of "old" drugs, included in the so-called "consolidated use" lists: these are cases with more limited evidence, but characterized by an important and consolidated use in normal clinical practice, to a large extent indications relating to the paediatric population or to onco-haematological conditions.

With this tool, it is also possible to include drugs for which an available and reimbursed alternative is already on the market: in this case, the standard is not aimed at covering an unmet therapeutic need, but rather the need for long term sustainability of the NHS, in fact the requirement for inclusion – in addition to the always necessary robust scientific evidence – is the principle of appropriateness and cost-effectiveness, i.e. a lower cost for the NHS than the alternative authorized for the same indication. The tool that highlights the economic advantage for the NHS, in these cases, is always the evaluation of the impact of expenditure compared to the analogue on the market, which must therefore demonstrate an advantage following the inclusion in the lists pursuant to Law no. 648/96.

Finally, the latest innovation regarding Law no. 648/96, introduced with the decree of 2 August 2019 on the prices of drugs reimbursed by the NHS, is the simplified negotiation of prices for drugs included in the lists pursuant to Law no. 648/96, in order to introduce a further element of expenditure governance also for these unauthorized indications.

Despite the important period of time since its introduction, Law no. 648/96 still proves to be extremely valid and current today, as demonstrated by the constant number of requests received by AIFA over the years.

Law no. 326/2003, art. 48, National Fund for Orphan Drugs and Rare Diseases

The reference law for nominal access to unauthorized drugs is precisely the one established by AIFA as the national competent authority on drugs. One of the provisions contained in this regulation is in fact the creation of an *ad hoc* fund, managed directly by AIFA, based on the payment of the equivalent of 5% of the costs incurred for drug promotion activities by pharmaceutical companies. The fund is dedicated to the purchase of drugs not marketed in Italy, in the absence of therapeutic alternatives and for serious and particular conditions, with particular reference to orphan drugs. Unlike Law no. 648/96, where the reimbursement is for the indication, in this case the law addresses the issue of access for each patient, but always following a favourable evaluation by AIFA of the requests sent by the general practitioner or hospital, or the Region; the request model provides for a close collaboration between the doctor and the hospital pharmacist, who remains AIFA's main interlocutor for all aspects related

to the treatment, preventive and communication management schedule. Another difference with Law no. 648/96 is that in these cases the drug is purchased directly from the hospital and AIFA subsequently reimburses the cost incurred directly to the structure, based on the treatment protocol carried out. Here too, the reference criterion, for the purposes of evaluating the requests, is the presence of published studies of at least phase II, with the exception of rare diseases for which evidence of similar significance may also be sufficient based on the specific disease, in line with the related assessment criteria applied for the same clinical condition at European Agency (EMA) level. This tool has seen in recent years an exponential increase in requests, also linked to the progressively higher costs of innovative drugs which therefore make the use of off-label less and less sustainable for hospitals and regions. The establishing rule does not specifically define the access criteria, unlike Law no. 648/96, for this reason in the course of 2021 AIFA published reference criteria for the acceptability of requests for reimbursement through this Fund, applied in the evaluation phase of new requests.

Ministerial Decree of 7 September 2017 on "compassionate use"

A traditional way of accessing drugs in case of unmet need is compassionate use, which in Italy is regulated by a ministerial decree, which defines the way to access experimental drugs for serious and potentially fatal conditions, in the absence of therapeutic alternatives authorized or available; the decree is in turn based on the very general provisions present in European legislation (Directive 2001/83 for nominal uses, Regulation (EU) no. 726/2004 for compassionate use programs). Compassionate uses can therefore be either on a purely nominal basis or by indication, based on a precise protocol, but in any case, they provide for the availability of the drug free of charge by the owner company.

Also in this case, evidence from at least phase II studies is necessary, although an important exception is envisaged for rare diseases, as much more limited evidence is also sufficient, as long as there is at least one phase I study published with the drug object of the compassionate use and a solid rationale for its use in the specific rare condition by referral clinical centres. It is also possible to apply compassionate use to new indications of drugs already on the market as yet unauthorized, an important innovation compared to the pre-existing standard.

It is important to remember that the pharmacovigilance of drugs used through compassionate use follows the rules provided for drugs on the market and not that of experimental drugs, this precisely because the

prevalent use is related to drugs that have concluded or are about to conclude the registration process.

For compassionate use it is mandatory to acquire in advance – in addition to the availability of the free transfer by the owner company – the favourable opinion of the Ethics Committee of reference. AIFA does not authorize individual treatments, for which it nevertheless receives a notification from the Ethics Committee, while it receives in advance from the pharmaceutical companies and evaluates the protocols of the compassionate use programs, which subsequently publishes on its institutional portal in a specific list. One of the aspects that the new decree has not modified and which sometimes represents a limit for accesses through this tool is the way in which the drug is imported, which is for a single patient and requires periodic renewal. This limit emerged in particular during the pandemic, when the need for an immediate availability of certain drugs, for example in ICUs, was in contrast with the time required for importation for each patient. The state of extraordinary pandemic emergency has made it possible, in these cases, to apply a derogation, this opens up a reflection on the advisability of allowing such derogations even outside the pandemic context, at least for compassionate use programs that involve drugs to be used in urgent conditions.

A completely innovative aspect introduced in 2021 and still to be implemented, is that envisaged by the Consolidated Law on Rare Diseases no. 175/2021, which introduces a new National Fund at AIFA, established with the payment by the pharmaceutical companies of 2% of the expenses incurred for the promotion of drugs. This Fund, among other purposes, also provides for the financing of compassionate use registries of drugs for rare diseases. Compassionate use programs represent, in fact, in addition to an important early access option for patients to new therapies in conditions of unmet need, also an important opportunity for the collection of data from the almost real-life use of new drugs, as well as allowing to the health professionals of the structures involved an early familiarity with sometimes very innovative drugs, with a better ability to manage new therapies in the clinical context at the time of their effective marketing.

9. The Reorganization of Ethics Committees and Technical-Scientific Secretariats in Italy: SIFO's point of view

A. Pisterna, D. Garau, F. Decannas, A. Ucciero, M. Dell'Aera, A. Cristinziano

Clinical trials play a fundamental role in the search for new, more effective and safer medical therapies, and are ethical only if they are conducted in the interest of the scientific community and the community and in full respect of the rights and integrity of the participating subjects. The real revolution introduced with the Declaration of Helsinki and Good Clinical Practices is that clinical trials on humans must be promoted and conducted, but must satisfy conditions:

1) it must produce "knowledge" for the scientific community that can be used for the community (future patients);
2) must respect the rights of the participants and safeguard their integrity;

that is, the interests of science/community cannot prevail over the rights of the participating subjects

The need for "ethical evaluation"

Since the second half of the 1940s, the need has been felt for the formal codification of ethical guidelines for the conduct of research on humans.

With the Nuremberg Trials, which began on December 9, 1946, 20 doctors belonging to the Nazi party were accused of "*war crimes and crimes against humanity*" for carrying out medical experiments on human beings, particularly in concentration camps.

Sixteen defendants were found guilty: seven were hanged and nine sentenced to prison terms ranging from 10 years to life in prison.

The world was shocked by the revelations of the experiments conducted by these doctors: they were studies on the effects of extreme cold, high altitudes, exposure to harmful substances, poisons and infectious agents conducted on humans [Nuremberg Trials].

Since 1945, various texts have been released and used as a reference in the field of scientific research for an appropriate and responsible conduct of clinical trials:

- Nuremberg Codex (1947);
- Declaration of Helsinki (1964);
- Belmont Report (1979).

National reference legislation

With the Ministerial Decree of 27 April 1992, the guidelines of Good Clinical Practice (GCP), referred to in the European Directive, were implemented in Italy, and in the version adopted at European level in 1996 (Ministerial Decree 15 July 1997), they constitute the current regulatory reference from a methodological and ethical point of view. GCPs are an international quality standard for the design, conduct, registration and reporting of clinical trials involving human subjects. Adherence to the GCP publicly guarantees not only the protection of the rights, safety and well-being of the subjects participating in the study, in accordance with the principles established by the Declaration of Helsinki, but also the reliability of the data relating to the study.

The Declaration of Helsinki is a pillar of the ethics of research conducted on man as such or on his biological material or on his identifiable data. In this regard, it is worth highlighting that the Declaration of Helsinki, in the latest revisions, has placed the emphasis on research conducted on biological material, specifying that an informed consent must be acquired for the collection, storage and re-use *ad hoc* and when this is impossible, before the re-use of the biological material for tests other than those foreseen in the *ab initio* research, the relative favourable opinion must be obtained from the Ethics Committee. And this confirms that for the identifiable/coded biological sample, it will never be possible to speak of "donation" by the subject, but of "consent to use", since, at any time, the subject can revoke its future use.

Two other noteworthy passages in the Declaration of Helsinki are:

- that relating to particularly vulnerable subjects, as they are unable to personally grant consent (e.g. minors, psychiatric subjects, etc.): as also stated in the Oviedo Convention, these subjects can be involved in the clinical trial only if it cannot be carried out with comparable effectiveness in subjects capable of expressing consent;
- that relating to Placebo: the use, as a comparator drug, is ethical only in the absence of alternative therapies or as an additional therapy to the standard one or to mask the different pharmaceutical form between the control arms in case of blind design or for minor pathologies.

In parallel with the international ethical documents, a rich and constantly evolving reference legislation has also been developed in our country. Below is an excerpt of the main decrees, which apply to drug studies and, in principle, also to those involving experimental or observational studies with medical devices:

- **Decree of the Ministry of Health of 19 April 2018** - Establishment of the National Coordination Centre of Territorial Ethics Committees for clinical trials on medicinal products for human use and medical devices.
- **Law 11 January 2018, no. 3** - Delegation to the Government for clinical trials of medicines as well as provisions for the reorganization of the health professions and for the health management of the Ministry of Health (Chapter I).
- **Decree of the Ministry of Health of 7 September 2017** - Discipline on the therapeutic use of medicinal products subjected to clinical trials.
- **Decree of the Ministry of Health of 6 December 2016** - Updating of the existing tariffs and setting of tariffs relating for services not yet charged.
- **Determines no. 451 of 2016** - Self-certification of the minimum requirements of health facilities that carry out Phase I clinical trials pursuant to art. 3, paragraphs 1 and 2 of the decision of 19 June 2015.
- **Determination no. 1709 of 28 December 2015** - Updates to the decree of the Ministry of Health of 21 December 2007 containing: "Methods for forwarding the request for authorization to the competent Authority, for the communication of substantial amendments and the declaration of conclusion of the clinical trial and for the request for an opinion to the Ethics Committee ". Comparative table updated D.M. 21 December 2007.
- **Determines no. 809 of 2015** - Determines the minimum requirements necessary for health facilities, which carry out phase I trials pursuant to art. 11 of the Presidential Decree of 21 September 2001, no. 439 and pursuant to art. 31, paragraph 3 of Legislative Decree 6 November 2007, no. 200.
- **Decree of the Ministry of Health of 27 April 2015** - Procedures for exercising the functions relating to clinical trials of medicines transferred from the National Health Institute to the Italian Medicines Agency.
- **Decree of the Ministry of Health of January 16, 2015** - Provisions on advanced therapy medicinal products prepared on a non-repetitive basis.
- **Regulation (EU) no. 536 of the European Parliament and of the Council of 16 April 2014 on** clinical trials of medicinal products for human use and which repeals Directive 2001/20/EC.
- **Ministerial Decree 8 February 2013** - Criteria for the composition and functioning of Ethics Committees.
- **Determines AIFA 1/2013 of 7 January 2013** - Methods for managing clinical trials of medicinal products following the transfer of the function of the competent Authority to the Italian Medicines Agency.
- **Law 8 November 2012, no. 189** - Conversion into law, with amendments, of the decree-law 13 September 2012, no. 158 containing urgent provisions to promote the development of the country through a higher

level of health protection. Text of the decree-law of 13 September 2012, n.158, coordinated with the conversion law of 8 November 2012, n.189 containing: "Urgent provisions to promote the development of the country through a higher level of health protection".

- **Determination no. 9 AIFA 20 September 2012** - Adoption of the CT-3 guidelines (June 2011) of the EC for the implementation of Directive 2001/20/EC, of the ICH E2F guidelines (September 2011) and establishment of a national database on safety monitoring of medicinal products in clinical trials.
- **Ministerial Decree 12 April 2012 (Title II, Chapter I)** - Provisions on the import and export of human blood and its products (art. 8 Importation of experimental medicines).
- **Ministerial Decree 15 November 2011** - Definition of the minimum requirements for contract research organizations (CROs) in the context of clinical trials of medicines.
- **AIFA Resolution 7 March 2011** - Amendment of Appendices 5 and 6 to the decree of the Minister of Health 21 December 2007 concerning the models and documentation necessary to forward the request for authorization to the competent Authority for the communication of substantial amendments and the declaration of conclusion of the clinical trial and to request an opinion from the Ethics Committee.
- **Ministerial Decree 14 July 2009** - Minimum requirements for insurance policies for the protection of subjects participating in clinical trials of medicines.
- **AIFA Determination 23 December 2008** - Self-certification of the minimum requirements of Contract Research Organizations (CRO) in the context of clinical trials of medicines pursuant to art. 7, paragraphs 5 and 6, and of art. 8 of the Ministerial Decree of 31 March 2008.
- **Ministerial Decree of 7 November 2008** - Amendments and additions to the decrees of 19 March 1998, containing "Recognition of the suitability of centres for clinical trials of medicines"; May 8, 2003, containing "Therapeutic use of medicinal products undergoing clinical trials" and May 12, 2006, containing "Minimum requirements for the establishment, organization and functioning of Ethics Committees for clinical trials of medicines".
- **Ministerial Decree of 31 March 2008** (replaced by the Ministerial Decree of 15 November 2011) - Definition of the minimum requirements for Contract Research Organizations (CROs) in the context of clinical trials of medicines.
- **Errata-corrige to the AIFA Determination March 20, 2008** - Press release

relating to the AIFA Resolution March 20, 2008, containing "Guidelines for the classification and conduct of observational studies on drugs".

- **AIFA Determination March 20, 2008** - Guidelines for the classification and conduct of observational studies on drugs.
- **Ministerial Decree of 21 December 2007** - Methods for forwarding the request for authorization to the competent Authority, for the communication of substantial amendments and the declaration of conclusion of the clinical trial and for the request for an opinion to the Ethics Committee.
- **Legislative Decree no. 200 of 6 November 2007** - Implementation of Directive 2005/28/EC containing detailed principles and guidelines for good clinical practice relating to investigational medicinal products for human use, as well as requirements for the authorization of the manufacture or import of such medicinal products.
- **Ministerial Decree 12 May 2006** - Minimum requirements for the establishment, organization and functioning of the Ethics Committees for clinical trials of medicines.
- **Ministerial Decree 17 December 2004** - Prescriptions and conditions of a general nature, relating to the execution of clinical trials of medicines, with particular reference to those for the purpose of improving clinical practice, as an integral part of health care.
- **Legislative Decree no. 211 of June 24, 2003** - Implementation of Directive 2001/20/EC relating to the application of good clinical practice in the execution of clinical trials of medicinal products for clinical use.
- **Ministerial Decree of 8 May 2003** (replaced by the Ministerial Decree of 15 November 2011)- Therapeutic use of a medicinal product undergoing clinical trials.
- **Ministerial Circular of 2 September 2002, no. 6** - Activities of the Ethics Committees established pursuant to the Ministerial Decree. March 18, 1998.
- **Decree of the President of the National Health Institute of April 26, 2002** - Assessment of the composition and harmlessness of newly established drugs before clinical trials on humans. Identification of the documentation to be submitted to the National Health Institute pursuant to art. 4, paragraph 2, of the Presidential Decree of 21 September 2001, no. 439
- **Decree of the President of the Republic no. 439 of 21 September 2001** - Regulation for the simplification of procedures for the verification and control of new therapeutic and experimental systems and protocols.
- **Ministerial Decree of 30 May 2001** - Inspection assessments on compliance with the rules of good clinical practice.
- **Ministerial Decree of 10 May 2001** - Controlled clinical trial in general medicine and paediatrics of free choice.

The path of clinical trials

1) Clinical trial

The trials are characterized by the active intervention of the investigator. By clinical drug trial we mean "*any human study aimed at discovering or verifying the effects of a new drug or an existing drug tested for new therapeutic uses, with the aim of ascertaining its safety or efficacy. The experimentation is divided into different phases and is carried out first in the laboratory and in animal models (preclinical experimentation) and then on humans (clinical experimentation)*" [AIFA].

- **Before the session of the Ethics Committee**

In case of drug experimentation, the sponsor sends the protocol and all the documentation to the AIFA (Competent Authority) by uploading it to the portal of the National Observatory on Clinical Trials of Medicines (OsSC), which is the operational tool for the management of the authorization process for clinical trials (Phase I-IV) taking place in Italy. In parallel, all documentation must also be submitted to the Ethics Committee of the coordinating centre and to the Ethics Committees of the satellite centres (in the case of multicenter studies).

- **Activities of the Technical-Scientific Secretariat (TS Secretariat)**

Before the meeting, the TS Secretariat has the task of verifying the formal completeness of the documentation relating to the submitted protocols. For the purposes of the evaluation in collegiate session, he prepares evaluation forms that summarize the essential points of the study useful for the pre-evaluation of the ethical-scientific congruity of the clinical trial itself and assigns at least one supervisor to each study. In collaboration with the President, if necessary, he assigns the evaluation of any clinical studies to experts outside the EC, vice versa to a specific member as speaker.

- **After the collegiate session**

The TS Secretariat draws up the minutes of the session and sends the opinions to the relevant Offices that deal with the subsequent Authorization Resolution/Definition, for the start of the trial.

2) Observational Studies

They are characterized by the absence of active intervention by researchers, who limit themselves to observing the phenomena.

The procedure summarized above is essentially the same with the exception of uploading to OsSC as this part is only provided for experimental studies with the drug. Only in the case of observational studies with drugs, these must be notified in a telematic way to AIFA for the census in the

National Observational Study Register by filling in the appropriate form, which must be presented when submitting the study to the competent EC (see "Guidelines for the classification and conduct of observational studies on drugs" prepared by the AIFA).

Activities of a TS Secretariat: the example of the Intercompany CE of Novara

The TS Secretariat of Novara International Ethics Committee uses an IT platform, accessible from the dedicated web page, where external users can connect.

The website, through which the portal is accessed, is https://comitatoetico.maggioreosp.novara.it/.

The portal is managed by an external company, which provides IT support to the members of the Ethics Committee itself and to users for uploading the studies, if necessary: https://isharedoc.maggioreosp.novara.it/pce-server/webui/login/.

The sponsor registers on the EC web portal and uploads all documentation, including the CA's authorization. Once the documents have been loaded into the system, the study is submitted and ready to be taken over by the STS. The STS checks all the documents and sends any requests for integration, in case of deficiencies/inconsistencies. When the study is "complete", it is included in the first useful date for the collegial assessment.

At the end of the session, the minutes are produced, showing all the individual opinions discussed collectively, which are also uploaded to the web platform on the page of each individual study.

Finally, the TS Secretariat sends the minutes to the members, transmits the opinions to the CA of reference and enters the data of the clinical trials with the drug in the OsSC. Under the current legislation, the competent Authority is no longer the General Manager, but only AIFA!

It also takes care of the paper and computer archiving of all documentation.

Periodically, on the basis of the data extracted from the IT databases of the TS Secretariat, a report is drawn up which summarizes the activity data of the clinical studies submitted for the opinion of the EC of Novara.

Website - activity report: https://comitatoetico.maggioreosp.novara.it/attivita/report-attivita/.

Starting from 2017, a systematic recognition of the therapeutic uses was started, the so-called compassionate use protocols pursuant to the Ministerial Decree of 7 September 2017, starting from their approval until the possible interruption of treatment. To this end, an active dialogue was established with the clinician, who was asked to provide a periodic report on the start, progress of treatment or clinical outcome.

Indicators of "process" (temporal trend in terms of starting and/or ending the use of the drug) and "outcome" (in terms of improvement or otherwise of the patient's clinical condition) were identified.

Website - therapeutic use report 2020: https://comitatoetico.maggioreosp.novara.it/attivita/report-attivita/report-usi-compassionevoli/.

- **Voluntary Harmonization Procedure - VHP**

The main objective of Regulation (EU) no. 536/2014 is to streamline and simplify the procedures that will be integrated and coordinated at European level.

The evaluation of the trials will be coordinated by a single national Competent Authority, which will act as the contact person and which will provide a first evaluation of the study, on the basis of which the Competent Authorities of the other Member States will provide their comments and their final decision on authorization. This coordination between the European drug regulatory agencies will lead to the authorization of an identical study protocol in all the states involved.

In fact, the arrival of new therapies (think of biologics and drugs for rare diseases, whose case series is by definition very limited) has required the need to formulate more robust data, obtainable only with an adequate sample size. For this reason, companies have started looking for many centres in different EU states.

This need therefore required regulatory harmonization of the authorization procedures present in the various States. In this context, Italy has taken steps to be competitive in the European challenge, with two pilot projects: the Voluntary Harmonization Procedure (VHP), which involves the CE and AIFA, and the Fast Track, which instead involves the Ministry of Health and AIFA, and has instituted a fast procedure for evaluating drug trials. The VHP pilot project will be detailed below.

Voluntary Harmonization Procedures – VHP

Definition

"… a procedure applicable on a voluntary basis for multi-centre phase I-IV clinical trials, which are conducted in multiple EU member states, and which allows the coordinated evaluation and authorization of clinical trials in a single contemporary solution for all the states involved in the trial".

Guidelines on the operating procedures of the project for use by Ethics Committees and Sponsors who want to join the pilot project - Version 1.0

Talk about VHP had already begun prior to the new Regulation (EU): in 2004, in fact, the Directors of the EU drug agencies decided to set up a group, called Clinical Trials Facilitation Group (CTFG) with the aim of coordinating and standardizing the conduct of multinational clinical trials in the Member States [*Guidance document for sponsors for a Voluntary Harmonization Procedure (VHP) for the assessment of multinational Clinical Trial Applications*]. This group drew up a document where, for the first time, there was talk of harmonization procedures.

In 2013 AIFA became the National Competent Authority for the evaluation/authorization of clinical studies. In May 2016 the Italian pilot project started, to involve the CEs, excluded from the initial VHP. VHP means a procedure applicable on a voluntary basis for multicentre Phase I-IV clinical trials, which are carried out in several EU Member States, and which allows the coordinated evaluation and authorization of clinical trials in a single simultaneous solution for all states involved in the trial.

SUBJECTS INVOLVED

OUTCOME OF THE EVALUATION

1. To be approved;
2. Not to be approved;
3. Approval subject to condition

The Sponsor requests the VHP assessment from the VHP-Coordinator and selects the CE Coordinator from the list provided by AIFA. If CE collaborators are involved, the sponsor sends the relative documentation for the VHP procedure and, as soon as available, the centre-specific documentation.

During the VHP process, the sponsor chooses a competent authority of reference (AC-Reference) which will carry out all the technical-scientific assessments and will then draw up an Assessment Report (AR) which will be sent to all the other competent authorities involved.

VHP can have one of the following outcomes:

1) can be approved;
2) not to be approved;
3) can be approved with conditions.

In the latter case, the procedure closes with the positive opinion of all the competent Authorities, but the approval is subject to one or more conditions that the Sponsor must comply with before the closure of the procedure. In this case, the timing extension is envisaged.

GLOSSARY

VHP-C: VHP Coordinator
CTFG: Clinical Trial Facilitation Group
AR: Assessment Report
DAR: Draft Assessment Report
CA: Competent Authority
NCA: National Competent Authority
Ref-NCA:Reference NCA
GNA: Grounds for Non-Acceptance

CTFG/VHP/2013/Rev3 March 2016

The conditions derive from what is reported in the ARs. In fact, these are accompanied by a list of "queries", objections and criticalities in the final phase: the Grounds for Non Acceptance (GNAs). The NCAp and CE also participate in the drafting of the GNAs but the final list will be sent to the sponsor by the Reference-NCA.

The documentation that is evaluated within the VHP project is essentially represented by the *core* of the project: General information (Cover Letter containing EudraCTnumber, CTA form, List of NCAs involved); information relating to the Protocol: Protocol including synopsis in English; information relating to the IMP: IMPD, IB; information relating to NIMPs; Additional information: Scientific advice and PIP summary report (if applicable). Centre-specific documentation is not covered by the VHP and therefore will not be evaluated.

DOCUMENTS EVALUATED*

General information – Cover Letter, EUDRACT, CTA form, list of NCAs involved
Protocol information and synopsis
Information related to the **IMP** – IMPD, IB
Information relating to I**NIMP**
Additional Information – Scientific Advices and PIP summary report (if applicable)

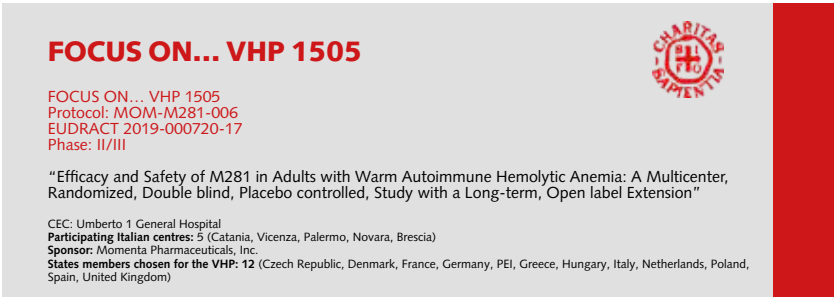
* The specific documentation centre is not subject to the VHP and therefore will not be evaluated

To ensure that the requests for evaluation submitted through VHP are not delayed, AIFA has sent the guidelines that describe in detail the operating procedures that must be followed during the joint evaluation activity, with

the relative deadlines to be respected by all the subjects involved. We have three successive phases for a total amount of 90 days. In the event of "conditional approval", an extension of the timing is envisaged in the transition between the second and third phase.

- **Experience of a local VHP CE**

Taking an example of the application of VHP procedures in the Novara Ethics Committee, we can consider an experimental study submitted for evaluation in a harmonized procedure in the second half of 2019 (protocol code VHP 1505).



This is a phase II/III clinical trial entitled "*Efficacy and safety of M281 in adults with warm autoimmune haemolytic anaemia: multicentre, randomized, double-blind, placebo-controlled study*".

It is a multicentre, randomized, double-blinded, placebo-controlled Phase 2/3 study to evaluate the efficacy, safety, tolerability, PK and PD of M281 compared to placebo. WAIHA is a rare disease and is the most common form of autoimmune haemolytic anaemia, characterized by the presence of hot auto-antibodies directed against red blood cells. The conventional treatment of this pathology is represented by corticosteroid therapy, which is not free from long-term side effects. Second-line treatments are based on immunosuppressive drugs, such as azathioprine, cyclophosphamide, and rituximab. However, these too can have severe side effects. The study aims to evaluate the efficacy and safety of the M281 monoclonal antibody for the treatment of these patients.

The chosen EC Coordinator was at the General Hospital Umberto I in Rome, the Italian centres involved were 5 and the European Member States involved 12.

The enrolment of 2 patients in the haematology department of the major university hospital of the Novara charity was envisaged.

Let's go over the details of the timescales that have taken place over the course of 3 months:

- in June Novara agreed to the project, subsequently the TS Secretariat received the TA to have the members enter the comments. Once completed, this was forwarded to the CEC;
- in mid-August the list of general objections received led to conditional approval. Consequently, the sponsor amended the protocol, which was sent back to the Ethics Committees, with a request for either accepting or not the additions made. The revised protocol was accepted by the CEC and by AIFA;
- finally, the EC of Novara gave a favourable opinion in the meeting of 27 September.

In particular, the objections raised by our members were related to the study design. Objection: "In paragraph 5.9 of the protocol, it is stated that the site is responsible for providing the placebo for the trial. How does this statement reconcile with the maintenance of the double-blind study?".

From a comparison with the STS of the CEC of the General Hospital Umberto I in Rome it emerged that other CEs had raised various objections. In fact, a conditional approval has been formulated. This document contains the cover letter signed by the sponsor, produced in response to these objections.

FLOW CHART – VHP 1505

- **7 June:** VHP evaluation availability requested by CEC Rome
- **11 June:** CEI Novara membership
- **June 13:** reception of "Template Assessment" blank for insertion of CEI Novara comments
- **25 June:** submission to the CEC of the "Template Assessment" filled in with comments

The study receives conditional approval

- **19 August:** AIFA sends the documents relating to the approval on condition of the study to the CEC
- the CEC forwards them to the CEI Novara, with a request for feedback
- **21 August:** CEI Novara responds by accepting the additions (new protocol)
- **19 September:** the sponsor sends the approval of AIFA and the CE Coordinator to the CEI Novara (uploaded on OsSC), with a request for approval within 20 days

The study was approved on 27 September 2019 by the CEI of Novara

The Ethics Committee: definition

(Article 2, paragraph 1 letter m)

According to the Directive of the European Parliament 2001/20/EC, the Ethics Committees are defined as independent bodies, composed of healthcare and non health figures, which are responsible for guaranteeing the protection of the rights, safety and well-being of the subjects of the trial and to provide a public guarantee of this protection, for example by issuing

opinions on the trial protocol, on the suitability of the investigator (s), on the structures and on the methods and documents to be used to inform trial subjects before obtaining informed consent.

The ethical, scientific and methodological evaluation of clinical studies by the Ethics Committee refers to the provisions of Legislative Decree 24 June 2003, no. 211, from the Declaration of Helsinki in its most updated version, from the Oviedo Convention, from the rules of good practice and from the updated guidelines of the European Agency for the Evaluation of Medicinal Products regarding the evaluation of the efficacy of Clinical Trials (fig. 1).

Fig. 1 – Regulatory evolution of Ethics Committees in Italy.

The regulatory evolution of the Ethics Committees has had some keystones, starting with the decrees of 1992 and 1997, transposing European directives, aimed at standardizing the paths and documentation to be presented for study protocols and which provide important legends for univocal definitions between the different professionals. The legislative decree of 2003 updates the previous legislation, introducing the concept of experimentation on minors and on subjects unable to express their consent, up to the Balduzzi law decree and the Lorenzin law, which represent a further boost to have a homogeneous behaviour in Italy, as in the rest of Europe.

All the aforementioned legislation defines the tasks and responsibilities of the local Ethics Committees, always remembering that the protection of the rights of the subjects must be placed at the centre of any clinical research evaluation (fig. 2).

Fig. 2 – Functions.

Evaluation elements for the purposes of the EC opinion (Article 6, paragraph 2 of Legislative Decree 211/2003)

1. relevance and methodological correctness of the proposed study;
2. favourable risk/benefit ratio of the proposed treatment;
3. methods of informing the patient and obtaining informed consent, as well as the justification for research on people who are unable to give their informed consent (vulnerable subjects);
4. competence and qualification of the investigator and of the personnel involved;
5. suitability of the structures in which the experimentation takes place;
6. possible conflicts of interest;
7. use and dissemination of results;
8. eligibility of insurance coverage, if applicable;
9. economic aspects: the costs of the trial must not be borne either by the patients or by the National Health Service.

Hereby are reported the points referred to in the Ministerial Decree of December 2007 (Appendix for the release of the PU) and with the assessments required of the EC by the Ministerial Decree of December 17, 2004 on independent research (Fig. 3).

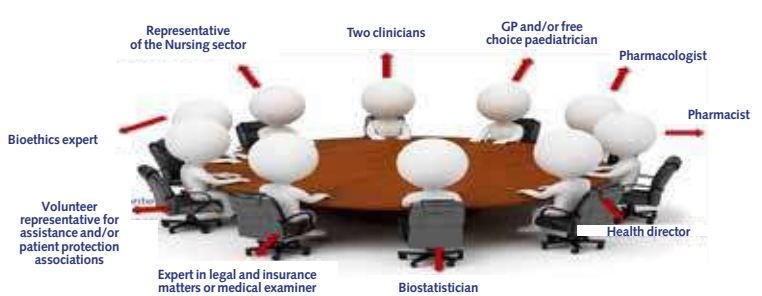


Fig. 3 – Minimum composition of the Ethics Committee (Ministerial Decree 12/5/2006).

Law 8 November 2012, no. 189 "Balduzzi law" - Chapter III - Provisions on drugs

Article 12, paragraph 10
Reorganization of Ethics Committees:

a) a committee for every million inhabitants, without prejudice to the possibility of providing for an additional Ethics Committee, with competence extended to one or more scientific hospitalization and treatment institutes;

b) the choice of committees to be confirmed takes into account the number of single opinions for clinical trials of medicinal products issued over the last three years.

With regard to the composition, the decree of 2013 introduces, compared to the previous Ministerial Decree of 2006, new professional figures, to be consulted in specific study settings, as well as expanding the number and components, not only in the health sector.

The same decree brings together the two components of the secretariat, in a single technical-scientific type (Figs. 4-5).

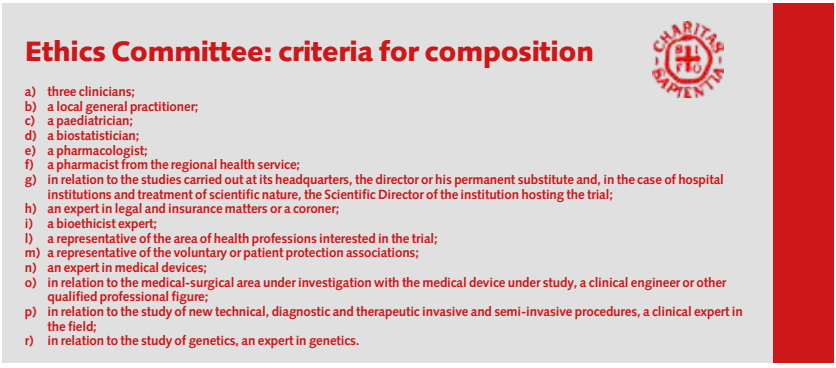


Fig. 4 – Ethics Committee: criteria for its composition.

Fig. 5 – Current composition of the Ethics Committee.

The role of the Pharmacist within the Ethics Committee

The pharmacist does not issue opinions, the issue of the opinion is collegial!

In this context, the pharmacist's activity can be divided into three roles (Fig. 6):

- the one specific to his profession, which manages experimental drugs, documenting all the phases, from receipt in the hospital pharmacy warehouse to delivery to the ward. Not disjointed there can be the activity of galenic preparation.
- member of the Ethics Committee itself, as a pharmacist, or as an expert in medical devices;
- member or manager of the technical-scientific secretariat.

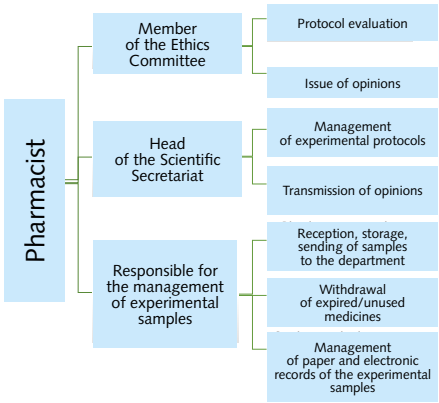


Fig. 6 – The three roles of the Pharmacist.

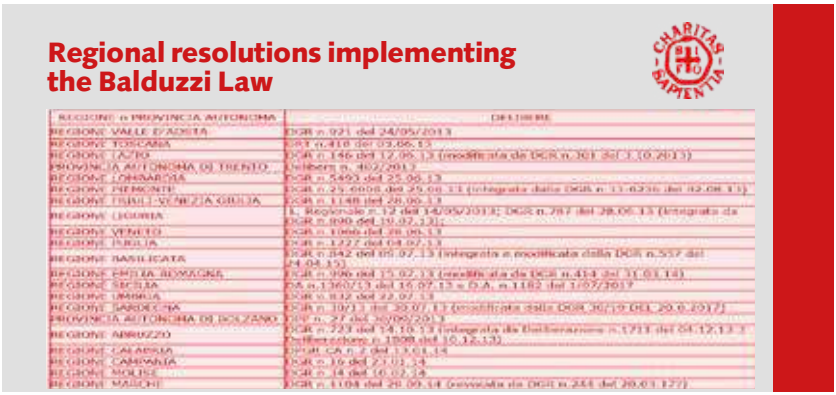


Fig. 7 – Regional resolutions for the implementation of the Balduzzi Law.

Law 11 January 2018, no. 3, "Lorenzin Law"
Entry into force of the Law 15 February 2018

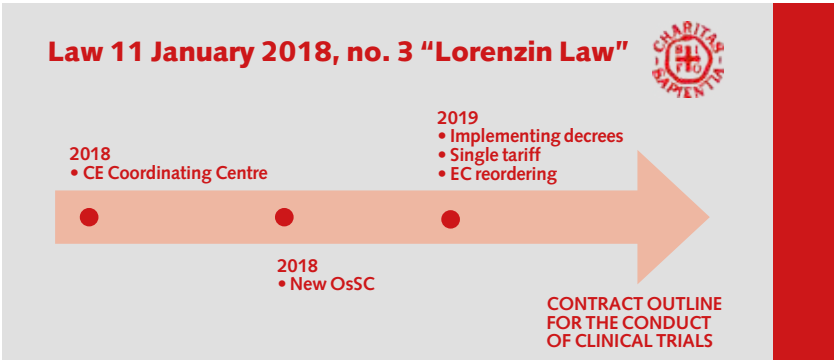


Fig. 8

Art. 1
Delegation to the Government for the reorganization and reform of the legislation on clinical trials within twelve months, from the date of entry into force of this law

- Legislative decrees must be adopted for the reorganization and reform of the provisions in force concerning clinical trials of medicinal products for human use, introducing specific reference to gender medicine and paediatric age;
- identification of the requirements of the centres authorized to conduct clinical trials from Phase I to Phase IV, with preference for centres that ensure, in Phase IV, the involvement of patient associations;
- identification of the methods for supporting the activation and optimization of clinical centres dedicated to Phase I clinical trials, both on patients and on healthy volunteers, to be conducted with a methodological approach of gender medicine, providing for the definition, by decree of the Minister of Health, of the minimum requirements for the same centres also in order to have a more homogeneous presence on the national territory;
- identification of suitable methods to protect the independence of the clinical trial and to guarantee the absence of conflicts of interest;
- simplification of purely formal requirements regarding the methods of submitting the application for the opinion of the Ethics Committee and conducting and evaluating clinical trials;
- simplification of procedures for the use for clinical research purposes of biological or clinical material residual from previous diagnostic or

therapeutic activities or any other title held, subject to the provision of informed consent;
- definition of the evaluation and authorization procedures of a clinical trial, ensuring the involvement of patient associations, especially in the case of rare diseases;
- guarantee that those in charge of validating and evaluating the application are free of personal and financial conflicts of interest and ensure their impartiality by means of a declaration made pursuant to Articles 46, 73 and 76 of the consolidated act as per Presidential Decree 28 December 2000, no. 445;
- the establishment, at the National Health Institute, of a national list of qualified individuals with adequate experience, selected through public notices, on the basis of predefined criteria and requirements;
- the definition of procedures for verifying the investigator's independence

Reorganization of the Ethics Committees
1 National Coordination Centre (CCN) of Territorial Ethics Committees
40 Territorial Ethics Committees
3 Ethics committees of national significance
- **one reserved for experimentation in the paediatric field;**
- **they perform the same functions as the Territorial Ethics Committees.**

Art. 2 National coordination centre of Territorial Ethics Committees for clinical trials on medicinal products for human use and medical devices
Paragraph 1
The National Coordination Centre of Territorial Ethics Committees for clinical trials on medicinal products for human use and medical devices, hereinafter referred to as the "Centro di coordination" (Coordination Centre), with functions of coordinating, directing and monitoring of the activities of evaluation of the ethical aspects relating to clinical trials on medicinal products for human use delegated to the territorial Ethics Committees […].
Composition of the Coordination Centre
Maximum fifteen members, of which two indicated by the Conference of Regions and Autonomous Provinces, two indicated by the most representative patient associations at national level

The members of the Coordination Centre are appointed by decree of the Minister of Health and, except for those who represent patient associations, must have documented knowledge and experience in clinical trials of medicines for human use and medical devices, in accordance with the competences identified by the decree of the Minister of Health in *the Official Gazette* no. 96 of 24 April 2013.

The **members of the Coordination Centre must not be in conflict situations,** they must be independent from the sponsor of the trial, from the clinical trial site and from the investigators involved, as well as from the financiers of the clinical trial.

The presidents of the National Bioethics Committee, the National Committee for Bio safety, Biotechnologies and Life Sciences and the National Health Institute participate in the meetings of the Coordination Centre.

Ministerial Decree of 19 April 2018 *Official Gazette* n.107 of 10 May 2018

- The meetings are attended by law by the **Presidents:** of the National Bioethics Committee, of the National Committee for Bio safety, Biotechnologies and Life Sciences, of the Istituto Superiore di Sanità. (National Health Institute).
- The **Director General of the Italian Medicines Agency,** who also ensures coordination with the Office of the same Agency to which the function of Secretariat of same Centre is attributed.
- The members of the Coordination Centre remain in office for 3 years and can be renamed.

Art. 2

National coordination centre of Territorial Ethics Committees for clinical trials on medicinal products for human use and medical devices

It intervenes, at the request of the individual Territorial Ethics Committees, with **support and consultancy functions** also in the field of evaluation of clinical trials on medicinal products for human use, may be subject to the evaluation procedures of clinical trials requiring a review following the reporting of adverse events shall monitor the activities carried out by the Territorial Ethics Committees and reports cases of non-compliance with the terms prescribed by Regulation (EU) no. 536/2014 to the coordinators of the Territorial Ethics Committees concerned.

In cases of inertia or, still, in cases of non-compliance with the terms prescribed by the aforementioned regulation, the Coordination Centre **proposes the abolition of the non-compliant Territorial Ethics Committee** to the Minister of Health.

It identifies the single tariff charged to the trial sponsor, to be applied uniformly throughout the national territory at the time of submitting the application for authorization of a clinical trial or for substantial modification of a trial.

It establishes the amount of the attendance fee and the eventual reimbursement of travel expenses for participation in the meetings of the Centre.

Fig. 9 – Organization and functioning regulations of the Coordination Centre.

Art. 2 (Activities and operating methods)
The Coordination Centre usually meets once a month. Decisions are adopted by a majority of those present and, in the event of a tie, the vote of the President prevails. For matters of particular importance, decisions are taken on the basis of a qualified majority of two thirds of the members (e.g. proposal to suppress a Territorial Ethics Committee).

Art. 2 Law 11 January 2018, no. 3 "Lorenzin Law", paragraph 7
The committees are identified within sixty days from the date of entry into force of this law, **by decree of the Minister of Health,** subject to agreement in the Permanent Conference for relations between the State, the Regions and the autonomous provinces of Trento and Bolzano, **Territorial Ethics Committee up to a maximum number of forty** (Time expired).

In identifying the Territorial Ethics Committees, the following criteria must be taken into account:

a) the presence of at least **one Ethics Committee for each region;**
b) **the reorganization of the Ethics Committees,** provided for by art. 12, paragraphs 10 and 11, of the decree-law 13 September 2012, no. 158, converted, with amendments, by **Law 8 November 2012, no. 189, within the terms provided for by the aforementioned legislation;**
c) **the number of trials evaluated** as coordinating centre during the year 2016.

Reconnaissance of the Ethics Committees Meetings of 18, 24 April and 9 May 2018
The technical panel analyzed the criteria for the preparation of the decree scheme of art. 2, paragraph 7.

- AIFA presented the data relating to the activities of the Ethics Committees as shown in the records on the AIFA observatory.
- The AIFA tables are not representative of the many activities carried out by the Ethics Committees since not all the studies presented to the Ethics Committees must be registered on the AIFA observatory.
- The tables containing the data relating to the Ethics Committees were sent to the Regions for appropriate assessments.
- Appropriate tables have been prepared to be filled in by the regional referents for clinical trials.
- The type of studies that fall into the individual categories must be described.

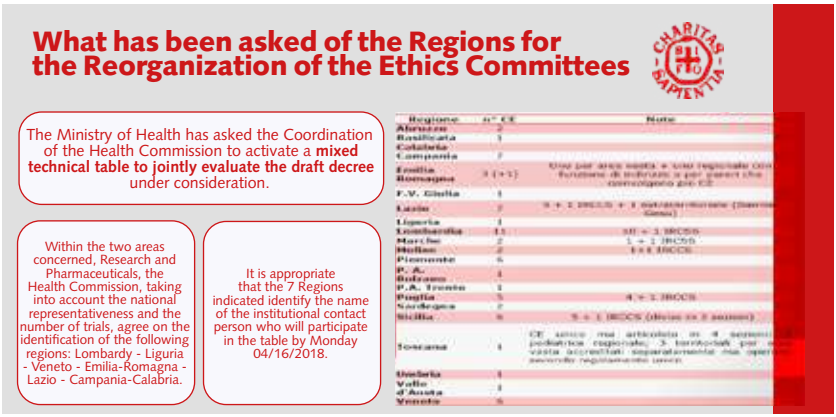


Fig. 10 – The Reorganization of the Ethics Committees.

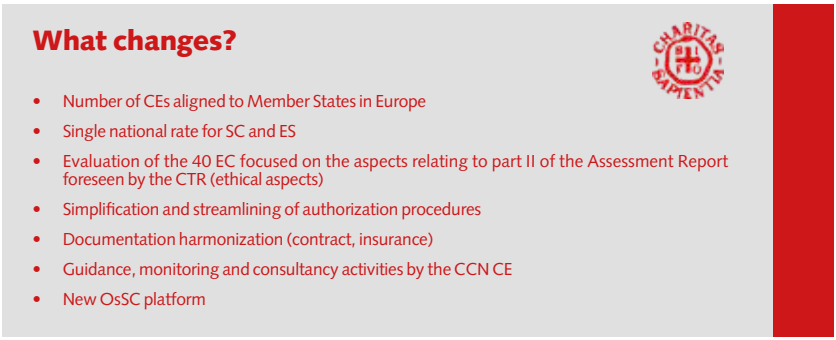


Fig. 11 – What changes?

Certainly it will be possible to grasp the improvement aspects with the new regulation of the Ethics Committees, that it is possible to carry out

innovative research with high scientific rigor by simplifying the procedures and not weighing down the path with further constraints and restrictions. In fact, from the experience of the pandemic we have witnessed an acceleration in this direction with a single National Ethics Committee to evaluate anti-Covid drug studies, the approval times of this single Ethics Committee for Covid studies has been reduced to 14 days. The pandemic has forced the rapid activation of study protocols to address Covid, keeping the ongoing trials on all other diseases active. Approval times have greatly reduced for these studies from 150 days to just about 14 days.

But it is worth considering the advantages and disadvantages of the new organization of the Ethics Committees.

In anticipation of the Single National Committee, envisaged by the new regulation, this reduction may lead to a dispersion of skills but also an increase in the workload for the 40 recognized Ethics Committees. On the other hand, this dispersion could be read positively as a separation of competences: the committees that will not be authorized to evaluate clinical trials pursuant to Regulation (EU) no. 536/2014 could be kept for the evaluation of studies other than clinical trials (e.g. observational studies, studies on biological material of human origin, compassionate use, etc.). The Ethics Committees authorized to evaluate clinical trials with drugs will be overworked.

On the other hand, having committees with well-defined competences can contribute to the standardization and simplification of procedures and processes desired where, in fact, there are strong differences between individual regulations of the Territorial Ethics Committees.

Clinical research sponsors must follow heterogeneous procedures and requests for documentation, which often lead to the production of different but redundant documents and which involve a waste of precious time in order to approve a study.

It is clear that the whole system must adapt as soon as possible to the new skills required, since there would be a risk of flooding rather than simplifying a system that was already complicated at the outset.

In this regard, it is interesting to understand what is the opinion of the experts on the current difficulties present in the operation of clinical trials (Fig. 12).

These difficulties will most likely be overcome with the full application of the new legislation, but the importance of involving patient associations in studies must certainly also be underlined.

It is also important to highlight the opinion of experts on drug management trials (Fig. 13).

From the results of the survey on the topic of experimental drug management, the common opinion of the experts of a greater presence of

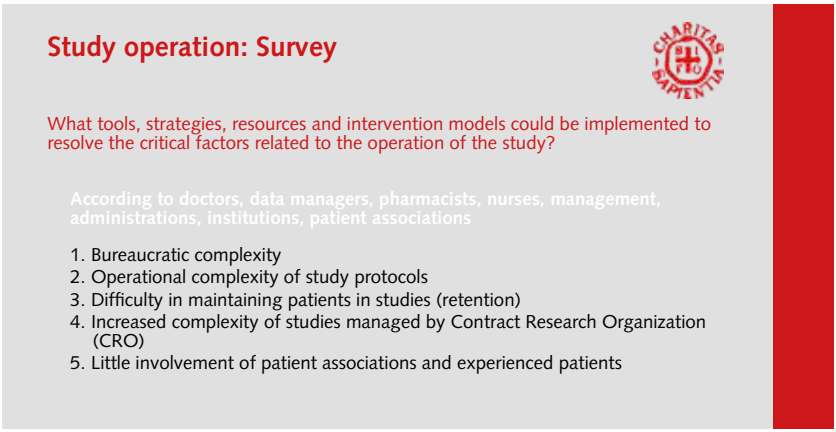


Fig. 12 – Study operation: Survey.

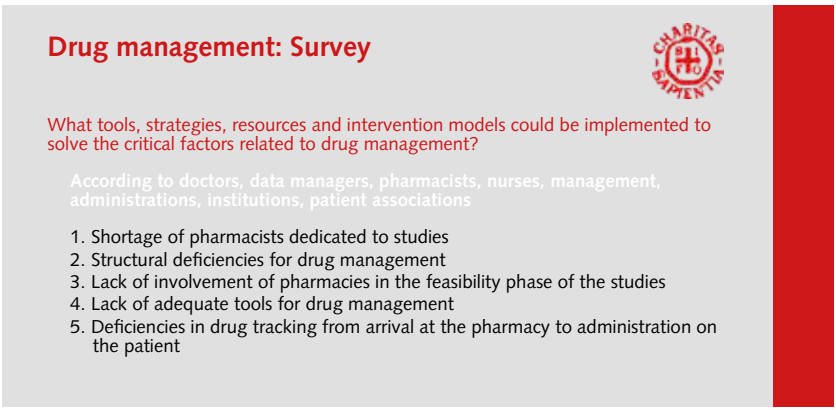


Fig. 13 – Drug management: Survey.

Pharmacists to be dedicated to studies with all the ensuing implications is evident.

Therefore investing in the figure of the Pharmacist, who becomes a meeting point in the multidisciplinary group involved in the studies, has now become a condition that cannot be renounced due to his professional skills in the field of medicine, but also in the management of the Medical Device.

This presence becomes even more relevant in the application of the new European legislation, as the pharmacist can be the link between the Ethics Committee, the experimental centre in which the experimentation takes place and the sponsor of the same.

10. AIFA Determination of 19 June 2015 concerning the minimum requirements necessary for Healthcare Structures that carry out Phase I trials (Resolution no. 809/2015)

A. Del Vecchio, M.L. Fabrizi

The AIFA determination establishes the requirements that the centres and laboratories, both public and private, that carry out Phase I clinical trials must meet.

What is meant by a Phase I clinical study, not only from the point of view of the methodology of the clinical trial, but also from the regulatory point of view, is explained by the Presidential Decree no. 439/2001, which defines them as a set of studies on healthy volunteers or patient with a newly established drug, for the purpose of determining the tolerability profile and the pharmacokinetic/metabolic profile and, in sick subjects, also with the aim of evaluating the efficacy indices for drugs for which the expectation of a therapeutic effect justifies the administration of substances with unacceptable risks in healthy volunteers (Article 2, paragraph 1, of the Presidential Decree).

Previously with the Ministerial Decree of 19 March 1998, "Recognition of suitability of centres for clinical trials of medicines", on which the determination has a specific impact, detailed minimum requirements were established, among other things, for the private structures involved in Phase I trials on healthy volunteers, while for the centres that carry out Phase I trials on patients it was provided that it was sufficient that the private facilities, in addition to the required general health authorizations, were:

a) accredited, in the sense of having an agreement with the National Health System;
b) with recognition of suitability for testing following an inspection by the NHA (National Health Agency) competent for the area;
c) that the experimentation was multicentre with the participation of at least one public structure.

With the Presidential Decree of 21 September 2001, no. 439, it was envisaged that Phase I studies can only be conducted in accredited centres, present in the specific list of the Ministry of Health and that the Ministry publishes the minimum requirements for centres that perform Phase I studies on patients.

Also at international level, specific documents have been prepared for Phase I studies, in consideration of the fact that in these studies experimental drugs

are used for the first time in humans and that therefore they may constitute particular unknown risk factors; in this regard, the EMA document "*Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products*", which entered into force in February 2018, establishes strategies to be used during the studies of Phase I.

The AIFA Determination constitutes the adoption of a regulatory act which, in addition to implementing the provisions of previous provisions, integrates and updates detailed technical aspects which, starting from 2008, had been the subject of non-mandatory indications, but strongly recommended by the GCP Office of AIFA.

The Resolution is made up of 6 articles, an Annex and 3 Appendices (Appendix 1 - Clinical Unit Requirements; Appendix 2 - Laboratory Requirements; Appendix 3 - List of Standard Operating Procedures).

The articles of the determination provide for provisions regarding the possibility that private facilities, including the relative analysis laboratories used for this purpose, can carry out Phase I studies on both patients and healthy volunteers and, in particular, reference is made to the aforementioned DM March 19, 1998.

The clinical departments, both public and private, can be permanently dedicated to Phase I clinical studies on patients, or temporarily dedicated, as long as they meet the requirements established by the determination for the period of the clinical study.

The private structures that carry out Phase I studies on patients must be accredited, i.e. affiliated with the NHS and recognized as suitable following an inspection, usually at least three years, by the ASL competent for the area by ascertaining the minimum requirements for the exercise of the health activities referred to in Presidential Decree 14 January 1997, no. 47, and with certification of compliance with the rules on hygiene, health and safety for the activities that are carried out.

The trial must be a multi-centre with the participation of at least one public structure. From the above it is clear that outside public hospitals or hospitals equivalent to them or outside private clinics affiliated with the NHS, i.e. in ASL clinics or private clinics, it is not possible to conduct Phase I trials on patients.

Experiments on healthy volunteers can be conducted "exclusively at Phase I Units" of public hospitals or equivalent to them and of IRCCS, including the relative analysis laboratories used for this purpose, and in private structures. These structures must comply with the requirements set out in the annex to the determination and related appendices which, for private structures, replace the annex to the Ministerial Decree of 19 March 1998. The private structures must also have certification, following a preliminary check at least

every three years by the ASL competent for the area, of compliance with the rules on health and safety for the activities that are carried out and of the minimum requirements for the exercise of health activities referred to in Presidential Decree 14 January 1997, no. 47, applicable to the structure.

The phrase "exclusively at Phase 1 Units" would seem to indicate that it should not be clinical wards, but *ad hoc* centres for healthy volunteers in a hospital setting. In fact, the technical annex to the specification specifies that phases I can be conducted not only in single units dedicated to this, but also in "specialist departments", provided that for the period of the trial they use structures, procedures and personnel in possession of the required requisites from the annex itself, including, obviously, the specific ones provided for healthy volunteers, indicated in the annex with the initials "Vs".

Moreover, it would not be advisable to use the same hospital ward at the same time for patients and healthy subjects; furthermore, some of the aforementioned requirements for healthy volunteers could hardly be applied to clinical patient wards if not structured, or at least temporarily, adapted for this purpose.

Structures with a mixed public/private character, as well as structures for which the characteristic of a public structure is not unequivocal, such as foundations, companies or other, and which have not been recognized by ministerial decree equivalent to public structures, are to be considered private structures and therefore the requirements and procedures envisaged for the latter apply to them.

This clarification resolves a series of different interpretations, as many mixed structures (University Consortia with private structures, Companies with Hospitals and private partners, etc.) for the sole presence of a public part, believe that they do not have to follow the requirements established for private structures, but at the same time, since they are not public hospitals in all respects, they are not (and cannot objectively be) required to follow certain requirements for the latter.

It must also be taken into consideration that both private and mixed centres, in cases where they are centres of excellence in the health research sector, receive the recognition of the IRCCS (Institute for Scientific Hospitalization and Care) and are therefore equivalent to purposes of clinical trials, to public facilities, in accordance with current regulations.

Facilities that carry out non-profit trials must have a Clinical Trial Quality Team (CTQT).

This obligation is aimed at obtaining, even in the absence of a promoting pharmaceutical company or a CRO, a quality management system which, through adequately trained personnel (the CTQT) to be dedicated to

compliance with the GCP, allows to ensure Phase I the quality of the individual aspects of clinical trials.

The determination provides that the medical director of the clinical centre or the director of the laboratory must notify, within 7 days from the moment he becomes aware of it, in writing to AIFA any deviation concerning the lack of the previously self-certified and/or critical deviations from GCPs, including corrective actions planned and/or implemented. AIFA will decide the measures to be taken (inspection, suspension of the Centre's activity or other).

This provision anticipated art. 52 of Regulation (EU) no. 536/2014 on clinical trials which establishes that the sponsors of the trials must notify the regulatory authority of serious violations of the regulation itself and of the GCPs.

The need to define the requirements of the various health structures authorized to conduct Phase I clinical trials derives from the fact that experimental drugs are used for the first time in humans and that therefore they can constitute particular risk factors that are not known; hence the obligation established by the determination of the possession of structural, procedural, organizational as well as scientific requirements, to identify, evaluate and manage risks during the planning and conduct of Phase I clinical trials.

In this part of the chapter some aspects relating to the organization and staff will be briefly described, which must guarantee the quality of the experimentation and the reliability of the data, with particular regard to the role of the hospital pharmacist in Phase I clinical trials.

As mentioned, the determination includes an attachment 1 which reports the minimum requirements necessary for the structures that carry out phases I and is practically an introduction to the following 3 appendices. The annex includes concepts already included in the articles such as the methods of self-certification, the types of clinical structures that can be self-certified, the need to notify AIFA of serious deviations that may occur, the possibility of GCP inspections.

In this annex the activity of the CTQT, a team supporting the investigators No Profit with regards to quality management. Very often, in fact, these investigators need help in the application of GCPs in clinical studies such as, for example, for monitoring activities or the revision of the documents necessary to start a clinical trial.

The determination provides that the quality team can be dedicated to Phase I of the structure or can operate for all trials No Profit of the hospital structure, including those of Phase I. The CTQT must have an internal Regulation that specifies staff, operating methods and tasks, which are mainly those of assisting the Non-Profit sponsor and the investigators:

- before the start of the study;
- during the execution of the study;
- at the end of the study.

The staff involved in the team may include the figure of the hospital pharmacist who, among the main tasks, must guarantee the quality of the trials in collaboration with other health personnel provided for in the organization chart *Non-Profit* in accordance with the GCP.

Appendix 1: Clinical Unit Requirements

This appendix reports the requirements of the Clinical Units both of a general and specific nature.

General requirements

The determination provides that the centres comply, in the applicable parts, with the act attached to the Presidential Decree of 14 January 1997, and related regional regulatory applications, which establishes the minimum requirements for the exercise of health activities by public and private structures. The determination of this act lists a series of paragraphs, including:

- that relating to the "general minimum requirements", which substantially concerns the aspects of quality that are mandatory, at national level, for each health facility (such as the adoption of a document which explains: the objectives, the internal organization, the '' organization chart; the definition of the need for personnel in numerical terms for each qualification, in relation to the types of activities, possession of the required qualifications; a staff training-updating plan, with indication of the person in charge; an inventory of the equipment supplied and a plan for documented maintenance; the preparation of a collection of internal regulations and updated guidelines for carrying out the most relevant technical procedures;
- that relating to the "minimum requirements for the management of drugs and medical material (for the pharmacy service, if any)" which concerns the structural and technological requirements that the Pharmacy Service must have (such as space for receiving the material and for its registration; storage for drugs and medical-surgical devices; room or space for chemical preparations; furnishings and equipment for the storage and storage of medicines, medical-surgical devices and other relevant materials; refrigerators for the storage of medicines to be kept at a determined temperature, equipped with temperature recorders, alarm system and, possibly, connected to uninterruptible power supplies or to a preferential power supply line; adequate spaces for the outgoing movement of drugs and other sanitary material).

The AIFA determines explicitly, within the general requirements, in point j) of the paragraph "Organization of the structure", that the unit must have a dedicated and adequately equipped room for the reception, storage and management of the experimental drug (and, where applicable, the comparison product), which is accessible only to authorized personnel; the experimental drug, of course, in the case of public facilities must previously be sent to the hospital pharmacy.

Furthermore, in the same point it is clarified that, if the Phase I Unit is a private centre, not provided with a pharmacy service, this structure must have a pharmacy with requirements equivalent to those of a hospital pharmacy pursuant to the Ministerial Decree of 21 December 2007, art. 7, which provides that the medicines required for the trial must be sent by the sponsor to the pharmacy of the health facility where the trial is located, which will arrange for their registration, appropriate storage and delivery to the investigator.

Finally, the AIFA determination identifies, in the paragraph "Personnel in service at the Unit", among the personnel who must be present in a Phase I Clinical Unit and who, specifically, must be appropriately trained on the Rules of Good Clinical Practice (GCP), in addition to the medical director, the pharmacologist and one or more doctors with specific skills, a pharmacist in charge of managing the drugs in that Unit (storage, dispensing, accounting of the experimental drug, other tasks related to the management of drugs and emergency drugs).

A particularly important aspect is covered by the way the drugs are stored both at room and controlled temperatures; to this end, the determination in the paragraph "medical equipment" provides that the refrigerators/freezers in which the experimental drug is stored are equipped with continuous temperature recording and connected to the reception of the facility (or to another equivalent service) that ensures the presence/24h availability; there must also be a continuity generator. All equipment must undergo routine maintenance and related documentation must be available.

Among the staff in service, whose names and relative functions must be described in an organization chart, it determines (to which reference is made) identifies other specific figures to guarantee the quality of clinical studies.

Quality requirements

In line with the obligations regarding the general quality requirements envisaged for all health facilities by the aforementioned Presidential Decree and in line with the obligations deriving from the GCP, the AIFA determines, in order to guarantee the quality of Phase I clinical trials, that the 'Unit has an appropriate quality assurance system, compliant with the requirements of

the Ministerial Decree of 15 November 2011 (Article 3, paragraph 1, letter b) which provide, among other things:

a) the adoption of a quality manual;
b) a documented quality assurance activity;
c) compliance with the GCP of all activities;
d) an adequate documentation system to ensure the traceability of all activities;
e) written POS (including modules/models aimed at demonstrating the activity), for each aspect related to the study, which the Resolution lists by dividing them into POS for the general aspects and POS for the clinical aspects. This list also includes procedures that directly involve the Pharmacy such as those relating to the management of the experimental drug in accordance with the GCP, in which the aspects relating to the premises for the storage of drugs, the methods of preparation, those for the accounting of the drug and registration (paper and/or computerized), the methods of delivery of the experimental drug to the Pharmacy and from this to the Experimental Unit;
f) independent audits and storage of reports, on the clinical structure and on the laboratory to ensure compliance with current regulations and SOPs.

For the purposes of managing the quality system, the medical director must designate a quality manager who is in possession of the requirements set out in the Ministerial Decree of 15 November 2011.

The possession of the requirements must be self-certified by every facility that intends to participate in Phase I trials at AIFA at least 90 days before the start of the activity with a model reported in a subsequent AIFA Determination (Resolution no. 451 of 29 March 2016).

AIFA on its website (https://www.aifa.gov.it/web/guest/ispezioni-di-buona-pratica-clinica/) publishes the list of self-certified structures divided by region and indicating the state (active or suspended), which is updated whenever necessary. On the basis of these self-certifications, the AIFA GCP Inspection Office may carry out an inspection to verify the possession of the requirements of the Determination by the clinical centre and/or the Phase I laboratory.

At the time of writing this article, the health structures self-certified to AIFA in the "active" status are a total of 273, of which 140 clinical centres and 133 laboratories.

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11. The Standards of Good Clinical Practice (GCP)

P. Di Basilio, F. Galliccia

1. Background and historical context: GCP and standard on clinical trials

The need to regulate clinical trials on humans, both from an ethical, scientific and methodological point of view, arises in the scientific community following the sequence over the course of history of dramatic events in which, for research purposes, fundamental human rights were violated. Just think of the case of the Tuskegee 1932/72 study for syphilis, or Elixir Sulfanilamide, in which the use determined, in 1937, the death of more than 150 subjects or the known case of thalidomide, which was used in pregnant women in 1958 with harmful effects on unborn children that were observed only later in 1962.

The first real important step was represented by the code of "Nuremberg Code" in 1946, which represented an ethical Decalogue to be followed for any clinical research on human subjects, adopted by the Nuremberg court, after the discovery of the atrocities committed in the concentration camps during the Second World War by Nazi doctors, among which the figure of Josef Mengele, known as the black angel of Auschwitz, sadly stands out.

This was followed by the promulgation of the Geneva Declaration, during the assembly of the World Medical Association in Geneva in 1948, and amended several times over the years, and of the Declaration of Helsinki in 1964, in which a set of ethical principles concerning the whole medical community are declined as regards human experimentation, in that it is considered a keystone of ethics and which has also been revised several times over the years.

The first guidelines in the field of experimentation, the GCP (Good Clinical Practice), however, were prepared in 1995, in the first draft, by the International Conference for the harmonization of technical requirements for the registration of drugs for human use (ICH) (international body, founded by the countries of the European Union, the United States of America and Japan, which includes the main world regulatory authorities) and implemented in the EU by the European Medicines Agency (EMA) in 1996, at the end of the process of harmonization of international standards on experimentation.

GCPs represent an international standard of ethics and scientific quality to

be followed when designing, conducting, recording and communicating the results of a clinical trial with the participation of humans.

The intent of the rules on clinical trials was to guarantee the quality of clinical trials while maintaining absolute respect for human rights and human dignity. In fact, using effective and safe drugs inevitably implies that they are subjected to specific studies on the people who will then have to use them and this must be done by ensuring first of all the ethics of the research but also by adequately balancing the risks with the possible advantages of treating the disease. The evolution of the approach in the field of medicines in favour of a more extensive experimentation is evident in the paediatric field. Only some time ago it was unthinkable to be able to subject children to experimentation but a more far-sighted mentality has understood that it is better to test medicines also on children, to have safer drugs available, rather than treat them with off-label drugs, tested only on adults and which do not take into account the peculiarities of the paediatric age. The paradigm shift has also affected the reference words of the clinical trial: patients who were previously called "subjects" of the trial, implying some form of subordination, are, in recent times, called "participants" to emphasize the collaboration in the medical field of those people who take part in the trial, participation that must be as "informed" as possible.

2. Objectives and structure of the GCPs

The main objectives of the GCPs are:

1. ensure the protection of the rights, safety and well-being of participants in clinical trials;
2. ensure the credibility of clinical trial data.

GCPs must be followed during all phases of a clinical trial, from design to data management and production, by all the structures and professionals involved, for various reasons, in the clinical trials. They are made up of 13 principles and a detailed part that sets out the means in which the principles are satisfied. The main figures to whom the GCPs address, in addition to the participants in the experimentation, are the Ethics Committee, the investigator and the sponsor of an experiment (also called Sponsor), and a specific chapter is dedicated to each of these "protagonists".

The GCPs consist of the following chapters:

Introduction

1. Glossary
2. Principles of GCP of the ICH

3. Review commission of the institution/independent ethics committee (IRB/IEC)
4. Investigator
5. Promoter of the study (sponsor)
6. Experimental protocol and amendment (s) to the protocol
7. Investigator's brochure
8. Essential documents for conducting a clinical study

From the first provisions to date, the standard has followed several evolutionary stages, but adhering to the GCP standards remains the only way to ensure the integrity and reliability of data and at the same time maintain respect for patients' rights and their safety. We must not forget that the GCPs are born as Guidelines and therefore with a less prescriptive value than a real standard, hence the need for the various states to introduce them in their respective legislation in order to make them binding. In Italy, the first GCPs of 1996 were implemented with a decree of the Ministry of Health, the Ministerial Decree of 15 July 1997.

Subsequent European directives have strengthened and clarified the obligations and procedures for applying GCPs in clinical trials also at EU level.

In the first place it was the Directive 2001/20/EC which also confers legal dignity on GCPs at the EU level. In fact, the directive, precisely with a view to guaranteeing the quality of clinical trials in compliance with human rights and human dignity, establishes the provisions for the application of good clinical practice and considers them as a "set" of scientific requirements, internationally recognized quality and ethical standards that must be observed, reiterating that it is only adherence to these requirements that guarantees the protection of the rights, safety and well-being of the subjects of the clinical trial. (Article 1, paragraph 2, Directive 2001/20/EC).

Subsequently, the basic principles of GCP, for the execution of clinical trials, are taken up and set out in Directive 2005/28/EC (GCP Directive).

These directives have been implemented in Italy with the following legislative decrees: Legislative Decree no. 211/2003 (transposition of Directive 2001/20/EC) and Legislative Decree no. 200/2007 (Transposition of 2005/28/EC). Also the new European Regulation on clinical trials (the so-called Clinical Trial Regulation no. 536/2014), intended to supplant the previous Directives, entered into force only in January 2022 (due to the delays of the EMA for the implementation of the computer system management of trials at European level) makes explicit reference to the GCPs and to the related Declaration of Helsinki.

3. The Principles of GCP

The Principles of GCP are 13 and originate from the Declaration of Helsinki of the World Medical Association. They constitute the founding pillars of GCPs.

Listed below are the principles that every investigator and sponsor should have engraved in their minds.

2.1. Clinical trials must be conducted in accordance with ethical principles which originate from the Declaration of Helsinki, and which comply with the GCP and applicable regulatory provisions.

2.2. Before a study begins, likely risks and inconveniences must be weighed against the expected benefit to both the individual study subject and society. A study can only be initiated and continued if the anticipated benefits justify the risks.

2.3. The rights, safety, and well-being of the study subjects are the most important considerations and must prevail over the interests of science and society.

2.4. Available non-clinical and clinical information relating to an investigational product must be adequate to support the proposed clinical study.

2.5. Clinical studies must be scientifically valid and must be described in a clear and detailed protocol.

2.6. The study must be conducted in accordance with the protocol that has previously received approval/favourable opinion from an Institution Review Board (IRB)/Independent Ethics Committee (IEC).

2.7. Medical treatment and medical decisions made in the interest of individuals will always fall under the responsibility of a qualified physician or, if applicable, a qualified dentist.

2.8. All individuals involved in conducting a study must have the education, training and experience necessary to perform their specific duties.

2.9. Informed consent freely given by each subject must be obtained prior to their participation in the study.

2.10. Any information relating to the clinical study must be recorded, processed and stored in such a way as to allow accurate reporting, interpretation and verification.

Addendum (R2)

This principle applies to all registrations mentioned in this guideline regardless of the type of media used.

2.11. The confidentiality of the documents that could identify the subjects must be guaranteed, respecting the rules of confidentiality and confidentiality provided for by the applicable regulatory provisions.

2.12. The products being tested must be prepared, managed and stored in compliance with the applicable Good Manufacturing Standards (GMP). They must be used in accordance with the requirements of the approved protocol.

2.13. Systems must be implemented with procedures that guarantee the quality of every single aspect of the study.

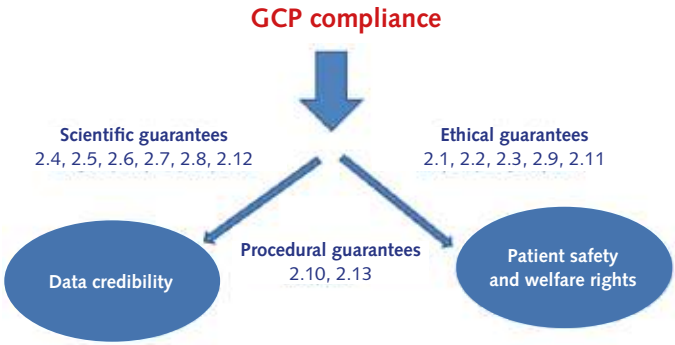
Addendum (R2)

Such systems must be focused on the aspects of the trial that are essential to ensure the protection of subjects and the reliability of the results.

The GCP Principles can be divided into three broad categories according to the aspect of the guarantee to which they refer. We therefore distinguish the three great guarantees of GCPs:

1. Ethical guarantees
2. Scientific guarantees
3. Procedural guarantees

The diagram below divides the various principles into three categories.



It is clear that the protection of GCPs is not limited only to the participants in the clinical trial but through the guarantee of the reliability of the data it protects all future patients who will then have to be treated with that drug.

4. The evolution of the legislation on clinical trials and the culture of risk

The GCPs, however, were originally conceived and developed at a time when research relied on paper-based recording systems and in which activities, such as monitoring, required by GCPs, were necessarily carried out directly on site and with the use of long periods and staff often dedicated full time.

Compliance with the quality standards required by the GCP and by the law, during the conduct of clinical trials, involves the implementation of systems with a considerable commitment on the part of the sponsors and third parties involved (e.g. Clinical Research Organization - CRO) in terms economic and personnel resources.

Over time, however, the context in which clinical research takes place has changed considerably, having to deal with increasingly numerous studies with a rather high degree of complexity in which the use of electronic systems has become widespread, even if necessary.

Furthermore, the awareness that, despite the considerable economic investments and technological evolution in the sector, some problems related to quality are still recurring (the error can be minimized but not eliminated), has determined the need to reinterpret the management of quality systems and of the processes underlying the clinical trial, in order to optimize the available resources and, at the same time, exploit the efficiency of computer systems at a wider range. This need has led to a revision and adaptation of the standard to the scientific and evolutionary context of the research, maintaining the objective of achieving quality results without, for this reason, obviating the obligation of compliance with regulatory requirements or the guarantee of protection of patients.

Therefore, since quality has a cost but not working in quality means not doing things well and paying an even higher price, it became essential to seek new approaches and look into other sectors in which already tested methodologies had given effective results in management processes. In this scenario, the concept of risk and its management, successfully used for many years in various sectors, have provided a key to reinterpreting the standard in a more functional way.

Thus the culture of risk, as an approach for identifying and evaluating errors and the subsequent actions taken to mitigate them, which had spread in the healthcare field and in the pharmaceutical business world, arrived in the clinical trial sector.

Risk and risk management were already used in the pharmaceutical world

before they were even addressed in the standard. In fact, in the pharmaceutical production sector, the need to guarantee the patient, as the last user, a high quality final product (the drug) had found an answer and support in the application of a risk-based approach to quality systems, allowing to identify quality problems early on during development and production. However, the perception of risk and its extent, understood as the combination of the occurrence of an impairment and the severity of the damage itself, can vary between the various stakeholders and regulatory agencies. It was therefore necessary to define a common approach (ICH Guideline Q9 on Quality Risk Management – EMA/CHMP/ICH/24235/2006 Committee for Human Medicinal Products, September 2015) and provide guidance on the principles and tools of risk management with shared elements of interpretation of risk management, thus creating mutual awareness of the most efficient tools used to make choices and decisions regarding quality that would provide a qualitatively safe and valid product.

The management of quality systems according to risk has fully become part of the Good Manufacturing Practices, becoming a real regulatory requirement for manufacturers of medicines, who must have a quality system based on risk and that inspections in that sector are required to verify.

But the risk, considered in the health field as linked to clinical practice, is also always present in clinical trials, where even if it cannot be completely eliminated, it is at least assessable and controllable.

The sponsors of the studies and the CROs delegated by the same had, for some time, experimented with benefits in terms of time and costs, the approach based on risk assessment for activities such as monitoring, but it was necessary to identify a meeting point through a coordinated, homogeneous and shared vision between the various players involved, maintaining the requirements of a research characterized by scientific rigor, ethics and quality.

A new interpretative key had to be provided and the ICH updated the first version of the ICH GCPs (called ICH-GCP E6 R1) making changes by inserting various addendums in the original 1996 text. In the resulting version, the ICH GCP E6 so-called R2, the implementation of new more efficient methods is encouraged both for the design, the conduct and the registration of the trials, highlighting the advantages that can derive from the combination of an approach based on risk assessment and the support of tools advanced technologies. The standards for electronic registration and storage of essential documents are thus updated.

If on the one hand, with the revision of the GCP, the requirements in some fields are underlined and increased, as in the case of electronic systems, on the other hand elements of flexibility are introduced for activities such as,

for example, the monitoring or validation of computerized systems taking into consideration the major criticalities that emerged from the analysis of the related risks.

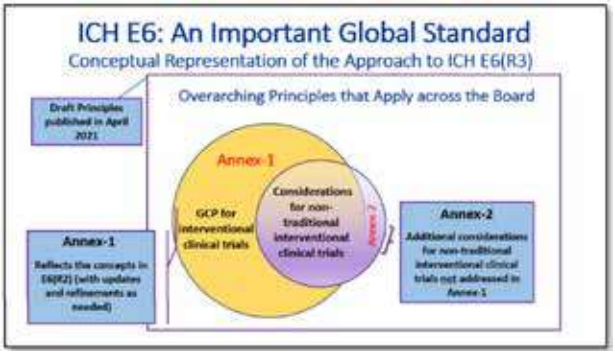
But the revision of the GCP was not the only regulatory change.

The awareness that many experiments present only minimal additional risks and that understanding and evaluating them can simplify the processes by providing a new impetus to experimentation, has further prompted towards the adoption of a new regulatory instrument that would collect the reports from the various stakeholders (industry, public and private researchers, associations and scientific research bodies, universities, patients and public health care facilities) relating to the need for simplification. Therefore, the real change is represented by the new European Regulation (CTR 536/2014), already mentioned above, which prefigures and supports an orientation based on a proportionate approach to risk both in the definition phase and in the conduct of the clinical trial. The Regulation, unlike the Directive 2001/20/EC which has regulated the experimentation so far, is a binding legislative act and has the applicative value of all its elements throughout the European Union, while the Directive needs to be transposed into the legal systems of the various States members. The Regulation can therefore be seen as a real catalyst for harmonization across the EU.

The CTR introduces elements of flexibility and identifies those areas **in the design** and **conduct** of the trial in which it is possible to implement a proportional approach to the risk, based on the consideration that some studies involve a minimum additional risk to the safety of the subjects or to the integrity of the data, compared to the normal clinical practice. Based on this, less stringent rules or forms of adaptation are provided for what concerns monitoring, safety reporting, traceability of the IMP and content of the TMF.

The importance of a Regulation lies in providing a common framework for the standard at European level to ensure that the proportionate approach to risk does not become a total structural derogation from the rigorous standards of quality and safety by the stakeholders.

At the ICH level, work is now underway on the new version of the GCP called R3 in which the risk-based approach has become the fundamental framework. The R3 Principles have already been published and the other parts that follow an Annex structure (such as GMPs) are being prepared according to the scheme below.



One of the inspiring concepts of the new GCPs is the concept derived from architecture and then adopted in the IT field that "less is more": this approach, in an increasingly complicated experimental world, aims to focus on what is really important, leaving out marginal details.

Regulatory inspections

Meaning and legal basis

In this context, the inspections conducted by the various regulatory bodies to verify compliance with the GCP take on relevance and significance. In fact, in order to guarantee the quality of clinical studies so that the results of a trial can be considered reliable and credible and therefore usable for submitting requests for authorizations for the marketing of medicines (Marketing Authorization Application - MAA), it is now essential to verify the compliance of the studies to the GCP and to the standard.

The definition of inspection is in the same GCP ICH (R2) (1.29) and in the Legislative Decree no. 211 (Transposition of Directive 2001/20/EC), art. 2, paragraph 1, lett. n): "*the carrying out, by one or more regulatory Authorities, of an official review of documents, structures, records and any other resource considered by the Authority to be connected to the clinical study; the review may take place in the trial centre, at the facilities of the study sponsor and/or the CRO, or in any other location deemed appropriate by the regulatory authorities*".

The significance of the GCP inspections is within the scope of the GCPs themselves but these inspections are not carried out systematically on all studies and acquire greater relevance when they concern studies that support the application for marketing authorization. It is Regulation no. 726/2004,

art. 57, to provide a stronger legal basis for GCP inspections, when these are requested during the evaluation of the documentation submitted to the European Medicines Agency (EMA) for authorization requests within the EU. The Regulation entrusts indeed the European Medicines Agency with the task of taking a decision on the applications that rely on studies for which Directive 2001/83/EC (Annex1) had already established the need to respect ethical principles equivalent to those valid in the EEA and to adhere to Directive 2001/20/EC, the GCP and the Declaration of Helsinki.

Sure enough, if doubts arise during the assessment of product quality and safety and GCP compliance, the Agency has the right to request an inspection.

In Italy, the execution of inspections is under the responsibility of the AIFA GCP Inspection Office and can take place before, during or after the implementation of clinical trials (Legislative Decree 6 November 2007 no. 200 to art. 24).

When not carried out for specific reasons, such as in the case of a request from other offices within AIFA or external bodies (e.g. Judicial Authority, EU Commission, etc.), or from the EMA (for centralized procedures for the authorization of medicines) or by the Director General of AIFA, the inspections follow the routine planning of the Office on the basis of risk assessment criteria linked to factors such as the number of subjects enrolled, critical hospital structures or never inspected, characteristics of the subjects, relevance of the study, etc. The inspections may concern any facility or subject in any capacity involved in the conduct of a clinical study and generally take place at the trial centre, at the facilities of the trial sponsor, at the contract research organization facilities (CRO), or in other places deemed appropriate by such Authorities. In particular, any place or structure, within the aforementioned places, interested in the experimentation can be subject to regulatory inspection and at any time of the conduct, before, during or at the end (see also GCP 2015-2017 Inspection Report published on the AIFA website: https://www.aifa.gov.it/-/rapporto-ispezioni-gcp-2015-2017-classificazione-e- analysis-delle-devissioni-alla-good-clinical-practice).

The AIFA GCP Inspectorate operates through its own procedures and non-conformities with GCPs are described in an inspection report that is provided to the decision-making body in order to determine the usability of the trials for regulatory purposes.

Deviations from GCPs are divided according to their severity into three categories, in accordance with the reference EMA procedure. The categories are as follows.

Classification of deviations according to the EMA procedure

Criticism (CR)

- Definition: Conditions, practices, processes or deviations from GCPs that adversely affect the rights, safety, health, well-being of individuals and/or the quality and integrity of data.
  Non-compliance with relevant regulatory requirements.
- Possible consequences: Data rejection is required (particularly when the trial is completed and it is no longer possible to correct the deviations in itinere) and/or legal action.
- Note: A number of major deviations, inadequate data quality and/or absence of original documents can constitute a critical deviation. Fraud is included in this group.

Major (MA)

- Definition: Conditions, practices, processes or deviations from GCPs that could adversely affect the rights, safety, health, well-being of individuals and/or the quality and integrity of data, as well as non-compliance with other regulatory requirements.
- Possible consequences: They can be grounds for data rejection and/or legal action.
- Note: A number of minor deviations may constitute one major deviation.

Minor (ME)

- Definition: Conditions, practices, processes or deviations from GCPs that are not expected to adversely affect the rights, safety, health, well-being of individuals and/or the quality and integrity of data.
- Possible Consequences: Deviations classified as minor indicate the need to improve conditions, practices and processes.
- Note: Many minor deviations may indicate inadequate quality assurance and their addition could equal one major deviation with its consequences.

Recommendations:

- Definition: Deviations can lead to recommendations on how to improve quality and reduce the possibility of the same deviations happening in the future.

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a) Quality in Phase I clinical trials: the Italian context and the role of the GCP Auditor

L. Martena, D. Di Tonno

Quality is often a difficult concept to define, as it can take on different nuances depending on the context to which it refers. However, what is clear is that the term quality by itself implies dynamism. The application of the established standards, in fact, involves a process review phase and the implementation of any improvement actions.

What is described above was regulated by W. Edwards Deming himself through the so-called "Deming Cycle" (*PDCA - Plan, Do, Check, Act*).

In clinical trials, quality is regulated in Chapters 5.0 and 5.1 of Revision 2 of the Good Clinical Practice (GCP).

It is the responsibility of the Sponsor to implement a quality management system during all phases of a clinical study, which must include systematic checks aimed at verifying compliance with the standards set by the quality system itself. These controls include GCP audits, i.e. "*A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)*" (ICH-GCP R2, Chap. 1.6).

In the Italian context, current legislation pays particular attention to Phase I studies, from the authorization/approval phase to their closure. This legal requirement arises from the fact that Phase I clinical trials "per sé" could entail a greater risk to the health of the participant. In this way, all the requirements of the legislation are aimed at ensuring the protection of the health and well-being of the participants in the studies, as well as the validity of the data collected during the study.

The minimum requirements that a clinical/laboratory unit (Phase I unit) must possess in order to carry out Phase I studies are defined in "AIFA Determina" no. 809/2015 (Italian Regulatory agency Regulation).

The legislation in fact provides that the personnel belonging to the Phase I unit are qualified and adequate for the activities to be carried out, trained in Good Clinical Practice and inserted within an organization chart (Appendix 1, par. A, pt. 4, lett.. b).

The Auditor, who must be in possession of the requisites established by art. 5 of the Ministerial Decree of 15 November 2011.

Each Phase I unit is obliged to receive, every year, at least one quality system audit and at least one audit on a trial conducted during the year (study-specific audit).

By carrying out the audits, the Auditor verifies the compliance of the structure with current legislation and standard operating procedures, therefore he/she must be independent and know the applicable legislation and guidelines.

For the audit preparation, the Auditor may ask the structure for some documents of the quality system or of the study being audited.

The quality system documents include:

- Phase I staff organization chart;
- List of activities carried out by the structure internally and those contracted externally;
- Job Description and Curriculum Vitae of the unit staff;
- Standard Operating Procedures and other instructions;
- Forms in use;
- Documentation relating to external suppliers of products and services.

The study-specific documents, on the other hand, include, but are not limited to:

- Study protocol (and any amendments);
- Informed consent template and study information sheet (and any amendments);
- Blank of the Case Report Form (CRF);
- Laboratory manual.

Through the analysis of the aforementioned documentation, the Auditor is able to carry out a preliminary assessment of the structure and select the points to be investigated during the execution of the audit itself.

During the verification process at the unit, the Auditor proceeds as follows:

- further investigates the verification of the documents of the unit (whether they are of quality or study-specific);
- conducts interviews with unit personnel;
- visit the facility of the phase 1 unit (hospital pharmacy, laboratory, clinical engineering, rooms identified to host Phase I patients in which the Investigational Medicinal Product is administered).

During the final meeting, the Auditor presents any findings emerged and subsequently draws up the audit report, which must be filed by the phase 1 unit (Appendix 1, par. C and Appendix 2, par. B).

The audit report must contain a description of what was viewed and examined during the verification phase, as well as the findings detected. These must be based on precise normative references and classified according to an appropriate grading.

At the end of the audit, the Auditor issues a certificate attesting to the verification.

As can be seen from the legislation issued by the competent Authority, the concept of quality assurance is not only governed to recall and apply international directives (such as GCP), but also to further sensitize the staff participating in clinical studies on the importance of act according to reference standards that aim to guarantee the health and well-being of the participants and the integrity of the data produced.

b) Quality in Phase I clinical trials: the Italian context and the role of Quality Assurance

A. Ortenzi, A. Argentiero

AIFA Determination no. 809/2015 has defined the minimum requirements for the Units (clinical centres or analysis laboratories) that conduct Phase I clinical studies. Among the requirements there is the presence of a Quality Assurance (QA) Manager, in possession of the requirements indicated by the Ministerial Decree of 15 November 2011.

The QA is the professional responsible for the Quality Management System, that is the formal set of all the connected and interdependent activities that influence, in the world of clinical research, the quality of the scientific data produced.

The aforementioned AIFA Determination has raised the quality standards of the experimental centres that conduct Phase I clinical trials in order to guarantee an analysis of the safety parameters necessary for the subsequent investigation phases.

For this reason, it is necessary to provide systems and procedures that can, even better, guarantee the safety of the subjects and the quality of the data produced.

The main task of the QA lies in the structuring and revision of the Standard Operating Procedures (SOPs), that is written and detailed instructions of the activities and processes that take place in the structure.

The QA reviews the SOPs after they have been drawn up by an expert in the process in question and ensures that they are in compliance with the latest revision of Good Clinical Practices, with current legislation and that they are consistent with other company procedures in force.

The QA is also involved in the planning process of the training activities and in the scheduled periodic checks.

As regards training, the QA draws up a training plan that includes specific training for each member of the organization chart (Doctors, Nurses, Clinical Research Coordinators, etc.) making sure that the training activities are carried out and documented.

The introduction of this chapter aims to describe how the application of the regulatory requirements required for the conduct of Phase I clinical trials in public and private facilities takes place.

In order to optimize the processes and make them effective, the figure of the QA and the Auditor with documented experience in GCP, respectively assume a role of relevance be it for the coordination of the activities necessary

for adherence to the mandatory requirements at the clinical centres and self-certified laboratories, and as a control in a perspective of continuous implementation of the quality of the processes and services provided.

The macroscopic aspects to consider in order to centre its Quality Management System (QMS) are:

1. **Profit/No Profit Trials:** in the second case it is necessary to have a Clinical Trial Quality Team (CTQT - Ministerial Decree 17 December 2004).
2. **The Clinical or Laboratory unit is located in a Public/Private structure:** Ministerial Decree of 19 March 1998, "Recognition of the suitability of centres for clinical trials of medicines".
3. **If it is a Clinical/Laboratory Unit (AIFA Determination 809/2015).**
4. **If Phase I SC is performed on Healthy Patients/Volunteers (AIFA Determination 809/2015).**

Once the macroscopic variables have been identified, it is necessary to define the macro categories that make up the specific QMS for Phase I clinical trials in relation to the requirements expressed by the guidelines of the Regulatory Bodies and the reference regulations:

1. Infrastructure and equipment;
2. Staff;
3. Training;
4. Quality assurance activities and documentation.

The *modus operandi* of QA is to involve, in a profound and effective way, every single department of the hospital, or research laboratory, involved in the processes described by the legislation using the figures appointed by the Medical/Laboratory Director in order to document the methods of execution of the activities and implement them when necessary.

1. Infrastructure and equipment

The first assessments will be aimed at assessing the Infrastructural requirements (Presidential Decree 14 January 1997, Approval of the act of guidance and coordination for the regions and autonomous provinces of Trento and Bolzano, regarding the minimum structural, technological and organizational requirements for the health activities by public and private structures) with particular reference to the aspects described in Appendix 1 (Presidential Decree of 14 January 1997).

At this level, the importance of involving structures such as the Medical Management, Hospital Hygiene and the competent Technical Offices is reiterated by requesting documentation or at least verifying its presence, in order to make it available in the event of audits and controls.

In the case of self-certified laboratories such as for the Pharmacy and other

Services involved, it is mandatory to verify the regional accreditation also for public hospitals. In particular, for Laboratories, it is necessary to verify the presence of an internal Quality Management System that complies with the relevant Good Laboratory Practice parts.

As regards the control of the equipment, it is necessary to plan a system of multiple controls in order to guarantee the reduction of risk in accordance with the "Swiss-cheese" model prescribed by the ICH guidelines.

The declination of this system can be structured by providing three control levels:

1. **Corporate:** in accordance with the corporate certification (if present);
2. **Phase I Clinical Unit/Self-certified Laboratory:** the medical equipment used within the unit/laboratory for conducting Phase I clinical trials;
3. **Individual equipment:** specific labelling applied to or nearby the equipment.

For the first two levels described above it will be necessary to provide a manager; for the third level, responsibility becomes shared with the operator who must verify that the appropriate signs certify the usability of the equipment on the basis of scheduled maintenance.

2. Personnel

Another macroscopic area on which to focus the attention of the QMS is certainly the management and placement of personnel.

The normative references describe the need to establish roles, according to a minimum staffing and a hierarchical structure, that is the organization chart, which describes the relationships both for the clinical units and for the laboratories.

The QA collaborates in the fulfilment of these requirements with the Medical Director who for each of the requested figures determines the number of personnel to be included based on the resources present and the needs.

The documentary aspect, both of the letters of appointment and of the organization chart, must describe the changes over time in relation to the turnover of the personnel involved as well as the duties and responsibilities in relation to what is described in the procedures.

It should also be considered that in the list of Appendix 1, lett. A, point 4 of the AIFA determination, some of the figures shown are not provided for by the organic plants of the hospital structures which therefore must be financed with specific and difficult to stabilize contracts. In particular, the figures of the research nurses or Clinical Research Coordinators, in the case in which he is committed to clinical trials and/or in which he also carries out ordinary activities.

This aspect therefore leads to a criticality that requires continuous monitoring and requires effective preventive measures agreed with the Medical Director, the PI and the bodies responsible for hiring and contracts.

3. The training

Training represents a fundamental moment in which there is the transmission of knowledge from a trainer to a trainee. Leaving aside the notional aspects, the Training Plan has the task of structuring, solidifying and reinforcing both technical-operational and approach aspects in a comprehensive way.

The concept of training in clinical research plays an essential role: to stimulate personal and professional growth within a context of collaboration between components from different academic backgrounds.

The aspects abovementioned are important if contextualized within a self-certified UCF 1/Laboratory, where the planning of the training and its execution are required by the AIFA Determination. The legislation, in fact, requires training that accents all aspects related to a Phase I clinical trial (first and foremost, GCP, emergency management, clinical research methodology).

4. The quality system

One of the key principles – and also the most critical – in the world of clinical research is the concept of Quality, which all organizations that deal with clinical trials must aspire to (pharmaceutical companies, CROs and experimental centres).

Quality is a concept strongly linked to compliance with ethical, scientific and documentation management requirements, identifiable in the current legislation on clinical research and in Good Clinical Practice.

The QMS is the set of all connected and interdependent activities that influence the quality of a product or service.

At the base of the QMS we find the following requirements:

- An organizational structure (organization chart);
- The definition of processes;
- The responsibilities of the individual;
- Written procedures;
- The necessary resources (human and technological);

It is essential that the various points mentioned above are interconnected and that at the basis of this interconnection there is a clear verbal and non-verbal communication, in order to achieve a common goal that coincides with the welfare of the company as a whole.

The QMS is based on four key principles:

1. *Managing* (Organize);
2. *Planning*;
3. *Delivering*;
4. *Measuring*.

1. *Managing*

The structure must organize a QMS to be applied to all aspects of the clinical trial, with a focus aimed at ensuring the protection of the study subjects and the reliability of the results.

Once the strategic direction to be taken has been defined, it is important that each activity involved has a person responsible for supervising and managing the activity itself.

The different activities must be organized by applying a risk-based approach, based on the following steps:

- Identification of critical data and processes;
- Risk identification;
- Risk assessment;
- Risk control based on acceptability limits;
- Risk communication;
- Risk review;
- Drafting of a risk report.

2. *Planning*

The planning will define the inputs and outputs, establishing which tests, procedures and methods to use during the different activities. The principles of planning are as follows:

- Every research and development activity must have a realistic and effective plan;
- The plan must be subject to continuous review;
- Amendments and deviations must be checked;
- There must be evidence of ongoing planning.

3. *Delivering*

In order to ensure success, anyone involved in carrying out the activities must be made aware of the required tasks, responsibilities and related reference standards.

The execution of the assigned tasks must correspond to what is described according to a standardized approach (written procedures), approved by the person responsible for the entire process in accordance with the organizational chart, and communicated to anyone involved in the activities.

4. *Measuring*

Verification is the final part of the Quality Cycle and checks that the processes have – or have not – met the established standards.

The verification process involves the following phases: Quality Control (monitoring), Quality Assurance (audit) and inspection by the Regulatory Authorities.

Regarding the verification activities, the QA ensures that the QMS is followed and functions optimally, planning targeted, timed and periodic checks on some internal steps of implementation of clinical studies and production of the related documentation. This "internal quality control" activity is not to be confused with that of auditing, which corresponds to a verification activity independent of the operating structure in question. The purpose of these controls is to reveal any non-conformities or deviations, as well as to favour a continuous implementation of the processes.

Abbreviations

QA	Quality Assurance
ICH	International Conference of Harmonization
QMS	Quality Management System
SC	Clinical Trial
RAQ	Quality Assurance Manager
GCP	Good Clinical Practice
SOP	Standard Operating Procedure

12. Clinical research and the role of the National Coordination Centre of Local Ethics Committees

C. Petrini, C. Mannelli

Introduction

The development of biomedical research, which in recent years is experiencing a moment of great prosperity, represents a fundamental pillar for the growth of every country. The implications deriving from innovation in this area are in fact not limited to the health context, but significantly permeate the cultural, economic, and ethical dimension of society, with concrete and measurable effects for the individual and for the community.

Encouraging and promoting the development of research that stands out for its robustness of scientific rigor and respect for ethical requirements must therefore be a priority. So, if the recognized role of scientific rigor is central as a guarantor of the quality and solidity of the method, that relating to ethical requirements should not be underestimated. The ethical requirements provide assurance regarding the respect of fundamental principles and the full protection of those involved in research, in compliance with international reference documents, including the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, the Convention on Human Rights and Biomedicine, the standards of Good Clinical Practice (GCP). However, it is necessary to highlight how the actions taken to verify the maintenance of these aspects must in no way represent, or be perceived, as a barrier to the development of science as, instead, they constitute an indispensable tool for promoting and enhancing reliable, inclusive, and responsible research.

In light of the dynamism that characterizes the evolution of research, the awareness of the value that the latter represents for individuals and for society highlights the need to adopt harmonized, homogeneous, and fluid paths. These aspects are aimed at increasing the skills in a fast and efficient manner therefore favouring its attractiveness. In this context, the need to rethink the legislation on clinical trials of medicinal products for human use and on medical devices was outlined with a substantial change of structure introduced by Regulation (EU) no. 536/2014 on clinical trials of medicinal products for human use (hereinafter: Regulation).

As part of the reorganization carried out by each Member State for the adaptation to the aforementioned Regulation, one of the aspects introduced

by Italy – in which the reorganization is still in progress – was precisely the *National Coordination Centre of the Local Ethics Committees for clinical trials on medicinal products for human use and on medical devices* (hereinafter: Coordination Centre) which has a significant task that will be dealt with in detail in this chapter.

The Coordination Centre: regulatory framework

The function and the importance acquired by the Coordination Centre cannot be separated from some brief references to the legislative and regulatory framework in which it is inserted.

On 27 May 2014, Regulation (EU) no. 536/2014 was published in the *Official Journal of the European Union*. The Regulation, which replaces Directive 2001/20/EC of the European Parliament and of the Council, was created with the aim of "ensuring the robustness and reliability of data on clinical trials throughout the Union, guaranteeing respect for rights, the safety, dignity and well-being of individuals", standardizing, optimizing and simplifying the authorization procedures among the Member States. Although in force since June 16, 2014, the timing of application of the Regulation was bound, pursuant to art. 82, to the satisfaction of a condition: the verified functionality, by the Commission, of the EU portal – single point of access for the presentation of data and information concerning clinical trials – and of the EU database – containing data and information submitted for each trial to which a unique identification number is assigned. However, full compliance of the aforementioned IT infrastructures took longer than expected: the Commission's opinion on the verified full functionality dates back to 13 July 2021. Once the Commission's decision has been published in the *Official Journal,* pursuant to art. 99 of the Regulation, six months had to elapse for its application, which therefore became operational on 31 January 2022.

Pending the application of the Regulation, the Member States have carried out an internal reorganization aimed at implementing the new procedures. One of the main innovations introduced by the Regulation concerns, in fact, the division of the trial evaluation process into two distinct parts. Part I, governed by art. 6, concerns the general methodological aspects of the study protocol operated by a single Member State indicated by the sponsor. Among the elements that fall into this first phase of evaluation, the relevance of the clinical trial is recalled; the assessment of risks and benefits; the reliability and robustness of the expected data. On the other hand, all Member States concerned by the study are involved in Part II of the evaluation in relation to their territory. This assessment, governed by art. 7

of the Regulation, concerns, among other aspects, the compliance of the study with the requirements regarding informed consent; compensation or reward; of recruitment of subjects; collection, storage and use of biological samples of the subjects involved in the clinical research.

The art. 8 of the Regulation marks the times for decisions on clinical trials relating to Part II. Each Member State concerned is, in fact, called upon to notify the sponsor, through the portal, of the decision taken (authorization, authorization under certain conditions or refusal of the trial). This notification must be uploaded within five days from the date of communication or, if later, from the last day of the assessment pursuant to art. 7, through a single national decision. In this matter, it should be noted that, it is necessary to arrive, in a very short time, at a single national decision, the Regulation leaves the Member States full power to independently structure the internal procedures aimed at achieving this objective.

In Italy, one of the most significant steps taken in view of the adaptation to the Regulation is represented by the Law of 11 January 2018, no. 3 containing "Delegation to the Government in the matter of clinical trials of medicines as well as provisions for the reorganization of the healthcare professions and for the health management of the Ministry of Health". Chapter I of the aforementioned law is made up of three articles. The first article, concerning the reorganization and reform of the legislation on clinical trials, provides for the adoption of one or more legislative decrees in compliance with the following guiding principles and criteria:

a) reorganization and coordination of the provisions in force, in compliance with European Union regulations and international conventions, in compliance with international standards for the ethics of medical research on human beings;
b) identification of the requirements of the centres authorized to conduct clinical trials from phase I to phase IV;
c) identification of ways to support the activation and optimization of clinical centres dedicated to phase I studies on both patients and healthy volunteers;
d) identification of suitable methods to protect the independence of the clinical trial and to guarantee the absence of conflicts of interest;
e) simplification of formal requirements for submitting the application for the opinion of the Ethics Committee and for conducting and evaluating clinical trials;
f) simplification of procedures for the use of residual biological or clinical material for clinical research purposes, subject to the provision of informed consent, in compliance with high quality standards;

g) definition of the evaluation and authorization procedures of a clinical trial, ensuring the involvement of patient associations, especially in the case of rare diseases;
h) application of information systems to support clinical trials;
i) identification of general criteria for the discipline of teaching systems of specific training courses in the field of clinical research methodology and conducting and managing clinical trials and drug testing;
j) implementation of mandatory continuing education programs in medicine;
k) reformulation and rationalization of the administrative sanctioning apparatus with particular regard to the responsibility of the investigator and the structures involved;
l) revision of the legislation relating to non-profit clinical trials and observational studies, in particular for low-intervention clinical trial;
m) reorganization of the legislation referred to in the decree of the Minister of Health of 17 December 2004 in the sense of providing for the possibility of transferring data relating to the clinical research to the pharmaceutical company and their use for registration purposes, and to establish that the pharmaceutical company reimburse the expenses related to the trial as well as the loss of income resulting from the qualification of the study as a non-profit activity.

The Coordination Centre: institution and mandate

In light of these premises, we come to the second article of Law no. 3/2018 entitled: "National coordination centre of Local Ethics Committees for clinical trials on medicinal products for human use and medical devices" and the Ethics Committees for clinical trials. The article is dedicated to the reorganization of Ethics Committees at national level in order to trace a path of adaptation to the application of the Regulation by providing, in paragraph 1, the establishment of the Coordination Centre at the Italian Medicines Agency (AIFA). Law no. 3/2018 assigns the following functions to the Coordination Centre:

- coordination, direction and monitoring of the evaluation activities of the ethical aspects relating to clinical trials on medicinal products for human use delegated to the Local Ethics Committees (to which we will return shortly);
- intervention, at the request of the individual local Ethics Committees, with support and consultancy functions also regarding the evaluation of clinical trials on medicinal products for human use for the aspects referred to in paragraph 1 of art. 7 of the Regulation;

- evaluation of clinical trials requiring review following adverse event reporting;
- monitoring of the activities carried out by the Local Ethics Committees and possible reporting of cases of non-compliance with the terms prescribed by the Regulation;
- dissemination of general guidelines for procedural uniformity and compliance with the deadlines for the assessment of the aspects;
- identification of the minimum content of the contract stipulated with the centre involved in the clinical trial.

The Coordination Centre is composed of a maximum of fifteen members, including two indicated by the Conference of Regions and Autonomous Provinces and at least two indicated by the most representative patient associations on national territory. As sanctioned by art. 2 paragraph 4 of Law no. 3/2018, the Presidents of the National Committee for Bioethics, the National Committee for Biosafety, Biotechnologies and Life Sciences, and the Istituto Superiore di Sanità (National Health Institute) participate in the meetings of the Coordination Centre. The members of the Coordination Centre, designated by the Minister of Health, must have adequate and documented knowledge in the field of clinical trials of medicines and devices – except for the representatives of patient associations. Furthermore, the members of the Coordination Centre must not find themselves in situations, direct or indirect, of conflict of interest and must be independent from the sponsor, the site, the investigators and the sponsors of the clinical trial.

As can be seen from the above, the function of the Coordination Centre is closely linked to the definition of local Ethics Committee, introduced by Law no. 3/2018, to which it is appropriate to dedicate a brief mention. The introduction of these bodies represents a fundamental step in the reorganization of the Ethics Committees envisaged by Law no. 3/2018 in view of the application of the Regulation. In fact, article 2, paragraph 7, of the aforementioned law governs the identification of Local Ethics Committees, up to a maximum number of forty throughout the country, selected according to the following criteria:

a) the presence of at least one Ethics Committee for each region;
b) the reorganization of the Ethics Committees, provided for by article 12, paragraphs 10 and 11, of the decree-law 13 September 2012, no. 158, converted, with amendments, by law 8 November 2012, no. 189, within the terms provided for by the aforementioned legislation;
c) the number of trials evaluated as coordinating centre during the year 2016.

The appointment of the members of the Local Ethics Committees, of regional competence, must take into consideration the need to ensure the

independence of each committee together with the absence of hierarchical relationships between committees.

Parallel to the introduction of Local Ethics Committees, Law no. 3/2018 governs the identification of National Ethics Committees, with the same functions as the Local Ethics Committees, in a maximum number of three, one of which is reserved for clinical research in the paediatric field.

The first mandate of the Coordination Centre

By decree of the Minister of Health of 19 April 2018, the fifteen members of the National Coordination Centre of the Local Ethics Committees for clinical trials on medicinal products for human use and medical devices were appointed. The decree added the Director General of AIFA to the three participants by right indicated above, who is assigned the function of Secretariat of the Centre.

The members remain in office for three years and can be renamed.

With a view to guaranteeing, as per legislation, the homogeneity of the procedures and compliance with the time limits put in place by the various Ethics Committees active on the Italian territory, through the issue of specific directives, the first mandate of the centre produced and disseminated, among other things, the guidelines for the collection of informed consent to participate in clinical trials with the aim of providing investigators and Ethics Committees with useful information to "promote methods of collecting informed consent functional to ensuring that the decision of the person to participate or not in a trial is truly free and informed". The document, available on the AIFA website, on the page dedicated to the Coordination Centre, underlines how the process of collecting informed consent has often been reduced to an information form and a formal and bureaucratic signature. Furthermore, the information sheets, often written in complex and difficult to understand technical language, sometimes do not include all the information elements relating to the guarantees and needs of the participants.

In this perspective, the guidelines disseminated by the Coordination Centre are aimed at providing homogeneous indications for clear information, easy to understand even for non-experts and which makes use of adequate tools to ensure real communication between the parties involved in trials.

In order to promote homogeneity on the national territory, the following documents are attached to the guidelines:

- informed consent for patient participation in a clinical trial on medicinal products, in phase I, II and III;
- informed consent for parent (s) or legal guardian for the inclusion of a minor in a clinical trial on medicinal products in phase I, II and III;

- example of an informed consent form for a "mature" minor aimed at inserting a minor in a clinical trial;
- example of an information sheet for the minor;
- for a good practice of research biobanking;
- legal representation.

Furthermore, in compliance with the mandate established by Law no. 3/2018, the Coordination Centre has adopted a "Clinical trial agreement for the drug(s)" scheme and a "Contract for conducting clinical investigations on the non-EC marked or non-marked medical device for the use intended", despite the awareness of the need to reformulate both schemes within a short time, with the application, respectively, of Regulation (EU) no. 536 of 2014 on clinical trials of medicinal products and of Regulation (EU) no. 745 of 2017 on medical devices.

The beginning of the second mandate of the Coordination Centre

The current Centre, appointed by decree of the Minister of Health on May 27, 2021, took office on July 6, 2021 and is made up of fifteen members. In addition to the members appointed by the Minister, as in the previous mandate, the President of the National Committee for Bioethics, of the National Committee for Biosafety, Biotechnology and Life Sciences and of the National Health Institute, together with the Director General of the AIFA, agency that maintains the functions of the Secretariat of the Centre.

The tasks of the current mandate include the delicate coordination of the Ethics Committees for compliance with the Regulation, which became operational on January 31, 2022.

In this regard, the Coordination Centre has so far made available, on the basis of some models developed by the EU Clinical Trials Expert Group, the following documents that each Member State, for each clinical trial, will have to evaluate pursuant to art. 7 of Regulation (EU) no. 536/2014:

- *curriculum vitae* prepared by the investigator. All personnel involved in conducting a clinical trial must be qualified, in terms of education, training and experience, to perform their duties with respect to the specific trial being approved. In this regard, it should be emphasized that the Ethics Committees must evaluate, for each experimental site, the suitability of both the principal investigator and the other investigators;
- declaration of interests, prepared and signed by each investigator. The Ethics Committees must verify, for each experimental site, that the investigators have no financial or personal interests potentially capable of undermining their impartiality. The Ethics Committee, in assessing the

suitability of the investigators, must also evaluate, for all investigators and not only for the main one, if there are conditions, such as economic interests, marital relationships, cohabitation or kinship and institutional affiliations, which could influence their impartiality according to the Regulations and the legislation in force in Italy;

- specific site suitability, compiled by the sponsor for each trial site. In the document, the investigator agrees to declare that the site has the facilities and equipment to conduct the clinical trial and makes arrangements to ensure that all investigators and other people involved in conducting the trial have adequate requirements, skills and training in relation to their role in the clinical trial, in compliance with Regulation (EU) no. 536/2014 and the national legislation in force, and that all the conditions identified that could affect the impartiality of each investigator have been addressed;
- allowance for trial participants included in the application dossier by the sponsor. The sponsor must enter all the information relating to the allowances or reimbursements of expenses to be paid to the subjects involved in the clinical trials. In this regard, it should be noted that no incentives or financial benefits can be granted to subjects or their representatives, with the exception of an indemnity for loss of earnings directly linked to participation in the clinical trial, which must be adequately documented. The compensatory allowance for expenses and for loss of earnings, directly connected with the participation, can also be recognized for the accompanying person of patients who are unable to travel alone such as, for example, underage patients, incapacitated individuals, frail patients. Requests for indemnity and their motivation must be examined and, if necessary, approved by the competent Ethics Committee.

For the purpose of preparing these documents to be included in the dossier, the Coordination Centre has made available a guide in order to support the sponsor and clinical trial centres during the presentation of applications in the national territory, pursuant to the Regulation.

Some upcoming activities of the Coordination Centre

The adoption of the implementing decrees provided for by the aforementioned Law no. 3/2018 and by Legislative Decree no. 52 of 14 May 2019 had significant delays. The publication of the decrees will allow the Coordination Centre to carry out further activities.

Furthermore, new activities are necessary following the application of Regulation (EU) no. 536/2014, which took place on 31 January 2022, in the days immediately preceding the drafting of this chapter.

Contracts for clinical investigations on medical devices

The Coordination Centre is currently engaged in drafting the contract scheme for conducting clinical investigations on medical devices that are not EC marked or not marked for their intended use, as well as the contract scheme for conducting clinical investigations on medical devices already EC marked. In parallel with the drafting of the contract schemes, the Coordination Centre is also drafting a guideline document for the evaluation of clinical investigations with devices, in which both ethical criteria of reference and operational aspects for the application of the Regulation (EU) 2017/745 are set out.

Contract for clinical trials on non-profit medicines

At the time this chapter was drawn up, the decree of the Minister of Health 30 November 2021 was published on 19 February 2022, containing "Measures to facilitate and support the implementation of clinical trials of non-profit and of observational studies and to regulate the transfer of data and results of non-profit trials for registration purposes, pursuant to art. 1, paragraph 1, lett. c), of Legislative Decree 14 May 2019, no. 52". Pursuant to Legislative Decree no. 52/2019, the Coordination Centre intervened in the drafting of this decree, providing the Ministry of Health with an opinion on 2 September 2021. The publication of the decree allows the Coordination Centre to complete the drafting of the contract scheme for clinical trials of non-profit medicines, ready in draft. In particular, the contract scheme must take into account one of the most significant innovations that the decree introduces with respect to current legislation, namely the possibility of transferring data and results of non-profit trials for registration purposes (Article 3). This innovation was already envisaged by Legislative Decree no. 52/2019, which reads: "*In order to enhance the non-profit clinical trials, even at low intervention clinical trial, the transfer of the related data as well as the results of the trial is allowed for registration purposes. In such cases, the sponsor or concessionaire is obliged to support and reimburse the direct and indirect costs associated with the clinical research, as well as to pay, following any requalification of the same as a profit-making activity, the relative fees, including potential revenue deriving from the enhancement of intellectual property*".

Observational studies

Observational studies, not only with the use of medicinal products, provide valuable information for the advancement of knowledge, for the benefit of patients and, more generally, of all citizens.

On the basis of the aforementioned decree of 30 November 2011, "by means of AIFA provision, to be adopted within thirty days of the decree coming into force, the new guidelines for the classification and conduct of observational studies on drugs are defined". When the measure is adopted, the Coordination Centre will be able to continue and complete an activity already set up to favour the execution of observational studies. For this purpose it will be necessary to discuss with the Authority for the Protection of Personal Data regarding the application of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 concerning the protection of individuals with regard to processing of personal data, as well as the free circulation of such data and repealing Directive 95/46/EC (General Data Protection Regulation). With this comparison it is intended above all to favour the execution of retrospective observational studies (not only pharmacological), which at the moment suffers from some difficulties with respect to the requirements set by the legislation on the protection of personal data.

New local Ethics Committees

During the first mandate of the Coordination Centre and in the first phase of the second mandate, interactions with the Ethics Committees were limited as the founding decree had not yet been adopted, envisaged by Law no. 3/2018, of the 40 Local Ethics Committees, over which, pursuant to the same law, the Coordination Centre has competence. When this decree is adopted, the Coordination Centre will be able to activate not only the monitoring function attributed to it and not yet exercised, but also open direct collaboration with the committees themselves in order to make the procedures as efficient and homogeneous as possible.

Particularly relevant, in this regard, is the provision that the decree establishing the Ethics Committees, soon to be adopted, also establishes the possibility that the Local Ethics Committees express themselves not only on Part II of the evaluation report, pursuant to art. 7 of Regulation (EU) no. 536/2014, but also on Part I (see above, paragraph "The Coordination Centre: regulatory framework"), conjointly with the competent Authority. The possibility for the Ethics Committees to also express their opinion on Part I, although not explicitly provided for by Law no. 3/2018, is recognized by Regulation (EU) no. 536/2014 (art. 4). The Coordination Centre intends to support the Local Ethics Committees also for the purposes of better effectiveness in the collaboration between the committees themselves and the competent Authority.

Furthermore, the Coordination Centre intends to promote the quality of the activity of the new Ethics Committees also through training activities.

Above all, for the Centre's activity to be successful, collaboration between the Centre itself and all the parts involved is essential: not only the Ethics Committees, but also the institutions (Ministry of Health, AIFA, National Health Institute, Regions), patient associations, scientific societies.

The aim is not only the effective application of regulations, but also, and above all, a robust cultural promotion of the ethics of research, for the benefit of patients and the whole community, which benefits from the advancement of knowledge.

Some final thoughts

Italy is going through a phase of significant reorganization with regard to Ethics Committees and, at the time of writing, many profiles are still being defined. This contribution, taking into account the dynamics of the issue, has photographed the state of the art focusing on the function of the Coordination Centre as a point of reference in this moment of significant transition. Through the dissemination of models and best practices, the contribution of the Coordination Centre is part of the wider effort, at national and international level, aimed at tracing homogeneous, fluid and quality paths for research. In this perspective, the tools made available by the Coordination Centre - a dynamic material, which lives and improves through constant and productive dialogue with the various research stakeholders - are animated by the intention of combining the promotion of research development with full guarantee of compliance with ethical requirements.

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13. The processing of personal data in Research (GDPR-EU 2016/679): the experience of a Regional University Hospital - Ospedali Riuniti di Ancona (United Hospitals of Ancona)- operational guidelines on the processing of personal data in Clinical Studies

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The issue of the processing of personal data for medical, biomedical and epidemiological research purposes is one of the most delicate issues in the field of protection of the fundamental rights and freedom of data subjects (individuals).

The Oviedo Convention on Human Rights and Biomedics [1] highlights how human beings must be protected in their dignity and identity in order to guarantee to each person, without discrimination, respect for their integrity and other fundamental rights and freedom regarding the applications of biology and medicine.

Recommendation (97) 18 of the Council of Europe [2] on the protection of personal data collected for statistical purposes highlights how in the processing of personal data used for such purpose, including in the health sector, respect for fundamental rights and freedom must be guaranteed and, in particular, the right to confidentiality, both at the time of collection, and if they are kept for later use or for the circulation of statistical results with the obligation of secrecy for those who are in contact.

Similarly, the Council of Europe Recommendation (97) 5 [3] on the protection of health data reaffirms respect for fundamental rights and freedom, in particular the right to privacy, must be guaranteed in the collection and processing of health data, in such a way that they are collected and processed in a compliant and appropriate manner ensuring that they must be established by internal legislation, in order to allow a licit and fair treatment. As a rule, the collection and processing of health data must not be carried out except by health professionals or by persons or bodies working on behalf of health professionals.

The Declaration of Helsinki [4] establishes that in the field of research all the laws and regulations of the State in which the research is conducted must be taken into consideration, in order to implement all actions aimed

at guaranteeing the privacy of subjects involved in the research and the confidentiality of their personal data.

The processing of personal data for medical, biomedical and epidemiological research purposes is regulated at the level of principles and internationally by the indications mentioned above.

Further provisions have also been formulated at EU and national level aimed at regulating in a timely manner the processing of personal data for research purposes in the health sector, in order to define the boundary for the legitimacy of the processing.

It should be noted that, in general, the data relating to health do not require the consent of the data subject, if they are processed for "treatment purposes" [5] on the basis of art. 9, paragraph 2, lett. h) and paragraph 3 of the GDPR which indicates as the purpose of treatment "*of preventive or occupational medicine, for the assessment of the working capacity of the employee, medical diagnosis, the provision of health or social care or treatment or the management of health or social care systems and services on the basis of Union or Member State law or pursuant to contract with a health professional and subject to the conditions and safeguards*" and specifies that health data may be processed for the aforementioned ("care") purpose "*by or under the responsibility of a professional subject to professional secrecy or by a person subject to the obligation of secrecy*".

As a result, therefore, that the healthcare professional subject to secrecy must not request the patient's consent for the processing of personal data necessary for the healthcare provision, whether in case in which he operates as a freelancer and/or in the case in which he exercises his activity inside a public or private health facility.

If this is correct for the processing of personal data in the health sector for "treatment purposes", this does not apply to the research purpose, which appears to be only in a broad sense and potentially relevant to the treatment of the data subject, as in the case of clinical studies and/or pharmacological clinical trials and also, non-pharmacological clinical trials, such as observational and retrospective ones.

In this regard, art. 6 GDPR [6], which governs the legal conditions of lawfulness, establishes, among these, that the processing of personal data is lawful if the data subject has given consent.

Specifically, the consent must be free, explicit in such a way that the data subject can self-determine the choice and refuse or revoke the same at any time. Furthermore, in order for the consent given to be valid, there must not be an imbalance between the parties, such as to make it unlikely that it has been freely given, especially where the data subject is in fragile conditions.

Similarly, art. 9 GDPR referred to the processing of special categories of data, such as data relating to health or sexual life, as well as genetic data, provides among others, as a condition of lawfulness, the explicit consent of the data subject for one or more specific purposes. Furthermore, the aforementioned article identifies, as an additional legal basis, the archiving process carried out in the public interest, for scientific research or for statistic means based on the rights of the Union or national, provided that it is proportionate to the purpose pursued and following the adoption of appropriate technical and organizational measures such as data minimization and pseudonymisation.

With this disposition, therefore, a turning point is introduced between scientific research, based on a principle, and research conducted, without a normative provision, thus the latter, permissible by virtue of the manifestation of the consent given by the data subject, except for the observations that will follow.

At internal level, the Code regarding the protection of personal data [7] in art. 110 – Biomedical research and biomedical and epidemiological research - reiterates that the consent of the data subject for the purposes in question is not necessary when the research is carried out on the basis of provisions of law, regulation or European Union law and, also if the research falls within those referred to in art. 12 *bis* of Legislative Decree 30 December 1992, no. 502 and subsequent amendments, so-called current and finalized health research. In such cases (research required *by law*), however, a data protection impact assessment must be conducted and made public.

Furthermore, in the field of medical, biomedical and epidemiological research not provided for by regulations, consent may not be collected, although it constitutes the legal basis of the processing, when due to particular reasons informing the data subjects is impossible or involves a considerable effort or risks making it impossible or seriously jeopardizing the achievement of the research objectives. In such cases, the research program must be subject to a motivational favourable opinion from the competent Ethics Committee and must be subjected to prior consultation with the Authority for the protection of personal data.

In this regard, the Authority for the protection of personal data has adopted a specific provision [8] which has clarified the conditions upon the occurrence of which the Data Controller is allowed to process personal data for research purposes regardless of whether there's the granting of consent.

Particularly in this provision the Authority highlights that this may occur in the case of conducting studies with previously collected data (including biological samples) for treatment purposes or other projects as well as for

conducting studies involving people who, due to seriousness of their clinical condition are unable to understand the information and validly give consent.

In such cases, the Authority affirms, in order for the studies to be conducted, it is necessary that the subject, records in the research project the reasons for which the information cannot be issued to the data subject and, therefore, the relative consent acquired, in consideration of the impossibility of informing him or her with a disproportionate effort or thus jeopardizing the achievement of the research purpose. In particular, reference is made to the ethical reasons, organizational impossibility and health reasons of the data subject.

These are reasons that must be promptly argued and explained by the subject and, in any case, the conduct of the study can only be started following the release of a favourable opinion expressed by the competent Ethics Committee and after prior consultation of the Guarantor Authority for the protection of personal data pursuant to art. 36 GDPR and art. 110 of Law no. 196/2003 and subsequent amendments

Regarding clinical trials of medicinal products, the 2008 guidelines of the Authority for the protection of personal data [9] issued on the subject are still current. This provision details in particular the roles assumed (Owner/Manager/Co-owner) by the various subjects who participate in various capacities in the study (Sponsor/Research Centre/CRO) defining their tasks and responsibilities, as well as the technical and organizational measures that each player must implement. be, also specifying the contents of the information and consent, the methods of exercising rights, transferring data abroad, storing data and simultaneously providing an information template and consent manifestation.

Even though, this provision is still current, it must, nevertheless, be reinterpreted in the light of the information provided for by Articles 13 and 14 of the GDPR (Information), which have introduced in the minimum content all necessary additional information to make the person concerned clearly aware about the methods and terms of the processing of his personal data, essential for self-determination.

Similarly, art. 26 GDPR (Joint data controllers) and art. 28 GDPR (Data Processor) regulate these relationships between the various partners of the firm and identify the mandatory clauses to be provided for in the agreements stipulated for this purpose.

It is noted that the EDPB Group with the 2020 provision [10] specified that when consent constitutes the legitimate basis for conducting research in accordance with the regulation, such consent of the use of personal data should be distinguished from other requirements that serve as deontological regulations or procedural obligation, such as informed consent.

The Group underlines that in reality the GDPR does not exclusively provide consent as a legal basis, but rather other legal bases that can serve as an additional guarantee, such as the public interest or connected to the exercise of public authority or the legitimate interest of the owner or of third parties, the latter subjected to stringent application parameters (evaluation of the purpose and its achievement in relation to the tasks entrusted to the owner, balancing with the fundamental rights and freedom of the data subject). It must be said, however, that the National Authority for the protection of personal data in this area has repeatedly expressed itself considering consent as a condition of lawfulness.

In implementation of the principle of accountability of the Data Controller's accountability pursuant to art. 5 GDPR and, therefore, responsibility for compliance with the general principles of the processing of personal data and for the purpose of proving the measures taken regarding processing related to research, this Company has adopted specific operating lines approved ultimately with the determination of the General Director no. 868 of 12 August 2021 (Annex 1) in order to make the processing of personal data in this field consistent and homogeneous for the multiplicity of studies conducted at this Company.

It is noted that the University Hospital of Ospedali Riuniti of Ancona (United Hospitals of Ancona) is the seat of the Regional Ethics Committee (CERM), which carries out its activity with reference to the clinical studies proposed by the aforementioned Company, as well as by the Single Regional Health Authority and by the Hospital Marche Nord, entities of the SSR (HIH).

Precisely this organizational structure and the need to define good practices also in terms of uniformity on the territory in terms of data processing in clinical studies has guided the Company, in collaboration with the aforementioned Bodies, to implement and disseminate virtuous paths in this context to provide a framework of homogeneous and shared rules to be observed by the sponsors and experimental centres that submit clinical trials or trials that are conducted at one of the SSR (HIH) companies to the Regional Ethics Committee.

These operational guidelines take into account the regulatory path and its evolution and are a particularly useful tool, both for the promotes and for test centres, as they have been formulated according to a check list logic easily usable during the preparation of the documentation to be submitted to the Ethics Committee.

In addition, these operational lines are accompanied by formats that take into account first of all the mandatory documentation that must be prepared and its minimum content, in view of the plurality of concrete cases that can

be determined in this context, but at the same time constitute a tool easy-to-use and to understanding for non-professionals, in order to guide them and make them aware of the importance of data protection from the design phase of the study in compliance with the principle of protection *by design and by default*[1].

The Company proceeded to divulge these operating lines among its principal investigators and among the sponsorsfurther instructing them, pursuant to art. 29 GDPR, in relation to this type of treatment on its correctness and lawfulness and therefore, compliance with sector legislation.

In fact, it must be remembered that the data processed in the health sector constitute a precious asset as they allow, on the one hand, if studied and analyzed, a growth in the improvement of care and in the overall development of society, guaranteeing the satisfaction of the health needs of the population, on the other hand, a risk that has a significant impact on the rights and freedom of the related subjects due to their vulnerable condition.

Personal data, precisely for the reason of their ability to identify, profile and characterize a single individual, first of all constitutes an asset of the person who must be the object of particular protection and safeguarding, as an illegitimate treatment could have grim consequences on the ability of self-determination of the subject and therefore consequently see violated the rights connected to the personal data unlawfully processed.

So it constitutes the obligation of the data controller, and even more so for the Company who mainly processes data falling within the particular category, to take all necessary and adequate actions to preserve the

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[1] Art. 25 - General Data Protection Regulation - Reg. (EU) no. 679/2016: "*Taking into account the state of the art and the implementation costs, as well as the nature, scope, context and purpose of the processing, as well as the risks with different probabilities and gravity for the rights and freedom of natural persons constituted by the processing, both at the time of determining the means of processing and at the time of the processing itself, the data controller implements adequate technical and organizational measures, such as pseudonymisation, aimed at effectively implementing the principles of data protection, such as minimization, and to integrate the necessary guarantees into the processing in order to meet the requirements of this regulation and protect the rights of data subjects. The data controller implements adequate technical and organizational measures to ensure that, by default, only the personal data necessary for each specific purpose of the processing are processed. This obligation applies to the amount of personal data collected, the scope of the processing, the retention period and accessibility. In particular, these measures ensure that, by default, no personal data is made accessible to an indefinite number of individuals without the intervention of the natural person* […]".

protection of such data and the rights connected to them, as "guardian angel" of the same.

This protection must not be experienced as a mere "bureaucratic" fulfilment [11] but as a tool for the Company's competitiveness and capable of attracting the interests of the various stakeholders [12].

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7. Legislative Decree 30 June 2003, no. 196 containing the "Code regarding the protection of personal data", as amended by Legislative Decree 10 August 2018, no. 101.
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Annex I

PRACTICAL GUIDELINES IN THE FIELD OF DATA PROCESSING PERSONNEL IN CLINICAL STUDIES

(Version 2.0 dated 27.03.2021)

These indications are issued on the basis of the following regulatory provisions.

EU Regulation 2016/679 of the European Parliament and Council of 27 April 2016 concerning the protection of individuals with regard to the processing of personal data, as well as the free circulation of such data (hereinafter EU Reg. 2016/679).

Legislative Decree 30 June 2003, n. 196 containing the "Code regarding the protection of personal data", as amended by Legislative Decree no. 101 of 10 August 2018.

Deontological rules for processing for statistical or scientific research purposes issued by the Data Protection Authority on 19 December 2018.

Provision containing the provisions relating to the processing of particular categories of data issued by the Data Protection Authority on 5 June 2019.

Guidelines for the processing of personal data in the context of clinical trials of medicines issued by the Data Protection Authority on July 24, 2008, as applicable.

This document pursues the aim of providing a framework of homogeneous and shared rules to be observed by the sponsors and experimental centres that submit to the opinion of the competent Ethics Committee (Marche Ethics Committee or INRCA Ethics Committee) clinical trials or studies that are conducted at one of the SSR (HIH) Companies.

It should be noted that for this type of processing the condition of lawfulness is represented by the explicit consent of the data subject pursuant to art. 6, paragraph 1, letter a), EU Reg. 2016/679 and by art. 110 and 110 bis of Legislative Decree no. 196/2003 and subsequent amendments. In fact, it deals with the processing of personal data for scientific research purposes in the medical, biomedical or epidemiological and/or statistical fields not provided for by specific provisions of the law.

If, on the other hand, the above data processing is carried out, for the same purposes, on the basis of specific provisions of the law, the conditions of lawfulness are represented by the legal obligation pursuant to art. 6, paragraph 1, letter c), in any case it is necessary, by the subjects involved in the experimentation, to carry out a specific impact assessment pursuant to art. 35 of EU Reg. 2016/679, to be made public.

Also for retrospective and/or observational studies it is necessary to acquire specific consent as a condition of lawfulness, pursuant to the aforementioned art. 6, paragraph 1, letter a), EU Reg. 2016/679.

The consent therefore, must be acquired, unless as mentioned, the trial and/or study is conducted on the basis of specific legal provisions.

Furthermore, consent may not be acquired due to particular reasons or in the event that its acquisition involves a disproportionate effort or, in any case, risks making it impossible or seriously jeopardizing the achievement of the purposes of the research. To this end, among the particular reasons are to be found in the occurrence of the following situations:

- ethical reasons attributable to the circumstance that the data subject concerned ignores his condition
- reasons for organizational impossibility attributable to the fact that failure to consider the data referring to the estimated number of data subjects who cannot be contacted to inform them, compared to the total number of subjects intended to be involved in the research, would produce significant consequences for the study in terms of alteration of the relative results or, also, as deceased or not contactable
- health reasons attributable to the seriousness of the clinical state in which the data subject is, due to which he is unable to understand the indications provided in the information and to validly give consent. In such cases, the study must be aimed at improving the same clinical state in which the data subject finds himself.

If such circumstances occur, the study protocol must specify the reasons and acknowledge that all efforts have been made in order to obtain consent.

In cases where consent is a condition of lawfulness of the processing and this has not been acquired, the trial must be subject to prior consultation with the Guarantor pursuant to art. 36 of EU Reg. 2016/679.

As part of clinical trials and/or studies, it is necessary to define the relationships between sponsors and trial centres and any CROs.

Furthermore, if the sponsor stipulates contracts with external subjects (for example research organizations, analysis laboratories or other subjects) also for monitoring, insertion, validation or statistical analysis of data, he must clearly define the type of relationship with them.

In particular, the relationships between all the subjects involved in the trials and the modalities with which the consequent relationships are regulated and, in general, the modalities with which during the trials and/or clinical study data is processed.

Specifically, if the trial and/or clinical study envisages the involvement, in addition to the Sponsor and the Investigating Centre, of an analysis laboratory, a CRO or even other legal and/or physical persons (third party legal entity) for specific activities of the trials and/or clinical study, a specific contract must be signed on the basis of which the aforementioned subject is entrusted with the processing of personal data as Data Processor pursuant to art. 28 of the EU Reg. If the relationship is not configured in terms of Company/Manager, it is necessary to provide for specific privacy policies so as to protect the rights and freedom of the said subject.

In particular when the treatment also concerns genetic information

it is necessary to provide adequate and detailed information regarding the specific profiles for the use of the aforementioned data and biological samples.

In the context of clinical trials and/or studies, generally, the relationship between the Sponsor and the Investigating Centre of independent ownership as the Sponsor and the Investigating Centre carry out their tasks with autonomous purposes and methods.

If otherwise the relationships, in relation to certain trials and/or clinical studies, between sponsors and trial centres are configured as joint ownership and/or company/manager, it is necessary to sign specific acts between the Sponsor and the Investigating Centre that regulate the relationships between the parties, in particular, indicating the responsibilities of each one with regard to the data processing carried out.

Any joint controller relationships must be defined from time to time on the basis of the provisions of art. 26 of EU Reg. 2016/679 and as summarized below. The content of any agreement must be made known to the data subject, attaching it in the documentation to be made available to the patient.

General indications

The information and consent to the processing of the personal data of the data subject must be separate from those relating to participation in the clinical trial and/or clinical study, such as those relating to informed consent, this in application of the principle of transparency (art. 12 EU Reg. 2016/679).

In the document containing the information on the processing of personal

data, the methods by which personal data are used must be indicated with specific reference to the methods of transmission, also statistical processing, publication of the results of the trial or study in compliance with the principle of minimization (pseudonymization or anonymization of data) (art.89 EU Reg. 2016/679).

In the document containing the information on the processing of personal data, the roles assumed by the various parties involved (sponsor, investigator centre, CRO or other third parties) must be defined in order to identify the Companies and/or joint companies, managers and/or co-responsible, those authorized to process the data and the consequent obligations as well as the subjects to whom the data must be communicated.

The forms relating to the relationships between the parties regarding the protection of personal data (sponsor, investigator centre, CRO, other third parties) must always be present and must be legitimately signed between the parties (digitally or by other suitable means).

Minimum content of the information

DATA CONTROLLER/AUTONOMOUS DATA CONTROLLER AND POSSIBLE JOINT CONTROLLER AND/OR DATA PROCESSOR

The identification data of the subjects indicated here and their contact locations must be indicated.

DATA PROTECTION OFFICER

The contact details of the data protection officer, where appointed, of the company/autonomous companies/joint controllers must be indicated.

PURPOSE OF THE PROCESSING

All the purposes of the experimentation or study must be indicated in a clear, concise and intelligible way, including the purpose of research, statistics, pharmacovigilance and any requirements for inspections, controls imposed by national and/or international legislation.

NATURE OF DATA

The nature of the personal data processed as personal data, sensitive data (data suitable for revealing the state of health, sexual life, religious beliefs, race origins), genetic data, biological samples must be indicated.

RECIPIENTS OF THE PERSONAL DATA

All the subjects who process the data or to whom the data are communicated for the purposes related to the experimentation or study must be indicated.

DATA RETENTION PERIOD

The exact retention period of the data by the data controller must be indicated.

RIGHTS OF THE DATA SUBJECT

The rights that the data subject can exercise and the methods with specific reference, in the case of a biological sample, of the possibility of its destruction following the withdrawal of consent, must be indicated, except in the case in which the data and biological samples no longer allow to identify the said subject.

LEGAL BASIS OF THE PROCESSING

The optional nature of the trial or study must be indicated and what happens if the data subject does not give his consent and that the lack of consent has no implications on the assistance to be given to the data subject.

METHOD OF TREATMENT

The methods for collecting, recording and using the data and the IT or paper tools used must be indicated, including the methods of archiving and conservation.

AUTOMATED PROCESS

The existence of an automated decision-making process based on the personal data processed must be declared; if it exists, it is necessary to provide the data subject with information on the logic used in these processes, as well as the importance and consequences for the same.

TRANSFER TO A THIRD COUNTRY OR TO AN INTERNATIONAL ORGANISATION

It must be expressly indicated if the data are also transferred by means of communication in countries outside the European Union; in this case, it must be specified whether this transfer takes place on the basis of an adequacy decision or through one of the methods provided for by Article 44 et seq. of EU Reg. 2016/679, for example adequate guarantees with or without the authorization of the supervisory authority, such as standard contractual clauses. In any case, the legal basis for the possibility of transfer abroad must be adequately documented.

Minimum content of consent

The consent must be issued by the data subject or, if this is impossible due to temporary or permanent incapacity, it must be issued by the entitled person.

The consent must preferably be expressed in written form, although it can also be issued in oral form, in which case specific mention must be made of its acquisition by those who are required to acquire it.

It must be made clearly and with reference not only to the specific purposes related to the trials or study but also with reference to the other purposes (for example the statistical purpose, pharmacovigilance and any requirements for inspections, controls imposed by national and/or international legislation, the possibility of transferring data to countries outside the European Union, if the transfer takes place on the basis of the consent of the data subject).

In the event that the experimentation or study also includes the enrolment of minors, the consent must be given by the legitimated subject.

In conclusion, in the consent the data subject must permit to the processing of his personal data and its transfer outside the European Union (if provided), with express indication of the recipients, for the purposes of the trials or study and with the methods and within the limits indicated in the statement.

Furthermore, when the trial is aimed at patients under age, it is necessary that these elements are verified with particular attention, especially with regard to the legitimacy of the subject who can express any consent on behalf of the minor.

In relation to the foregoing, the attached information and consent form to be used in the processing of personal data and genetic data for research purposes is approved (doc. N. 1).

INDICATIONS FOR THE PREPARATION OF THE AGREEMENTS GOVERNING THE RELATIONS BETWEEN JOINT CONTROLLER OR BETWEEN CONTROLLER AND PROCESSOR

The relationships that can be established in the management of data processing between the sponsor and the investigating centre (Company) are that of "controllers" or "joint controller" or "controller and processor".

In general, the relationship established between the Sponsor and the Experimental Centre is autonomous, therefore it is not necessary to prepare further documentation to regulate the relationship on data processing. In any case, the information must be clear about the role between Sponsor/CRO (where foreseen)/Investigating Centre and, therefore, their data and contact

locations and the autonomous purposes and methods of treatment must be indicated.

If, in any case, due to the peculiarity of the trials, the establishment, with regard to the processing of personal data, of relationships that are not attributable to that of autonomous Companies, the contents of the contracts/agreements that must be signed and applied by the parties.

Joint controllers agreement form

JOINT CONTROLLER

The identification data of the joint controllers and their contact locations must be indicated together with that of the data protection officer, as well as of the respectively appointed managers.

OBJECT OF THE AGREEMENT

The responsibilities and activities to be carried out by each of the joint controllers as regards their data processing competence must be defined with particular reference to the exercise of rights and the respective functions of communicating of the information to data subjects (for example data entry methods, data communication, responsible and/or authorized appointments, anonymisation/pseudonymisation/encryption operations carried out on data).

The agreement must contain an indication of the methods of exercising the rights by the data subject and the subjects to contact for this purpose.

Agreement form between data controller and data processor

In order to make the rules of any ownership/responsibility relationship homogeneous, the attached model agreement to be used in such cases and the contents of which are summarized below (doc. No. 2) is hereby approved.

DATA CONTROLLER AND DATA PROCESSOR

The identification data of both the holder and the data controller and their contact points must be indicated

OBJECT OF THE PROCESSING

The subject of the relationship between the controller and processor in relation to the trial or study must be indicated.

DURATION - NATURE AND PURPOSE OF THE TREATMENT

The duration of the relationship between the data controller and the data processor must be indicated, as well as the type of processing (collection, registration, organization, structuring, storage, adaptation, modification, extraction, consultation, use, communication, dissemination, comparison, interconnection, limitation, cancellation, destruction), as well as the purposes of the processing.

TYPE OF DATA

The nature of the personal data processed must be indicated: personal data, sensitive data (data suitable for revealing the state of health, sexual life, religious beliefs, racial origins}, genetic data, biological samples.

CATEGORY OF DATA SUBJECT

The type of subjects to whom the treatments refer must be indicated (patients, minors, vulnerable subjects).

OBLIGATIONS AND RIGHTS OF THE CONTROLLER AND PROCESSOR

It must be specifically indicated which are the duties of the owner and which the duties of the manager and the activities that each of them must perform individually, in particular the instructions for processing the data must be indicated by the owner, in the agreement must also be, inserted a clause that obliges the processing and his employees and collaborators to confidentiality and secrecy.

The methods by which the data processor collaborates with the data controller must be indicated with regard to any requests for the exercise of rights by the data subject and the methods of support in the eventuality of notification of violations to the supervisory authority and to the data subject and in supporting the eventual completion of the impact assessment and/or prior consultation in relation to the specific treatment.

The methods by which the data is managed after the conclusion of the relationship between the controller and the data processor must be indicated

The possibility of checking and inspecting the controller on compliance with data protection obligations in relation to the processing entrusted must be indicated.

TECHNICAL AND ORGANIZATIONAL MEASURES OF THE DATA PROCESSOR

The adoption of adequate technical and organizational measures must be indicated to guarantee a level of safety adequate to the risk.

SUB-PROCESSOR

Any recourse to other data processor must be indicated by the data processor and in this case the mandatory authorization of the controller must be indicated.

The commitment of the manager to sign the same agreement, i.e. having the same contents, with the aforementioned sub-manager must be indicated

Further indications

As regards the carrying out of the DPIA or Data protection impact assessment pursuant to the provisions of art. 35 of the King g. EU 2016/679, each company will use its own model/tool in use provided it is structured according to the minimum contents of the aforementioned art. 35 of EU Reg. 2016/679 (systematic description of the foreseen treatments and of the purposes, an assessment of the necessity and proportionality of the treatments in relation to the purposes, an assessment of the risks for the rights and freedom of the data subjects, the measures provided for risks and that demonstrate compliance with the European regulation on the protection of personal data). In the event that the DPIA is prepared directly by the Sponsor, the Hospital where the trial will be conducted will limit itself to assessing its completeness and reliability.

It is also necessary that specific instructions be provided to the personnel who process personal data at the Hospital. To this end, a model is attached that can be integrated and customized - for specific trials/clinical study - in relation to the data processing by the staff in charge (doc. N. 3).

The clauses of the contract for the trial and/or clinical study - which must always be present for all types - must comply with the indications provided above and therefore not contradict the content of the information and consent form for the processing of personal data; this also with regard to the relationships between the Sponsor/Experimental Centre and the CRO which must be specifically defined in the context of the contract itself.

Furthermore, in relation to studies that involve the use of software and/or medical devices that process personal data, it is necessary to obtain authorization from the competent office regarding compatibility with company systems and security measures in to be.

DOC. 1 - INFORMATION ON THE PROCESSING OF PERSONAL DATA

FOR SCIENTIFIC AND STATISTICAL RESEARCH PURPOSES PURSUANT TO ART. 13
OF THE 2016/679 EU REGULATION "GENERAL DATA PROTECTION REGULATION"

The Hospital […], in application of Regulation (EU) 2016/679 on data protection, informs that the processing of personal data is carried out in compliance with the fundamental rights and freedom of individuals. The processing of personal data will therefore be based on principles of correctness, lawfulness, legitimacy, transparency, indispensability and not exceeding the purposes for which the data is collected.

AUTONOMOUS DATA CONTROLLERS
AND RESPONSIBLE FOR DATA PROTECTION

1) Hospital (name, headquarters, telephone, PEC, represented by the General Manager, as Sponsor/Experimental Centre data protection officer contacts: telephone - e-mail.
2) Name, registered office, telephone, PEC, represented by, as Centre Sponsor/ Investigator Responsible for data protection contacts: telephone - e-mail - PEC.
In the event that the Sponsor has appointed the CRO to carry out some activities relating to the trial and/or clinical study, it is necessary to indicate the following data.
The Sponsor (name) has appointed the CRO (name, registered office, telephone, PEC, represented by) as the data processor pursuant to art. 28 EU Reg. 2016/679, for the following activities that involve the processing of personal data:
In the event that an Analysis Laboratory is involved in the trial, a third party compared to the Sponsor/Investigating Centre, must indicate as follows in 1.

In the case of the Laboratory Analysis data processor (Article 28 of EU Reg. 2016/679)
The Sponsor/Experimental Centre (name) has appointed the Analysis Laboratory (name, headquarters, telephone, PEC, represented by) as the external data processing manager pursuant to art. 28 EU Reg. 2016/679, for the following activities that involve the processing of personal data:

In the case of an Analysis Laboratory, Autonomous Data Controller for the processing of personal data.

(1) In the event that the Analysis Laboratory plays the role of data processor pursuant to art. 28 EU Reg. 2016/679 must be specifically named. If the Analysis Laboratory is appointed by the University Hospital, the attached form must be used (doc. no. 1) - (Attention! This note must be deleted when filling in).

The Analysis Laboratory (name, headquarters, telephone, PEC, represented by) is the Autonomous Data Controller with reference to the analysis and storage of biological samples.

NATURE OF PERSONAL DATA

The personal data processed are personal details (name, surname, date and place of birth, place of residence, tax code) and data relating to the state of health also genetic data if required by the study/clinical trial, therefore, the data falling within the particular category of data referred to in art. 9, paragraph 1 (special categories of personal data).

The personal data processed may also include biological samples.

PURPOSE OF THE PROCESSING

Personal data are processed for scientific research purposes in the medical, biomedical and epidemiological fields, in particular for scientific and/or statistical research purposes, in the context of clinical trials/studies.

We also inform you that your data and biological samples may be processed for scientific and statistical research purposes similar and additional to the original ones, provided that they are linked to the consent originally issued for scientific and statistical research purposes.

If the research involves the processing of genetic data, it is necessary to specify:

Where the study involves the processing of genetic data resulting in unexpected information that may bring you a concrete and direct benefit in terms of therapy, prevention or awareness of reproductive choices, the same will be communicated to you only if you have provided specific consent. In the event that the above unexpected information also concerns a third party belonging to your genetic line, the same will be communicated to the latter only if you have given specific consent.

RECIPIENTS OF PERSONAL DATA

Your personal data will be processed by authorized and specially trained personnel and in particular by:

- Sponsor of the study
- Monitor and Auditor (possibly appointed by the Sponsor)
- External data processor and any sub - responsible companies
- Insurance companies for the assumptions of liability
- National and foreign Authorities and Ethics Committee, within their respective competences
- Laboratories external to the Company and related to other public and private structures to which biological samples taken for the purpose of experimentation for sample analysis are transmitted.

The data may be disclosed only in an anonymous form by adopting anonymization techniques available to the state-of-the-art.

DATA RETENTION PERIOD

Personal data are kept for a period of seven years from the conclusion of the clinical trial. If the consent for the research is expressed, the sample can be kept until it is exhausted or for a maximum period of integrity …… and in any case for the time in which the sample maintains its integrity.

In case of interruption of the treatment, the biological samples taken will be destroyed.

In the event that the biological samples are delivered to Analysis Laboratories, third parties, with respect to the Sponsor/Experimental Centre, it is necessary to specify the following

The biological samples will be sent to the Analysis Laboratory which analyzes and conserves them, as an independent holder/external manager of the treatment. To exercise the rights referred to in EU Reg. 2016/679, in relation to this type of treatment, you can contact the same Laboratory.

TRANSFER TO A THIRD COUNTRY OR TO AN INTERNATIONAL ORGANISATION

Your data will not be communicated or transferred to a non-EU country.

In case of transmission to non-EU countries, the data will be transferred in compliance with the provisions of Regulation E and in particular in compliance with the provisions of art. 44 et seq., In order to guarantee the same level of protection envisaged within the European Union, through one of the following methods:

a) Personal data will be transferred to a non-EU country that guarantees a level of data protection adequate to the European level in accordance with a decision of the European Commission adopted pursuant to Article 45 of the GDPR.

b) In the absence of an adequacy decision pursuant to art. 4.5 GDPR, the data controller or the data processor may transfer personal data to a third country only if it provides adequate guarantees and provided that the data subjects have enforceable rights and effective remedies pursuant to art. 46 par. 3, lett. b). In particular, the Sponsor adheres to the standard contractual clauses for the transfer of personal data to third countries referred to in Commission Decision 2010/87/EU (as amended by Commission Implementing Decision (EU) 2016/2297 of 16 December 2016) and undertakes to respect them.

c) In the absence of an adequacy decision pursuant to Article 45, paragraph 3, or adequate guarantees pursuant to Article 46, the data subject must explicitly consent to the proposed transfer, after having been informed of the possible risks of such transfers, due to the lack of an adequacy decision and adequate guarantees, pursuant to art. 49 par. 3, GDPR (see the specific option provided in the consent to data processing).

LEGAL BASIS OF THE PROCESSING

The processing of your personal data, for the purposes indicated above, is optional but essential in order to carry out the services requested and/or necessary for the purposes of carrying out the trial and/or clinical study. Failure to consent to the processing of data will in no way affect your ordinary medical care.

METHOD OF PROCESSING

The data are processed both on paper and IT tools with methods suitable for guaranteeing integrity, availability and confidentiality in compliance with the security measures prescribed by law.

In particular, the paper documentation is kept in a closed place and not accessible except to those expressly authorized. Access to IT tools is allowed only after authentication with personal passwords issued only to authorized subjects who meet the security criteria. For the purposes described above, your personal data will be communicated to the subjects involved in the experimentation in a pseudonymized form to guarantee your privacy.

In particular, the doctor who will follow you in this trial/clinical study will identify you with a code that will be used in all treatment activities and in communications with the Sponsor. The data concerning you, collected during the study, will be transmitted to the Sponsor, recorded, processed and stored only using this code. Only the doctor and persons authorized will be able to link this code to your name.

The Sponsor's personnel adequately qualified and identified within the terms of the law will have access to the documentation relating to the study and to your original health documentation for monitoring activities, aimed at verifying compliance with the Protocol.

In any case, the processing is carried out exclusively by subjects bound by professional secrecy or office secrecy or by the obligation of secrecy and confidentiality.

Your data is not subject to any fully automated decision-making process including profiling.

RIGHTS OF THE DATA SUBJECT

You are the owner of the rights referred to in articles 15-22 of EU Regulation 2016/679; their exercise may be limited pursuant to the provisions of art. 23, from art. 17, paragraph 3, from art. 85, paragraph 2, of art. 89, paragraph 2, GDPR or, in any case, if it is provided for by a specific legislative provision in compliance with fundamental rights and freedom and as a necessary and proportionate measure. In such cases, the Data Controller will provide you with specific information on the reasons for the limiting the exercise of the specific right asserted with the request submitted.

For the modalities of exercise of these rights, can send a specific request in the modality provided by the company procedure available on the institutional website

at the following link https://www.ospedaliriuniti.marche.it/portale/index.php?id_sezione=422

(part to be entered by the Sponsor/CRO)

Indicate how the Sponsor, as autonomous Data Controller guarantees the exercise of the rights of data subjects as far as its competence.

CONSENT TO THE PROCESSING OF PERSONAL DATA

(EU Regulation 2016/679)

Title:
the undersigned: Name, Last name (Surname), born in…, resident at (address), CF (Area Code), Telephone/Mobile
(tick only if applicable) as Guardian/Curator/Support Administrator of … *(in the case of a minor subject, consent must be given by both parents)*
This declaration is made, pursuant to and for the purposes of articles 46 and 47 of Presidential Decree 445/2000 and subsequent amendments, aware of the criminal responsibility in the event of false declarations pursuant to and by effect of art. 76 of the same Presidential Decree

DECLARES
❏ To have received and read the above information on the processing of personal data above
❏ To be of age and not to be in a state of physical impossibility, incapacity to act or incapacity to understand or want (only in the case where it is not a minor or incapacitated person)

To be inserted only when the clinical study involves the carrying out of analyzes in external laboratories:
❏ To be aware that the Sponsor (or Testing Centre) transmits to Laboratories Analysis, third parties, biological samples for the analyzes provided for in the clinical trial/clinical study and that these samples can be stored in such Analysis Laboratories

MANIFEST CONSENT
❏ to the processing of their personal data produced and used by the subjects indicated in the Privacy Policy, for the purposes of scientific research, in the medical, biomedical and epidemiological and statistical fields
❏ the preservation of my biological samples, for the period of time in which they retain their integrity, for the conduct of other clinical studies having scientific and statistical purposes directly related to those of the study in question

To be inserted only when the clinical study provides for the processing of genetic data:
❏ to receive any expected information about me
❏ to communicate to third parties belonging to my genetic line any expected information concerning them.

To be inserted only if the transfer takes place on the basis of the data subject's consent
❑ to the processing of their personal data produced and used by the subjects indicated in the Information for the transfer to a non-EU country despite having been informed that such Country may not guarantee the same level of protection as European countries and with the awareness, therefore, that my personal rights and freedom could be exposed to a high risk of violation in terms of confidentiality, availability and integrity.

Place and date .....

SIGNATURE OF THE DECLARANT

Doc. 2 - DEED OF DESIGNATION OF THE PERSON IN CHARGE OF THE PROCESSING OF PERSONAL DATA

(pursuant to art. 28 EU Regulation 2016/679)

Between

Business name (address, telephone, PEC)	SSR (address, telephone, PEC)
DATA PROCESSOR	DATA CONTROLLER

The Hospital (Name) based in (address), in the person of the Director General, as Data Controller of personal data in the context of the institutional activities of competence, considering that:

the Hospital, as represented above, has assessed that in terms of structure, organization of means and people, knowledge, skills and Know How (Name of Person Responsible) possesses the requisites of reliability, capacity and experience to ensure, by signing of this Act, full compliance with the current provisions on the processing of personal data, including the security profile;

pursuant to and for the purposes of art. 28 of Regulation (EU) 2016/679 by this Act, an integral part of the aforementioned relationship, formally

APPOINTS:

Data Processor in the field *(indicate the trial and/or clinical study for which the appointment is made) (name of the person in charge - specify name, registered office, VAT number and/or tax code of the legal person, as well as name, surname, from/a of birth, tax code of the natural person who has the power to represent the legal person)*, who accepts.

The processor declares to be in possession of sufficient guarantees to implement the appropriate technical and organizational measures in order to meet the requirements of EU Regulation 679/2016 and guarantee the protection of the rights of the data subject.

The nature and purposes of the processing of personal data entrusted to the Processor are described in the contract of which this deed is an integral part. The Data Processor is prohibited from using the personal data processed on behalf of the Data Controller to pursue purposes other than those outlined by the latter, unless communication in writing to the Data Controller, which authorizes the different purpose. It is understood that, if the Processor determines different purposes and means of processing and additional to those identified in the contract, these will act as the Data Controller of such data, with the administrative and civil consequences provided for by the current legislation on the protection of personal data.

The appointment as Processor will be valid until the date of conclusion of the contract and the Controller undertakes to respect the obligations of confidentiality and secrecy regarding to personal data processed in execution of the same.

INSTRUCTIONS FOR DATA PROCESSOR

As part of the processing activities entrusted with the Appointment to Data Processor, the instructions that the Manager must follow in the course of the processing of personal data on behalf of the Data Controller are given below, in compliance with the regulations in force on the protection of personal data.

1. RELIABILITY AND DUTIES OF DATA PROCESSOR

- to process personal data in a lawful, correct and transparent manner in compliance with the provisions of EU Regulation 679/2016 and other provisions (national, regional and regulatory) regarding the protection of personal data including those governing certain specific categories of data; in particular, the Processor may process the data strictly necessary and solely for the purposes deriving from it without communicating them to others or spreading them;
- keep a register of treatments, separate from their own, with the contents referred to in art. 30, paragraph 2, of the EU Regulation;
- guarantee that the persons authorized to process personal data have been appointed in writing, with the inclusion in the appointment deed of a specific clause that obliges the authorized person to respect the confidentiality of the data processed; the Processor will also be required to transmit the aforementioned appointments to the Controller and to provide the authorized persons with the instructions necessary for the correct processing of data;
- adopt all the security measures necessary for the processing having regard to the service that the Manager is required to render on the basis of the signed contract; in particular, the Data Processor will be required to transmit to the Data Controller a description of the organizational and technical measures adopted in relation to the processing of the data covered by the contract and in any case to respect those put in place by the Data Controller in relation to the processing entrusted (for example: the encryption or pseudonymisation of personal data; application of backup and disaster recovery procedures; conducting internal and external audits on privacy matters; staff training; periodically updating programs aimed at preventing the vulnerability of electronic instruments and correcting defects; compliance with procedures technical and operational procedures provided by the Data Controller such as the management procedure of any data breach).
- comply with the instructions given by the Data Controller, in particular the procedures regarding data protection, the procedures in the case of computerized processing and the IT procedures adopted, where applicable to the service in question.

It is understood that the appointed Data Processor is the only responsible in case of unlawful or incorrect data processing and in this sense undertakes to guarantee and indemnify Data Controller of the damages and/or prejudices that may fall on this as a result of claims of third parties and/or data holders. The Data Processor is responsible

pursuant to art. 2049 of the Civil Code also for damages caused by its authorized persons;
- allow the Controller to periodically verify the fulfilment of the obligations deriving from the aforementioned EU Regulation and from this deed also through inspections and audits that the Controller is authorized to carry out also by means of a person expressly appointed for the purpose;
- undertake, where applicable due to the activity covered by the relationship, to fully implement the provision "Measures and precautions prescribed to Data Controller carried out with electronic tools in relation to the attributions of the functions of system administrator" of 27 November 2008 (*Official Journal* No. 300 of 24 December 2008) as amended on the basis of the provision of 25 June 2009. In particular, it is the responsibility of Data Processor to carefully assess the subjective characteristics of the persons to whom the appointment as System Administrator is to be conferred; proceed to carry out the individual designation of the subjects deemed suitable for the role of System Administrator (the appointment must contain an analytical list of the areas of operation allowed on the basis of the assigned authorization profile); keep updated and available for the Data Controller and the Guarantor an internal document showing the identification details of all the natural persons appointed as System Administrators with the list of the functions assigned to them; proceed, at least annually, to verify the work of the System Administrators in order to check its compliance with the organizational, technical and security measures with respect to the processing of personal data provided for by the regulations in force; adopt, if not already available, a system suitable for recording logical accesses (computer authentication) to processing systems and electronic archives by the System Administrators (the registrations (access log) must have characteristics of completeness, inalterability and possibility of verification of their integrity adequate to achieve the verification purpose for which they are required and must be kept for one year); allow the Data Controller to carry out all necessary checks on the timely compliance with the above instructions with reference to the System Administrators;
- ensure that in their organization any computer access to data processed on behalf of the Data Controller requires the assignment to each authorized person of a specific individual user that enables them only to process the information necessary for the authorized individual to carry out their work, verifying, at least annually, the permanence of the relevant authorization profile for the treatment by the authorized person;
- provide in the authentication process for the insertion of an identification code of the Authorized Person associated with a reserved keyword (password) of adequate complexity, communicated to the Authorized Person in a confidential manner and modified by the same on first use and subsequently at least quarterly.

2. COMMUNICATIONS TO DATA CONTROLLER

- assist the owner in meeting the requests of the subject concerned in relation to the exercise of his rights relating to the processing of the data covered by the contract, also providing for them directly, after obtaining the written authorization of the Data Controller and after consultation with the Data Controller;
- in case of violation of personal data, inform the Data Controller, immediately and without undue delay of the violation (and in any case no later than 24 hours after the event), in order to allow the Data Controller, if the conditions are met, to proceed with the notification to the supervisory authority within the established term (within 72 hours of knowledge of the violation) and/or to the data subject;
- assist the Data Controller in the impact assessment on data protection (in relation to certain treatments which, when they involve the use of new technologies, may, due to the nature, object, context and purpose, determine a risk high for the rights and freedom of the data subject) and in the activity of prior consultation with the supervisory authority if necessary for the processing of personal data entrusted with the contract;
- make available, if requested, to the data controller all the information necessary to demonstrate compliance with the obligations deriving from this contract and the EU Regulation 2016/679 and in particular inform the owner in the event that, in his opinion, he considers that the instructions given violate the aforementioned Regulation or other provisions on privacy and data protection. Data Processor, in any case, is required to do what is necessary for the correct fulfilment of the obligations deriving from the aforementioned EU Regulation and the provisions in force on the subject, allowing and contributing to the audit activities, including through inspections that the Data Controller is authorized to carry out also by means of a person expressly appointed for the purpose, and for the further purpose of verifying compliance with the obligations deriving from this deed.

3. APPOINTMENT OF SUB DATA PROCESSOR

- appoint, only in the event of a written authorization by the Data Controller, another person responsible for the execution of the specific processing activities carried out on behalf of the Data Controller on the basis of the contract; in this case, the Data Processor must stipulate a specific contract that binds the additional manager to the same obligations regarding data protection contained in this deed, providing in particular that in the stipulated contract there are sufficient guarantees to implement adequate technical and organizational measures in so that the processing meets the requirements of EU Regulation 2016/679. In any case, if the other data controller fails to fulfil its data protection obligations, the Data Processor retains full responsibility towards the Data Controller.

4. PROHIBITIONS

- The Data Processor cannot process, transfer, modify, correct or alter the personal data of the owner, nor communicate and/or disclose them to third parties, except in accordance with written instructions, unless this is required by the EU or by the laws of the Member State to which the Manager is subject. In this case, the Data Processor must inform the owner of this before proceeding with such processing, in any case following the instructions given, to minimize the scope of disclosure;
- It is therefore forbidden for the Data Processor to carry out any other type of processing that is not relevant to the purpose of the services offered and/or to make copies of personal data unless specifically provided for in the contract or authorized by the Data Controller or for the necessary activities related to security data (back up);
- Refrain from spreading and/or communicating the data outside the cases provided for in the contract or indispensable for the fulfilment of the same.

5. VALIDITY AND BINDING NATURE OF THE PROVISIONS

The parties acknowledge and accept the validity and binding nature of the provisions of this deed until the expiry of the study and/or trial, existing between the Data Controller and the Data Processor covered by the agreement. The violation of any provision of this Act, by both signatories, constitutes a substantial violation of the same, and may be cause for termination, if the legal requirements exist.

At the end of the same, all processing operations must cease.

Consequently, the Data Processor, at the time of termination of the contract, must immediately provide for the definitive elimination of the processed data from its information system and from its paper archives, giving written confirmation to the Data Controller, after transferring the data held.

If there are substantial inconsistencies between the provisions contained in this Act and those resulting from the contract in force between the parties, the provisions contained in this Act must be considered prevailing, as regards the obligations imposed on the parties regarding the protection of personal data and protection of the Interested parties involved in the treatments carried out on behalf of the Data Controller.

Ancona, date

INSTRUCTIONS TO STAFF
ON THE PROCESSING OF PERSONAL DATA FOR RESEARCH PURPOSES

These instructions are further and additional to those contained in the appointment authorized to process personal data pursuant to art. 29 EU Reg. 2016/679 that each facility manager must have expressly provided to all staff belonging to the same facility. Please note that these instructions are published on the intranet site under the heading "Legal Notice and Privacy", which you are asked to expressly read and which are reproduced below:

I) The personal data processed in the context of the aforementioned study/ experimentation cannot be disclosed except in anonymized form, that is to say in such a way as to exclude any direct and/or indirect identification of the data subject.

2) The communications of any personal data processed can take place only within the participating subjects (Company, Sponsor, External Data Processing Manager, Analysis Laboratory) on the basis of the study protocol, respecting the skills of each person and using forms of pseudonymisation in such a way as to guarantee the confidentiality of the data subject and the reduction of risks of violation of the same.

3) Use the personal password for the application provided in the study, different and additional to the one provided for access to company information tools, which must be known exclusively by the person who owns it. This password cannot be communicated to other subjects even if authorized since it is a personal password.

4) Treat personal data relating to the study in a different way from those processed for the institutional activity.

5) Release the information on data processing relating to the study and obtain consent on the basis of the form delivered; if the consent were to be issued by computer, a back-up of the related data will be necessary in order to have this information available for the purpose of exercising the rights.

If the trial/clinical study also provides for the processing of genetic data, it is necessary, in addition, to follow the following instructions:

1) Keep genetic data and biological samples exclusively in the premises intended for this purpose.

2) Keep the premises where data and samples are kept locked.

3) Provide forms of pseudonymisation, where possible, for the traceability of the biological sample

4) Adopt systems for the conservation, use and transport of biological samples in order to guarantee their quality, integrity, availability and traceability.

5) In case of transmission of reports relating to genetic analyzes, the transmission must take place by delivery to the person concerned or alternatively to a person delegated by him on the basis of written documentation which must be kept in the folder relating to the trial and/or clinical study.

6) To comply with the company procedures relating to the treatments carried out for research purposes and for the processing of genetic data and biological samples also as regards the methods of communication with patients and/or external subjects authorized to know such information for the part applicable to the treatments for research and statistical purposes published on the corporate website under the heading "Legal Notes and Privacy".
7) Promptly notify the Head of the Trial and/or Clinical Study of any problems, criticalities arising on this type of personal data processing and ask, in case of doubt, advice from the DPO and/or the company privacy contact.

14. Management of institutional and scientific activities with the CROs

E. Ottavianelli, C. Polimeni

Introduction

The hospital and territorial pharmacist are responsible for managing the drug in accordance with company and/or service procedures aimed at ensuring compliance with the identified processes, such as, by way of example but not limited to, the dispensation, preparation of the drugs, the method of storage, organization of spaces and documentation.

However, the pharmacist is not only responsible and referent for welfare activities but is also a central figure for the management of the drug also in the context of clinical trials.

Its involvement in clinical trials requires an adaptation of its operations to meet specific study procedures required by the sponsor of the trial.

Clinical trials could become a parallel and equally structured activity in which the pharmacist is involved: new rules, new skills, i.e. the need to know the regulations governing clinical trials, as well as knowledge of the market and the players involved, new stakeholders.

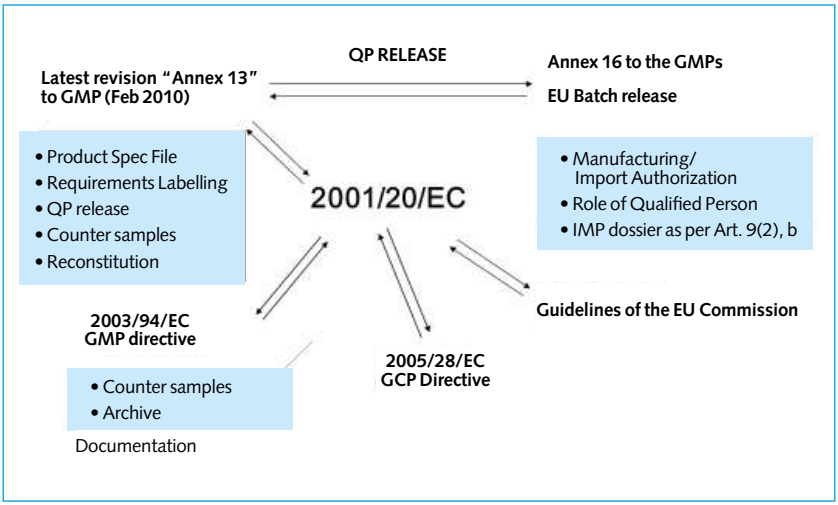


Fig. 1 – Regulation: the reference regulations.

A useful stakeholder in this area is the CRO (Contract Research Organization) with which to establish a constant and productive relationship so that the pharmacist does not feel overwhelmed by the "parallel activity".

In fact, CROs are an integral part of the "clinical research" system, widely defined by existing legislation, not least by the E6/R2 revision of the ICH Good clinical Practice, in which we find not only the definition, but a clear emphasis on the role and responsibilities.

Characterization of CROs in Italy

According to some recent estimates, the global market for contract research organizations (CROs) will grow at a very strong annual rate, more than 10% per year according to many.

The growth of the market is mainly attributed to the increase in research and development expenses, outsourced activities and the increase in the number of clinical trials. It will therefore be increasingly necessary to support a synergy between CROs and experimental centres, including hospital pharmacies, both operative parties in the development of new therapeutic opportunities and guarantors of data reliability.

Particular energies, in guaranteeing this synergy, must be directed to accommodate the transformations triggered by the Covid-19 pandemic, that is to make the management system of clinical trials in Italy more effective and efficient. Intense collaborations between stakeholders, pharmaceutical and medical device companies are guiding this significant market growth.

The CROs present on the Italian territory can still be represented by two macro-categories: Italian companies and those with foreign capital, but with offices in Italy. According to the latest information provided by AIFA (December 2019), 194 CROs operating on Italian territory were registered at the National Observatory for Clinical Trials (OsSC), of which 106 "Italian" and 88 "foreign".

The CROs that provide consolidated services (start-up, project management, monitoring, data management, statistics) are represented by:

- 61% from international companies, all present in Italy;
- 39% from Italian companies, some of which are associated with other companies abroad.

74% have their headquarters in Lombardy (of which 82% in Milan) and 17% in Lazio.

It should be noted that always more frequently the "contract organisations", in the field of clinical trials, also include highly specialized

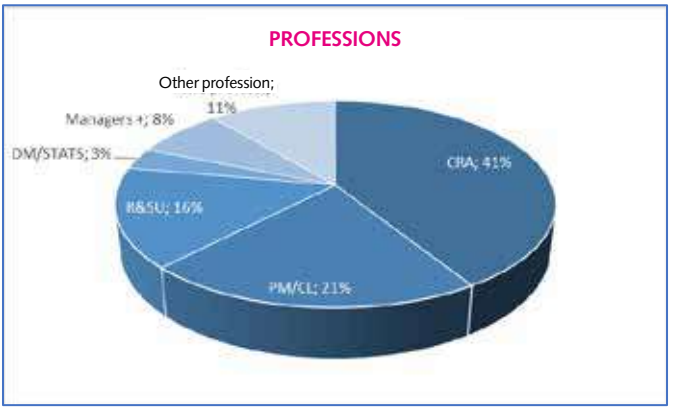
companies in the fields of technology, IT and "niche" services, therefore with organizational structures that are also different from the standard of more traditional CRO.

Human resources in CROs

CROs in Italy at the end of 2020 employed around 3,500 employees specialized in technical functions related to the conduct of clinical trials (i.e. excluding staff and administrative services) of which around 3,000 employed by CROs associated with AICRO (Italian CRO Association).

The Clinical Research Associates (CRAs) continue to represent the most used profession in CROs (with an estimated number of around 1,400 units), followed by Project Managers, Clinical Trial Assistance, Data Managers and Statisticians.

There is no role entirely dedicated to drug management, there is undoubtedly a skill, but we rely on specialized Contract Manufacturing Organization (CMO) figures for the production, storage, transport and destruction of the Investigational Medicinal Product (IMP), obviously also the collaboration with hospital and local pharmacies.



Survey 2019 – The status of associated CROs.

The general minimum requirements of the CROs in Italy imposed by the Ministerial Decree of November 15, 2011, require a well-defined organization of the CROs and a significant training effort both in the case of new resources and in updating existing ones. Manager Quality Assurance becomes responsible for an annual training plan, approved by

the management, which provides for the involvement of its own function, scientific societies or associations, masters promoted by third parties.

The management of the experimental drug is always represented in the training plans and it would be desirable to create training courses of interaction between the CROs and the hospital pharmacies, in order to be able to establish a constant exchange of skills and needs in the field.

Impact of the pandemic and perspectives on CROs

The pandemic has produced significant changes in the way CROs work, more precisely the major changes certainly go in the direction of remote activities. In fact, among the most cited categories of changes are an increase in home working/smart working temporary personnel, a transformation of contractual agreements towards stable teleworking (home-based positions), even for those roles previously excluded from these possibilities, the introduction of new technologies enabling remote working and document digital conversion (see table).

Although these changes may seem similar to those made in other sectors, it is important to remember the nature of pre-pandemic activities, which involved physical movements on the territory and operations to be carried out "on site" or in presence in the office.

As example, on-site monitoring visit carried out by the clinical monitor (CRA) has been transformed into a virtual visit with consequent adaptation of the experimental centres, including hospital pharmacies.

Categories	Relative frequency
Increase in Home Working	21%
Increased remote monitoring activity	18%
Increase in home based personnel	12%
Access to home based roles usually office based	12%
Increased computerized archives	10%
Introduction of new technologies	9%
Presence of personnel in geographical areas not previously considered	7%
Percentage decrease of SDV	7%
Other	1%
Introduction of new roles (i.e. In-House CRA)	1%

Survey 2019 – The status of associated CROs.

Interaction between cro and hospital/territorial pharmacies

The keywords to be considered as driven by a productive interaction between the two parties are: AWARENESS, COMMUNICATION, SHARING.

After about 25 years of conducting clinical trials in compliance with the GCP and subsequent applicable legislation, both parties are aware of the potential problems related to the management of the investigational drug both from direct experience and from disclosure of deviations found during inspections of the hospital/territory pharmacy at conferences or symposiums.

The hospital pharmacy inspection is normally performed during the investigational site inspection. At least one pharmacist on duty at the hospital pharmacy must be present at the inspection, who is familiar with the management of the experimental drug.

The inspection consists of four parts:

1. introductory meeting and general information acquisition
2. examination of the documentation relating to the trial being inspected
3. visit of the pharmacy
4. closing meeting with general explanation of deviations.

The pharmacy inspection is mainly intended to verify that:

- the premises, equipment and personnel are adequate for the management of the experimental drug;
- the procedures for managing experimental drugs are conducted in accordance with the GCP, examining the related paper and/or computerized records;
- for such registration, there are standard operating procedures and/or operational documents.

The deviations found following inspections are often attributable to three areas: structural, process, transport - highlighted in Table 1.

Table 1

Structural	Process	Transport
• Refrigerators without identification label • Refrigerators without continuous temperature control • No UPS connected to refrigerators • Lack of temperature records in the rooms where the drug to be kept at "room" temperature is stored • The location of the data logger for temperature detection is not justified by a study demonstrating showing that the instrument positioning is representative (worst case), with a conservative approach, for all possible locations of the experimental drug • Absence of alarms • Alarms for out of range of the temperature acoustic only (problem of availability of responsible personnel on public holidays) • Hood maintenance management	• Delivery of the experimental drug by the Pharmacy to the staff of the experimental centre • Gaps in the custody chain of the investigational drug • The process of taking charge of the experimental drug not properly documented (SOP and modules)	• Weaknesses in the procedures for transferring the experimental drug from the hospital pharmacy to the experimental site (distance-dependent criticality) • Transport within the hospital out of control and/or not documented, without traceability • Transport of the experimental drug at a controlled temperature without approved containers • Failure to identify the internal staff assigned to the transport of medicinal products

Extract from the AIFA Symposium - Rome, 5/11/2019

The above deviations are directly related to the responsibility of the pharmacist in the clinical trial regarding the correct implementation and surveillance of the following activities, in part directly related to the safety of the trial subject and the reliability of the trial results:

- Reception of Experimental Drug (IMP);
- IMP reliability control;
- Preparation, if applicable;
- Delivery of IMP to the division where the trial is carried out;
- IMP accounting;
- Quarantine;
- Return;
- Disposal;
- Documentation management;
- Equipment management;
- Archiving.

In fact, they are activities and responsibilities not far from the so-called routine activity.

So what changes? The context!

The clinical trial determines an operating context different from the routine which requires the pharmacist to comply with the operating procedures requested by the sponsor and/or different times for the implementation of the activities. The stakeholders involved are necessarily diverse and in any case assume specific roles in the management of a clinical trial.

The pharmacist must be aware of this and act accordingly. An internal and external communication plan must be agreed between the parties involved. The pharmacist will have to be involved in the feasibility phases of a study, in the risk assessment of a clinical trial and evaluate the impact of specific trial procedures with respect to internal resources (human and structural).

The sponsor will therefore have to evaluate processes, implemented by the CRA, in which the pharmacist becomes an essential contact point such as the main investigator.

What is the common denominator between CRO staff and hospital or community pharmacy staff?

Knowledge first of all of what is meant by experimental drug (IMP and control drug) and then its management in compliance with the GCP and applicable legislation.

IMP may not necessarily be a product under development that has not yet been placed on the market, but a product on the market tested in contexts or indications different from those foreseen and approved.

The identification of the documents necessary explore the knowledge of the IMP, such as Investigator Brochure (IB) or Summary of Product Characteristics (SPC).

Knowledge of the authorization process at the end of which it is possible to receive the initial visit of the CRA and therefore allow the use of the IMP.

The joint application of GCP and GMP (Good Manufacturing Practice) requirements.

The pharmacist will therefore become an active part in interacting with the CRA during monitoring activities, whether carried out on site or remotely.

It is necessary to know the areas that will be subject to verification and to share them in advance, starting from the selection phases of the centre (see boxes), to continue during the conduct of the clinical trial.

Qualification visit (IMP management)
At the pharmacy and/or ward

IP transfer from pharmacy to ward:

- Presence of SOP? How long does the transfer take on average?
- How is the temperature controlled? Is there an internal form to document the transfer?
- Does the form collect the necessary information?
  - When the transfer took place (date/time)
  - Who made the transfer
  - When the IP was delivered (date/time)
  - What kits/vials of IP were delivered (lot #, expiration date, # kits/vials)
  - The product remains in the pharmacy/ward for a few hours/days before being transferred/administered, where is it stored?
- Where are the original documents of the investigational product kept?

Qualification visit (IMP management)
At the pharmacy and/or ward

Preparation of the IMP (if applicable)

- Who? Where is it?
- Does the centre have internal forms and worksheets?
- Are empty files discarded according to clinical practice?

How is the temperature of the IP storage area monitored and documented?

- Min./max thermometer or a data logger ?
- How often is the temperature recorded?
- Is the temperature monitored 24/7?
- Is the temperature recorded manually or by computer? If manually, does the site use site-specific temperature logs? Or does the site agree to use study specific temperature logs?
- How is a temperature variation managed?

Conclusions

Clinical trials still represent a challenge for hospital/territorial pharmacies due to multiple factors, such as the regulations concerning trials, the specific stringent procedures of the study sponsor, the need to dedicate specific resources already involved in assistance activities, the training needs in the GxP.

The factors indicated above can be considered only constraints or begin to transform them into opportunities, into improvement objectives at the company system level.

Accepting, developing, sharing the minimum requirements necessary for the operating procedures to be applied in a clinical trial could result in a corporate quality system already structured to transform a challenge into a routine.

Participation in a clinical trial becomes a 360° opportunity for the company, of which the pharmacy is an integral part, namely:

- an investment for the company that can create a virtuous path and promote independent trials (*Non-Profit*);
- a benefit for patients who can access innovative treatments;
- a relationship of trust with the sponsors, pharmaceutical companies and CROs involved, which allows new and increasingly profitable collaborations.

Below is a handbook of recommendations useful for interacting with the world of CROs.

General recommendations

- Interact with the CROs not only in terms of operations, but above all in strategic terms, to guarantee a common path in view of a new regulation that sees everyone involved in processes yet to be defined.
- Sharing the common areas of "training" with the CROs, identifying the reciprocal "operational needs" in terms of procedures: it is necessary to carve out an educational and updating space in the field of clinical trials.
- Promote greater synergy between the academic, hospital and industrial components in order to offer modern training suitable for immediate use in terms of management of experimental drugs in research centres.
- Promote the hospital pharmacist as a valuable "consultant" in the protocol and risk planning phase assessment, strongly influenced by the correct management of the drug.
- Optimize interactions with CROs and sponsors in order to produce

adequate and timely documentation relating to the experimental drug, necessary for the approval request (the use of the European CTIIS platform will soon be necessary, with new documentation), through a common language.
- Encourage and promote the presence of hospital pharmacy staff at monitoring visits, in particular those for qualification and the start of the study, thereby raising the awareness of the PIs involved in clinical trials.
- Organize regular update meetings with the investigators of your own centres, to be updated on ongoing projects, detect critical issues, assess any risks on potential planned projects, provide adequate operational support.
- Facilitate the advent of technological and digital solutions, such as electronic approval flows, virtual visits with CRAs, electronic filing.
- No Profit trials.
- Encourage the sharing of ad hoc standard procedures with particularly active collaborative groups.
- Define a communication plan between the non-profit promoting clinical centre and collaborating centres.
- No Profit sponsor for optimizing the costs associated with the management of the IMP: evaluate whether the funding available allows for complete outsourcing or whether it is worth keeping some activities at the experimental centres.
- Contribute to the selection and over sight of the CMOs (Contract Manufacturing Organizations) entrusted with the IMP management.

References and thanks

- ICH Good Clinical Practice E6 (R2).
- Regulation (EU) no. 536/2014.
- Ministerial Decree November 15, 2011 Definition of the minimum requirements for contract research organizations (CRO) in the context of clinical trials of medicines.
- Legislative Decree no. 200 of 6 November 2007 Implementation of directive 2005/28/EC containing detailed principles and guidelines for good clinical practice relating to medicinal products being tested for human use, as well as requirements for the authorization to manufacture or import such medicinal products.
- AIFA Decision 19 June 2015 Decision concerning the minimum requirements necessary for healthcare facilities, which carry out Phase I trials.

- Guidance on the management of clinical trials during the Covid-19 (coronavirus) pandemic.
- Management of clinical trials in Italy during the Covid-19 emergency (corona virus disease 19).
- Eudralex vol. IV EU Guidelines to Good Manufacturing Practice for medicinal products for human use – Annex 13 Investigational Medicinal Products.
- 2nd AICRO report on the state of CROs in Italy.
- AIFA Symposium 2019.
- 9th National Report on Clinical Trials of Medicines in Italy 2020.

MyCROscope AICRO school: we thank in particular Drs. Andrea Carbone and Viviana Apicella of Medpace and Drs. Andrea Mazzini and Davide Mastroieni of STMPharma PRO for the authorization to use the slides.

The AICRO Board for the revision of the article.

15. General aspects of the Logistics of Clinical Trials, Path Certification, Management Software: National examples and implementation of standards and technical references

1. The logistics of the experimental sample in the Mater Domini AOU of Catanzaro

M. De Fina, M. Zito, A.E. De Francesco

The AOU Mater Domini of Catanzaro promotes scientific research integrated with health care and therefore clinical trials assume fundamental importance. The hospital pharmacist plays a central role in the management of the experimental drug and contributes to the success of the experiment itself, in compliance with the ethical and scientific quality standards of Good Clinical Practice (GCP). From 2016 to today, the number of clinical trials has gradually increased. Around 130 clinical trials have been launched which pertain to different therapeutic areas and different phases (Fig. 1).

Fig. 1 – Subdivision of clinical trials started per Experimental Phase.

According to the Ministerial Decree of 18 March 1998 (Annex 1, art. 4, paragraph 4, 6) and the Ministerial Decree of 21 December 2007 (art. 7) "*the medicines needed for the trial must be sent by the sponsor to the Pharmacy of the Health Facility, site of the trial, which will arrange for their registration, appropriate conservation, and delivery to the investigator*". The "Guidelines of the European Union of Good Clinical Practice (GCP) for the execution of clinical trials of medicinal products" were implemented in the Ministerial

Decree of 15 July 1997. These guidelines, regulating all aspects related to the clinical trials of medicines, also contain precise references to the correct management of medicines being tested.

According to the Ministerial Decree of July 15, 1997, as amended, the pharmacist must keep the documentation relating to the deliveries and inventory of the product at the site of the study, the use of the product by each subject, and the return to the sponsor or alternative disposal of the unused product. These records should include dates, quantities, lot or serial numbers, expiry dates, and unique code numbers assigned to the product under investigation and study subjects.

The UOC of Pharmacy of the Mater Domini AOU of Catanzaro, in compliance with this regulation, has structured an organizational procedure to manage the logistics of the experimental sample from the moment of receipt and acceptance up to the dispensing of the experimental kits.

For this purpose, a specific archive (Pharmacy File) is created and kept in the Pharmacy UOC, both in paper and digital format, containing the documentation relating to each clinical study, regularly approved by the Ethics Committee, as well as initiated and conducted at the AOU Mater Domini of Catanzaro. The Pharmacy File contains, among other things, the clear and detailed study protocol, the sample handling log, the randomization list, and all the documentation describing the medicine and its preparation.

Simultaneously with the receipt of the samples, a check is carried out on the qualitative-quantitative congruity between what was delivered and what is reported on the Transport Document (DDT), as well as the correct conservation method and the state of the experimental kits received (e.g. maintenance of the cold chain, integrity, correct labeling, etc.).

The successful receipt and acceptance of the experimental kit are noted on the "Receipt and acceptance form" (Fig. 2), where the responsible pharmacist will indicate all the elements useful for identifying the delivery.

The communication of the correct acceptance of the experimental kits to the sponsor takes place at the same time as the receipt by the identified responsible pharmacist.

In particular, the verification of the correct maintenance of the cold chain is carried out through the digital monitoring system (Temp Tale Device); the circuit of the recorded temperature, once analyzed, will be printed and duly archived in the dedicated Pharmacy File (Fig. 3). In case of non-compliance and/or non-usability of the samples, for example for reasons of unsuitable storage temperature, the same will be returned to the sponsor.

The storage of the samples takes place in rooms duly kept at a suitable temperature by what is indicated by the sponsor or in the Summary of Product

AZIENDA
OSPEDALIERO-UNIVERSITARIA
"Mater Domini"
Catanzaro
U.O.C. Farmacia- Direttore Dott.ssa De Francesco Adele

Protocol No Clinical study	Date and time of arrival at the hospital pharmacy	Signature of the receiving pharmacist	Details of the packing slip	Delivery date and time to the investigator	Investigator's signature (or title)	Proven drugs delivered
no. _____	Date ___/___/___ h __:__	Received from _____ Signature _____	no. _____ ___/___/___	Date ___/___/___ h __:__	Received from _____ Qualification _____ Signature _____	no. _____ _____ Lot: _____ Expiry date ___/___/___ no. _____ _____ Lot: _____ Expiry date ___/___/___ no. _____ _____ Lot: _____ Expiry date ___/___/___
Method of drug conservation		❑ Lower temperature 25°C ❑ Temperature between 2-8°C				
Operational unit:						
Testing manager:						

Fig. 2 – Reception/acceptance form and overall dispensing of the experimental kit.

Fig. 3 – The role of the digital temperature monitoring system: from the preparation of the shipment to the successful delivery.

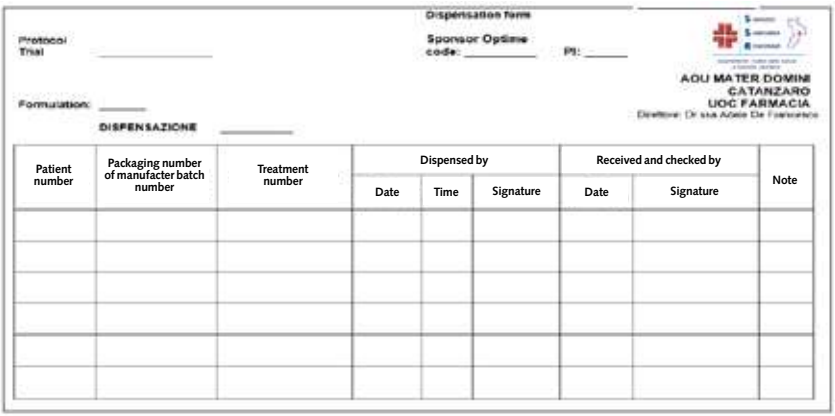
Characteristics (SPC), distinct from other drugs and/or devices, separated by protocol and by the investigator.

In the case of samples to be stored at a controlled temperature (2-8°C), they will be placed in specific refrigerators equipped with continuous recording software (e.g. Spy Log) which allows continuous monitoring of the temperature as well as an acoustic and visual alarm system which warns of any undesired change in temperature.

The distribution of the experimental kits to the investigator (Principal Investigator - PI) or his delegate can take place in two ways:

- for total quantity: the delivery of the samples is carried out in a single solution and therefore section 2 of the "Acceptance and receipt form" will be completed (Fig. 1);
- customized: the samples are delivered on a case-by-case basis, depending on the patients to be treated (Fig. 4).

The original signed copy of the dispensation form will be kept in the Pharmacy File dedicated to the related clinical study, as well as appropriately recorded in the reserved digital register.



Dispensation form

Protocol
Trial _____

Sponsor Optime
code: _____ PI: _____

AOU MATER DOMINI
CATANZARO
UOC FARMACIA

Formulation: _____

DISPENSAZIONE _____

Patient number	Packaging number of manufacter batch number	Treatment number	Dispensed by			Received and checked by		Note
			Date	Time	Signature	Date	Signature	

Fig. 4 – Personalized dispensing form.

The choice of delivery method is the result of an agreement between the responsible pharmacist and the PI. In the absence of different indications, the procedure for the total quantity is implemented, and the PI himself will be responsible, for all effects, for the correct storage and management of the samples.

The control of the expiry date of the managed samples must be performed by the pharmacist, in the case of personalized delivery, or by the investigator if the delivery took place in a single solution.

In the case of withdrawal due to product deficiencies, retrieval after the end of the trial, withdrawal of the expired product, etc. the sponsor will initiate the envisaged procedure, as foreseen by the Ministerial Decree of 15 July 1997, and produce the documentation of this retrieval.

The responsible pharmacist, in possession of the samples returned by the investigator and/or directly managed, can contact the sponsor to have the packs collected. The copy with original signatures of the return form must be kept in the Pharmacy File reserved for the relevant clinical trial, together with the delivery document to the sponsor.

The original data and essential documents of a clinical trial are recorded, archived, and kept so that they can be easily made available by the competent authorities, should they request them. Even if the sponsor interrupts the clinical development of a product being tested, according to the GCP, implemented with the Ministerial Decree of July 15, 1997, and therefore with the Legislative Decree no. 211 of 24 June 2003, the documentation will in any case be kept.

2. IRCCS Giovanni Pascale Foundation of Naples - Division of Pharmacy - Antiblastic Drugs Unit

P. Maiolino, G. De Feo

The Giovanni Pascale Foundation is a Scientific Institute for Research, Hospitalizion, and Healthcare (herein after IRCCS), which is based in Naples, Italy. The IRCCS is one of the most important cancer research institutes in Italy.

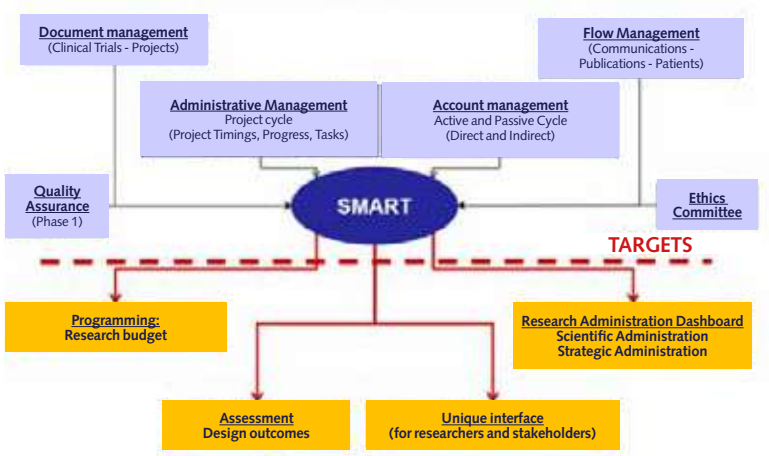
It is organized into Organ Departments where translational research is performed.

Over the years, the IRCCS has promoted Profit research activities. In 2017 sent AIFA the self-certification for the promotion and conduction of phase 1 studies, as required by AIFA Resolution 809/2015.

Table 1 together with Figures 1 and 2 show the trend and the type of studies that have been conducted at the IRCCS over the years (source Monitoring Clinical Studies 11th Report from May of 2021).

The IRCCS is equipped with an IT platform (SMART) which contains information and documentation relating to all the studies conducted at the IRCCS. SMART is accessible for the Ethics Committee, the Scientific Direction, the investigators, with the possibility of monitoring all the studies. The Secretariat of Ethics Committee is part of the Scientific Direction of the IRCCS.

The SMART platform



Year	Clinical trials N = 762		Observational trials N = 366		Total
	No – profit	Profit	No - profit	Profit	
2007	4	9	3	2	18
2008	8	16	3	5	32
2009	10	24	4	6	44
2010	17	24	13	2	56
2011	16	28	9	4	55
2012	14	25	18	8	65
2013	15	38	14	8	75
2014	14	46	30	5	95
2015	20	43	30	8	101
2016	31	48	25	8	112
2017	20	41	17	2	80
2018	22	54	39	3	118
2019	21	69	39	5	134
2020	68	20	6	50	143
Totale	280	483	249	116	1.128

Table 1 – Clinical studies activated by year.

Fig. 1 – Clinical studies activated by trial type and sponsor (2007-2020).

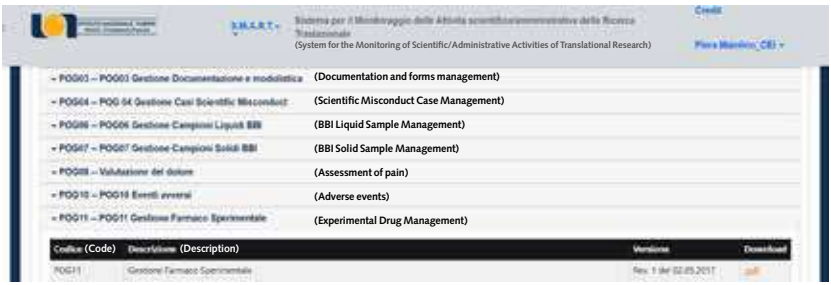
Fig. 2 – Single-centre and multi-center studies (2007-2020).

The Division of Pharmacy was involved in the OECI assessment process both in 2017 and 2021. The ISO 9001 UKAS MANAGEMENT SYSTEM 001 certification was renewed in November, 2021.

The Division of Pharmacy participates in all phases of drug management of the active clinical trials at IRCCS starting from pre-selection.

For the studies sponsored by the Pharmaceutical Companies, the Pharmacy must receive, not only the IMPs (investigational medical products) and AxMPs (auxiliary medicinal products), but also all the devices necessary for their preparation and administration. All aspects relating to the experimental drugs and auxiliary drugs are defined and detailed within the IRCCS clinical trials regulation. This insformation is reported in a specific form which is attached to the contract as an integral and substantial part of it.

The Division of Pharmacy is equipped with specific General Operating Procedures (POG) for the management of the experimental drug.



At the time of the SIV (Site Initiation Visit) conducted in the Pharmacy, an agreement is signed between the parties to clarify and define times and methods of delivery of the drug/devices and the documentation which needs to be available during the monitoring.

The experimental drugs are received and stored in dedicated cabinets and remotely alarmed refrigerators, with continuous temperature control.

Experimental drugs are stored in separate locked cabinets or special refrigerators reserved for experimental drugs. The trial and the name of the investigator are indicated on each cabinet, shelf, and/ or refrigerator. All cabinets, shelves, and refrigerators are equipped with continuous temperature detection systems. The refrigerators and freezers (-20°C and -80°C) are remotely alarmed; they are periodically maintained and calibrated.

All study documentation (pharmacy file) is archived at the Pharmacy. For phase I studies, fireproof and airtight cabinets are used.

ISTITUTO NAZIONALE TUMORI
IRCCS – Fondazione Pascale

FONDAZIONE GIOVANNI PASCALE
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO
Via Mariano Semmola - 80131 NAPOLI

DELIBERAZIONE DEL DIRETTORE GENERALE N. 409 del 30/05/2017

(Resolution of the General Manager n. 409 of 05/30/2017)

PROPONENTE: Direttore Sanitario

OGGETTO: APPROVAZIONE PROCEDURA OPERATIVA GENERALE - POG11 "GESTIONE FARMACO SPERIMENTALE" E RELATIVA MODULISTICA.

(Subject: Approval of the general operating procedure - POG11 "Experimental Drug Management" and related forms)

Istituto Nazionale Tumori Fondazione G. Pascale

VERBALE SIV (SIV REPORT)
SC FARMACIA (SC PHARMACY)

Pag 1 di 2

VERBALE SIV del ...../...../.....

Protocollo (Protocol)..... **PI**.....

Monitor

NOME	(First name)
EMAIL	(e-mail)
RECAPITO	(Delivery)

Farmaco in sperimentazione (Experimental drug)	SI (Yes)	NO (No)	Conservazione °C (Storage °C)

Farmaco concomitante (Concomitant drug)	SI (Yes)	NO (No)	Conservazione °C (Storage °C)

	SI	NO
Provision by Sponsor		
Experimental drug		
Concomitant drug		
Filters - shipment at the same time as the drug		
Infusion set		
Bags		

Pharmacy activity	SI	NO
Receiving drug		
Confirm in IVRS, in IXRS, Fax		
Drug loading on the Database - according to GCP		
Dose assignment of study drug		
Preventive communication of drug withdrawals)		

Documentation that can be requested from the Pharmacy	SI	NO
Room temperature datalogger calibration certificate		
Experimental refrigerators calibration certificate		
Copy of the daily environment T-log signed by the pharmacist		
Copy of thermographic discs or temperature reports signed by the pharmacist		
Possible certificate of drug disposal		

	VERBALE SIV SC FARMACIA	Pag. 2 di 2

Documentation of procedures required by the S.C. Pharmacy	SI	NO
Copy of study protocol		
Ethics committee approval		
Administrative resolution		
IB of the investigational drug		
Pharmacy Manual		
Certificate of analysis of the investigational drug		
Documentation certifying drug stability		
Possible temperature deviation ranges other than +/-1		
Possible supply of specific study data logger		
Acceptance of dataloggers provided by other Sponsors		
Acceptance of Monitoring visits every... months after an agreed appointment indicating the necessary documentation		
Authorization for the disposal of daily residues by the Sponsor according to current legislation, according to the procedures of the Institution		
Acceptance of stamped and signed thermographic disk copies		
Written acceptance of the SOPs, included in the regulation		
Withdrawal of temp-tale upon delivery or delivered by courier		
Withdrawal of expiring/expired medication		
Transport by refrigerated truck as an alternative to the temp		

Note:

ACCETTAZIONE VERBALE SIV (Verbal Acceptance SIV Report)

DATA (Date)	FIRMA (Signature)

Pharmacists can also assign the drug registered on the dedicated platforms (IWRS) where they complete the delivery notes for drugs supplied for the study.

The investigational drugs for oral use are delivered to the investigator following the assignment. The pharmacy does not deliver the experimental drug to the patient, since this is an assignement of the investigator who checks patients adhesion to the experimental therapy.

The experimental drugs are transported from the Pharmacy to the Antibalstic Drug Unit (ADU) with the use of bags that allow the temperature to be traced, recorded and archived through a computer programme throughout the transport.

.

Protocol for Transport of Antiblastic Drugs at Controlled Temperatures

The drugs for experimental use, including drugs for compassionate use/ EAP, are all prepared in the ADU Unit.

Every time a new study begins, the pharmacist illustrates the synopsis of the protocol and the preparation methods of the drug to the ADU nurses ,in a training session. At the end of the training, a training participation form is signed. The staff of the ADU participatie in continuous training courses and quality audits as part of the Phase I team of the IRCCS

The prescriptions of experimental drugs are transmitted by the doctor to the ADU with the computerized prescribing system (eCare- Santec classified MD CND V9099, personalized access, equipped with digital signature). The protocols are proposed by the investigator with the indication of the clinical study, the drug, and the dosage regimen. The pharmacist provides indications on set up, compatibility, and stability of the drug. Subsequently, the scheme is made usable on the computer system.

Training Course tab

031012 - Scheda Corso di Formazione
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO
"Fondazione Giovanni Paseale" – NAPOLI

Descrizione

Oggetto del Corso: (Subject of the course)

- ☐ FORMAZIONE (Training)
- ☐ AGGIORNAMENTO (Update)
- ☐ AFFIANCAMENTO (Training)
- ☐ ALTRO (Other)

Docente (Professor)

☐ INTERNO (Internal) ☐ ESTERNO (External) Nominativo: (Name)

Partecipanti (Participants)

Cognome Nome (Surname Name)	Firma (Signature)	Cognome Nome (Surname Name)	Firma (Signature)

Durata del corso: (Duration of the course)

Verifica Efficacia (Check effectiveness)

☐ COLLOQUIO (Interview) ☐ TEST SCRITTO (Written test) ☐ NON PREVISTA (Not expected) ☐ _____

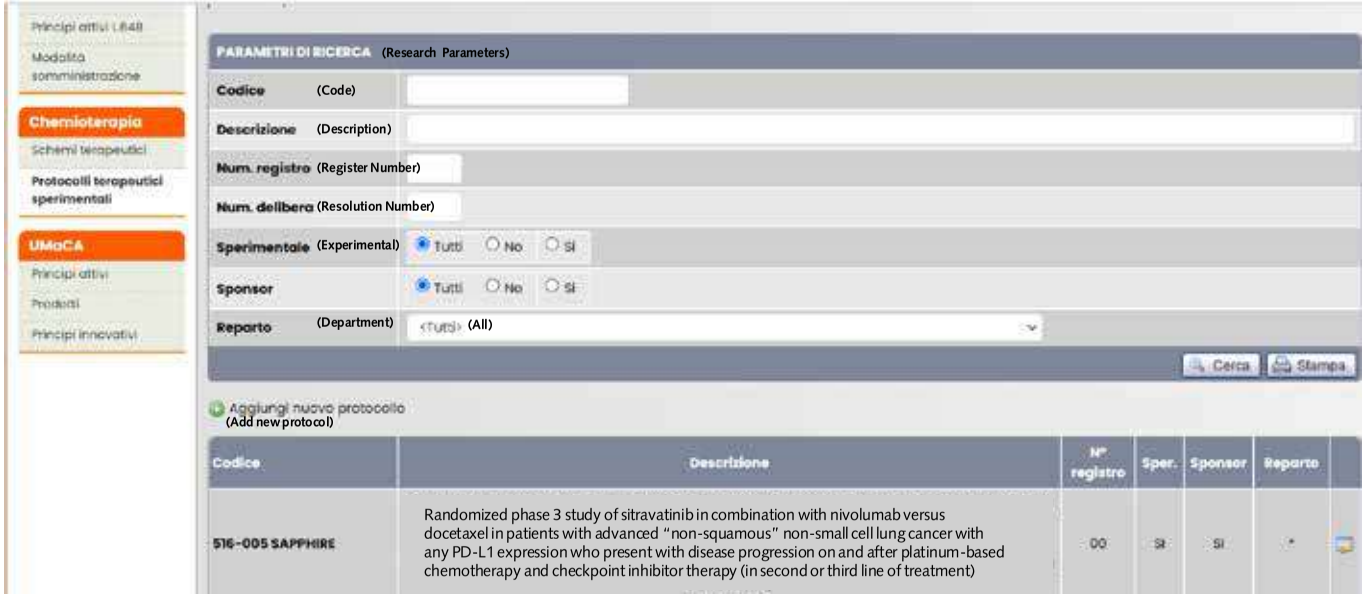
Direzione (Director) ..... Docente (Professor) ..... Data (Date) .....

All trials, both open and blind, are managed on the computerized prescribing system.

To date, the preparations are all manual: according to the indications given by the pharmacy manual, closed-circuit preparation systems are used.

The molecules being studied are both chemotherapy drugs and monoclonal antibodies.

In 2020, 3,833 prescriptions for experimental drugs were filled and in 2021, 3,833 prescriptions were filled.


Principi attivi L648
Modalità somministrazione
Chemioterapia
Schemi terapeutici
Protocolli terapeutici sperimentali
UMaCA
Principi attivi
Prodotti
Principi innovativi
PARAMETRI DI RICERCA (Research Parameters)
Codice (Code)
Descrizione (Description)
Num. registro (Register Number)
Num. delibera (Resolution Number)
Sperimentale (Experimental) Tutti No Si
Sponsor Tutti No Si
Reparto (Department) <Tutti> (All)
Cerca
Stampa
Aggiungi nuovo protocollo
(Add new protocol)
Codice
Descrizione
N° registro
Sper.
Sponsor
Reparto
516-005 SAPPHIRE
Randomized phase 3 study of sitravatinib in combination with nivolumab versus docetaxel in patients with advanced "non-squamous" non-small cell lung cancer with any PD-L1 expression who present with disease progression on and after platinum-based chemotherapy and checkpoint inhibitor therapy (in second or third line of treatment)
00
SI
SI

3. The logistics of the experimental sample in the UOC Clinical Pharmacy Production and Research, IRCCS-AOU of Bologna - Policlinico S. Orsola

M. Meneghello, F. Tombari, G. Piazza, S. Meneghetti, A. Stancari

The research activity is an integral part of the mandate and mission of the University Hospital of Bologna, recently recognized as a scientific hospitalization and treatment institute (IRCCS) of national importance with the decree of 19.9.2020 in the disciplines of "*assistance and research in transplants and the critically ill*" and the "*integrated medical and surgical management of oncological pathologies*", with a further strengthening of its leadership in the field of clinical and translational research, in the biomedical field as well as in the organization and management of health services, together with hospitalization services and high specialty.

Over the last few years, clinical research activity, with particular reference to clinical trials of medicines, has recorded a progressive increase which has brought our Polyclinic to the top place for the absolute number of trials in the national territory and also for the number of Non-Profit Trials (Table 1).

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Corporate Observatory on Clinical Trials
Year(s) of request for evaluation to the Ethics Committee 2018, 2019, 2020, 2021

Part 1 - GENERAL DATA - All types of Clinical Trials

Tab. 1 - Sperimentazioni valutate: per tipo promotore - per area osp-univ - per anno

	Sponsored		Spontaneous		Total	
Year	N° SC	%	N° SC	%	N° SC	%
2018	116	31,18%	256	68,82%	372	100,%
2019	153	32,21%	322	67,79%	475	100,%
2020	125	22,78%	434	77,22%	562	100,%
2021	142	24,27%	443	75,73%	585	100,%
Total	539	27,03%	1.455	72,97%	1.994	100,%

Table 1 - General data AOUBO Clinical Trials from 2018-2021 evaluated by the CE.

The Clinical Pharmacy Unit has been collaborating for years with the various corporate structures (Ethics Committee, Technical-Scientific Secretariat of Ethics Committee, Clinical Units, and recently with the Innovation Research Unit, etc.) in the management of functions and activities in support of trials Profit, Non-Profit clinics and compassionate uses approved by the Ethics Committee of the vast reference area.

In particular, the pharmacist is involved in the Investigational Sector Drug Service (IDS) and of the Compounding Centre Production Laboratories in the management of the activities envisaged by the GCPs and other specific pharmaceutical activities to guarantee the logistical aspects (order methods,

receipt control and confirmations, correct conservation and traceability of the experimental samples, distribution and documentation management, etc.) and technical-scientific ones such as: participation in the drafting/drafting of the trial protocol and documents also for the purposes of preparation, participation in the initial trial and monitoring visits, AIFA audits and inspections, Pharmacovigilance in Eudravigilance for No Profit studies, etc.).

The management aspects of clinical trials are multifaceted and require multidisciplinary skills which involve the involvement of different sectors of the Company in addition to the pharmacy. For the start of any clinical trial, whether spontaneous or sponsored, the presence at the centre of:

1. Facilities and equipment suitable for conducting the study;
2. Internal management procedures for conducting clinical trials;
3. Qualified and trained personnel;
4. Dedicated software for tracing studies, experimental material and eventual preparation at the centre.

1) Structures and equipment

For the correct conduct of pharmacological trials, rooms with a controlled temperature and equipment, such as refrigerators or freezers, are necessary, suitable, and dedicated to the conservation of the experimental material only. This suitability is guaranteed by special certifications present for each piece of equipment and for each storage room which must be kept in the pharmacy and exhibited in the event of centre selection visits, study start-up visits, audits, or inspections.

The certifications are obtained through tests that verify the correct functioning of the equipment. These periodic calibrations/revisions are performed by the Clinical Engineering Service which is responsible for them and defines their frequency (Fig. 1).

Fig. 1 – List of certificates and related documents.

These certifications make it possible to demonstrate that the experimental drug is stored correctly for the entire time it remains inside the pharmacy premises.

Among the premises subject to certification there are also laboratories if the drug is set up or prepared by the pharmacy.

The pharmacist is called upon to guarantee the correct storage of the drug even during the transport phases until delivery to the experimental centre. Therefore it is necessary to use adequately trained personnel.

In our reality, the deliveries of experimental material inside the Polyclinic, both drugs, and extemporaneous intravenous antiblastic therapies, are carried out through the use of designated boxes and electric means of transport. Delivery is guaranteed within 15 minutes of leaving the pharmacy premises. These timings are periodically checked as required by our internal quality procedures.

2) Internal operating procedures for conducting clinical trials

Fundamental to the correct management of the experimental material is the presence of SOPs (Standard Operating Procedures) to which all pharmacist staff must not refer. These SOPs can be company-specific or unit/department-specific operating instructions. To support the drafting of the SOP, collaboration with the corporate quality group is essential (Fig. 2).

3) Qualified personnel

The pharmacist/non-pharmacist staff involved in the management of the experimental material must be identified by an organization chart and a job description that defines their duties and responsibilities.

The pharmacist staff must be adequately trained through expressly designed courses that certify knowledge of the hospital's SOPs and GCPs (Good Clinical practices). These represent an **international standard** of ethics and quality necessary for the design, conduct, and registration of clinical trials conducted on humans (Fig. 3).

Among the activities that the pharmacist must carry out for the conduct of clinical trials, there are:

a. Communication of receipt of the drug (sending the packing list by mail or fax or via the IWRS system);
b. The notification of quarantine in the event of problems concerning the conservation of the shipment from the sponsor to the centre;
c. The return of the experimental material due to the conclusion of the trial or due to its expiry;
d. Any re-labelling of the investigational drug (following a re-test date);

Logistics: Methods of delivery

Transport of experimental material

Investigational Drug Service (IDS) – U.O. Pharmacy Unit Clinic,
AOU of Bologna, S. Orsola Hospital - Malpighi

TRANSPORT OF EXPERIMENTAL MATERIALS FROM A CLINICAL PHARMACY -
IDS TO INVESTIGATORS

File notes dated February 24, 2020, Author: IDS Coordinator Dr. ……

The transport service of the experimental material from the Clinical Pharmacy Unit, IDS sector, to the investigators in the wards is provided by the staff of the Hospital..... - Hospital Services (contract with the Bologna AOU following the tender) dedicated to the Clinical Pharmacy Unit for the transport from the pharmacy to the departments of the material set up in the pharmacy (Compounding sector, Galenic sector, Parenteral Nutritional Mixtures sector) as part of the normal care pathway.
Experimental material ready for transit to individual investigators is indicated on the blackboard located in the box of the goods acceptance area.

Experimental material to be stored at a temperature of 15°C-25°C
This material is taken from Room 12 from the shelves with the floors identified as "Experimental drugs in transit". It is delivered to individual investigators following the instructions given as "delivery notes" on the Experimental Drug Arrival Receipt.
This document is placed in a transparent folder fixed with adhesive tape on the closed box. Experimental material must be delivered to the investigators within 15 minutes of leaving Room 12. The Receipt of receipt of experimental drug countersigned by the recipient is delivered to the IDS sector.

Experimental material to be stored at temperatures 2°C-8°C
This material is taken from the IDS fridge (inventory No....., SpyLog inventory..... It is delivered to the individual investigators following the instructions given as "delivery notes" on the experimental drug arrival receipt. This document is placed in a transparent folder attached to the open thermal bag containing the experimental material with the relative documentation in a transparent plastic bag closed with the stapler. After removing the thermal bag from the fridge, insert the ice packs positioned in the freezer -20°C next to the IDS fridge. Once the ice packs are inserted, the thermal bag must be immediately closed and delivered to the investigators within 15 minutes. The Receipt of arrival of the experimental drug countersigned by the recipient is delivered to the IDS sector.

Fig. 2 – List of certificates and related documents.

Personal certification

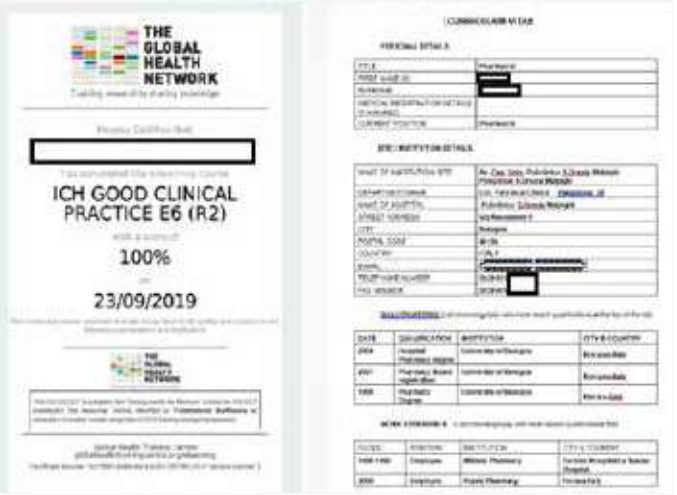


Fig. 3 – CV and GCP.

e. The procurement of PeIMPs when they are not provided directly by the sponsor.

The pharmacist must therefore have a global view of the entire journey of the experimental drug, from its arrival at the pharmacy to its disposal.

4) Allocated software

Very important for the optimal conduct of clinical studies is the presence of allocated software in the pharmacy that helps in the identification of the trial, in the traceability and in the correct management of the information.

The existence of a database containing all the information relating to the clinical trial and its approval by the Ethics Committee (Principal Investigator, Operating Unit involved, CE approval date, protocol, Pharmacy Manua, Investigation Brochure) allows you to carry out the various study-specific activities (Fig. 4).

Fig. 4 – IDS database search screen.

When transiting an experimental drug for the first time, it is essential to verify the approval of the study by the Ethics Committee and to have documents such as the Pharmacy Manual and Investigation Brochures. Some information useful for conducting the study and for the correct management of the experimental material can also be collected during the selection visits of the centre and at the start of the study (PRE-SIV and/or SIV). During these meetings it may be advisable to use a template to facilitate the collection of study-specific information.

During these preliminary meetings, based on the experimentation, it may also be useful to know what the goods receipt confirmation system will be (email or confirmation via IWRS) and what procedures should be followed to notify the presence of damaged or altered temperatures of materials.

Once the study has been identified and the presence of EC approvals has been verified, it is the pharmacist's duty to register the experimental material received in a special database. Our transit management database reports: Ethics Committee code, Sponsor study code, Study title, Approval date, Main Investigator, Sponsor, Description of the investigation drug(s), Notes for delivery (Fig. 5).

In the database, fields such as date of receipt, description of which ones and quantity, pharmaceutical form, storage method, lot and expiry date and delivery date are filled in (Fig. 6).

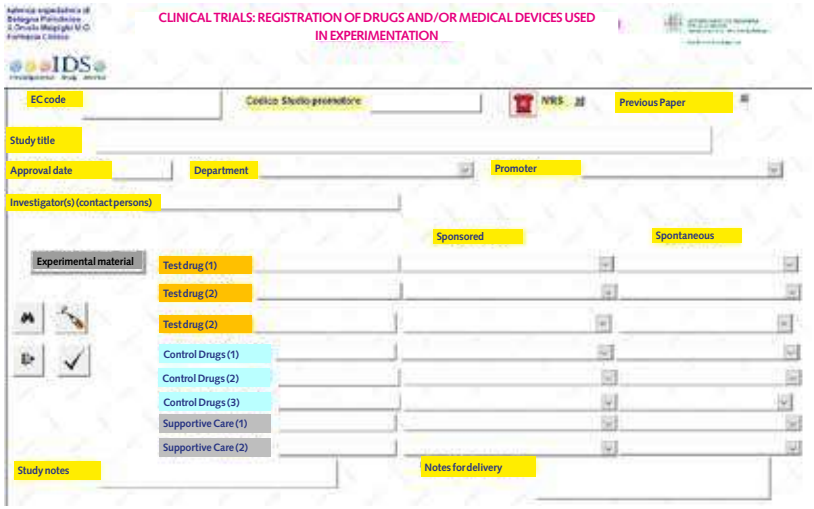


Fig. 5 – Experimental drug transit database search screen.

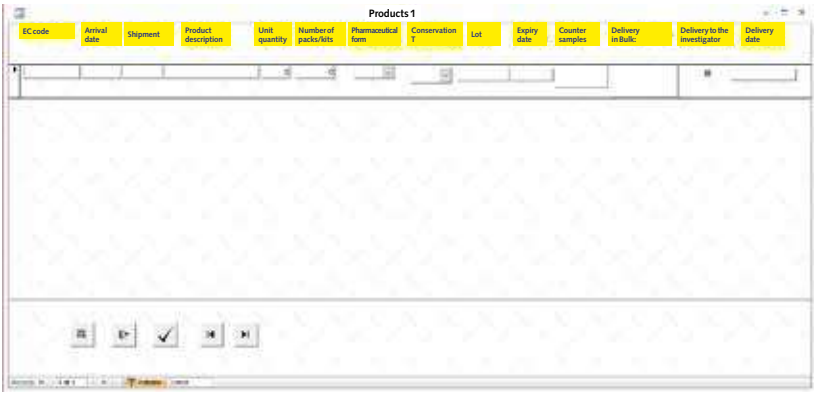


Fig. 6 – Experimental drug transit data base screen, experimental material reception fields.

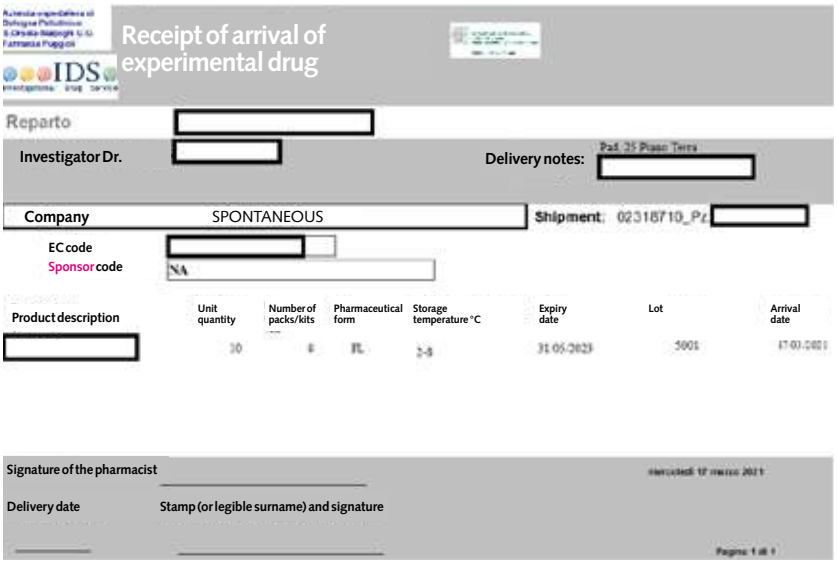


Fig. 7 – Experimental material delivery note.

A delivery receipt is then generated which makes it possible to certify that the single shipment has been delivered to the trial centre (Fig. 7).

The activity linked to the number of transits involving the IDS Service Pharmacy in the period 2018-2021 is shown in Table 2 and shows a progressive increase in the number of managed trials.

YEAR	Total number of transits
2018	2561
2019	2572
2020	2643
2021	3420

Table 2 – Total number of transits/year of experimental material.

Some of the experimental drugs that arrive at the Pharmacy do not pass directly to the wards but are sent to the Compounding Centre for preparation according to Legislative Decree no. 200/2007 of personalized experimental therapies for parenteral use in specific laboratories, with controlled contamination, certified.

For the management of the activity, the software is used with a module reserved for clinical trials for the entry and validation of trial protocols,

computerized management of prescriptions, preparation with traceability and serialization of products, and general accounting of the drug and by the patient.

The preparation of experimental parenteral therapies, particularly in the onco-haematological field, has recorded a significant increase over the last few years and represents a complex, non-automatable activity that requires highly specialized skills, also for the management of new experimental drugs (Fig.8).

Product description	Total sper	Total clinical practice	Total therapies	Product incidence of experimental setups on the total description
year 2020	4855	49613	57666	8%
year 2021	6991	53814	64915	11%
increase	+44%	+8,4%	12,6%	

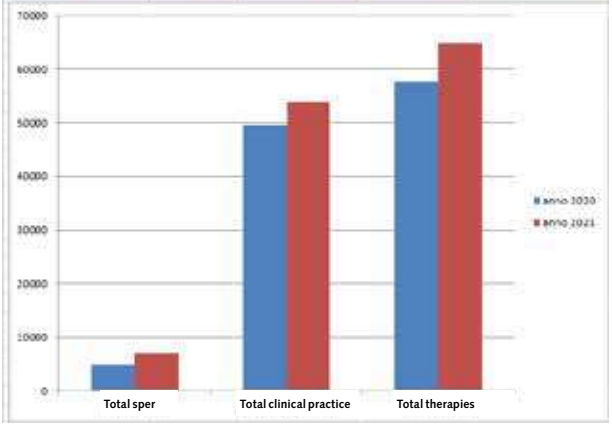


Fig. 8 – Production data of the Antiblastic Laboratories of the Compounding Centre.

In this context, the role of the pharmacist is emerging and heterogeneous due to his technical and organizational skills, which can make a difference in providing high-profile support to the wide range of studies' issues, especially those in Phase 1.

In conclusion, the management of clinical trials requires specific skills and interaction with various sectors within the hospital company ranging from clinical engineering, quality, and logistics but also constant interactions with sponsors and investigators. If all the various aspects are managed correctly, the standards necessary for the correct conduct of the clinical study are guaranteed. This not only guarantees the protection of the health of the patient participating in the trial, but also the correctness and reproducibility of the data collected.

4. Computerized management of the experimental drug: the experience of the SC Pharmacy of the IRCCS IRST of Meldola (Forlì) to guarantee traceability and safety

C. Masini, L. Gasperoni

The SC Pharmacy unit of the IRCCS Romagna Institute for the Study of Tumors "Dino Amadori" IRST, ISO 9001 certified, is responsible for the drug management of the Profit and No Profit clinical trials conducted at the Institute's headquarter, which consist of three Day Hospitals (Meldola, Forlì and Cesena) and a 36-bed hospital ward. The IRCCS IRST conducts numerous clinical trials of all phases, including low-risk phase 1 trials, covering a variety of solid and haematological cancer care settings. All the experimental therapies intended for the patient are set up inside the pharmacy laboratory, specifically in addition to the total management of oral therapies, we proceed with the management and preparation of chemotherapy, immunotherapy, non-oncological drugs, genetically modified microorganisms (GMMOs) and ancillary therapies. Inside the Institute there is a radio pharmacy, which is part of the SC Pharmacy, where investigational radiopharmaceutical products are also synthesized.

The SC Pharmacy unit of the IRCCS IRST has developed and refined its procedures over time for the management of the experimental drug to cope with the growth of the quality standards required by national and international legislation and the rise in terms of complexity and number of managed studies. To put it into context, during 2021 IRST recorded the treatment of over 650 subjects in 170 different clinical trials (Profit and Non-Profit) with drugs, with the pharmacy setting up over 6,700 experimental therapies. Responsibility for the reliability and management of the experimental drug is delegated by the investigator to the pharmacist and the SC Pharmacy unit is made up of three Clinical Pharmacists of Research (FRC) (CPR) dedicated to this activity and four laboratory technicians to support logistical operations. The oral and injectable experimental drugs are stored separately from the commercial ones in identified spaces, closed inside the pharmacy laboratory and separated by characteristics in cabinets for storage at 20-25°C, refrigerators for storage at 2-8°C and freezers for storage between -15 and -25°C or between -60 and -90°C. Each cabinet/refrigerator/freezer specific for the storage of experimental drugs shows for each shelf on its facade, a label identifying the drugs present, the trial to which they belong and the primary cancer site of the patients for whom the study is intended.

Each FRC (Clinical Pharmacist of Research (hereafter CPR)) is responsible, for supervising the management process of the experimental drug and for the correct storage and traceability of data. The CPR is involved in the initial phases of selection and initiation of the trial at the centre, he is responsible for the codification of the experimental drugs at IT level, collaborates with the clinician in the construction of the experimental therapy schemes and instructs and supports pharmacists and laboratory technicians in the activities of logistics management and preparation of the drug within the clinical trial. The strategic choice in the implementation of the procedures that regulate the daily activities of the pharmacy was supported by the parallel development of a software (IRST Computerized Medical Record - IRST CCE) with the aim of ensuring compliance with the GCP principles and offering levels of safety and simplification to allow the conduct of such a large number of studies. The result of this process has translated into a level of computerization useful for recording and tracing a large part of the activities related to the management of the experimental drug and in the development of a computerized accounting module, automatically fed through daily operations, which reports all the information related to the investigational drug in a comprehensive manner. The accounting module is based on the investigational drug serialization process. Serialization has the objective of securing the withdrawal phase of the experimental therapy from the storage location, eliminating possible confusion errors dictated by the simultaneous management of a large number of experimental drugs, allowing for complete traceability. Serialization is also essential to automatically feed the accounting forms in an exhaustive manner.

We briefly review the main phases of computerized management of the experimental drug, from the initial stages to delivery to the patient, return or disposal, applied by all the operators involved, with a focus on activity data within the SC Pharmacy unit throughout 2021.

Drug coding and therapy schemes

When a new trial begins, the experimental drug is coded in CCE IRST by filling predefined tables, an operation performed by the CPR and controlled by a second pharmacist. These tables are used to summarize the characteristics of the experimental product and to name it, specifying the trial to which it belongs. Furthermore, CPR collaborates with the investigator in coding the protocol therapy schemes on the CCE IRST, from which the computerized prescriptions derive. During 2021, 98 new trials were started, with the registration of 413 drug tables and 386 therapy schemes.

Clinical trial coding
The CCE IRST allows you to select the mask of a single trial to view all the useful information of the protocol itself. In this mask it is possible to associate the tables of the previously coded experimental study drugs and the therapy schemes. The mask therefore acts as a glue between the protocol, drugs and prescription and once all these elements are connected, it is possible to proceed with routine operations such as receiving, serializing experimental drugs, prescribing and assigning therapy.

Receiving
Once the arrival of the experimental drug has been recorded, within 24/48 hours of receipt, the transport document is registered in the CCE IRST, transferring the information relating to: document number, quantity, lot, expiry date, date of arrival, trial name and any sponsor kit identification number for each drug received. During 2021, 2,474 loading operations of experimental drug were recorded.

Serialization
CCE IRST produces unique serials for each unit received, linked exclusively to a specific trial as they refer to the drug-prescription-mask connection. The serial code contains information such as drug name, lot, expiry date, any identification number of the sponsor's kit and barcode for reading with an optical reader. The serialized labels are printed and applied to the individual drug packages, taking care not to cover those already present on the package. The serialization operation is the basis of the computerized accounting module for the management of the experimental drug. As this is a high-risk activity, a double check dated and signed by a different operator is required to verify correct serialization. If the clinical trial involves the use of drugs not supplied by the sponsor, but reimbursed, these are loaded to the trial inventory management (to ensure the traceability of logistical and administrative drug movements) and labeled according to GCP. Only at this point, the registration and serialization operations in the IRST CCE are carried out as previously described. During 2021, 16,405 experimental drug kits were serialized.

Prescription validation

The next phase is linked to the prescription of the experimental therapy through the computer application by the investigator. The pharmacist validates the computerized prescription on the CCE IRST and takes the drug necessary for the preparation of the therapy. If the therapy involves the assignment of unique code numbers assigned through IWRS, the assignment of the investigational drug through IWRS is performed by the pharmacist.

Stock unloading of experimental drug

CCE IRST requires the unloading from the stock of a quantity of experimental drug to guarantee the preparation of the validated therapy. The unload is tracked by reading the serialization code with an optical pen. Only drugs belonging to the trial can be unloaded, in fact, in the event of an incorrect operation, the drug-prescription-mask connection would fail and the unload would be prevented by an alert. At the end of the operations, the phase of prescription validation and therapy unloading involves a double check by a second pharmacist, providing documentary evidence.

Oral drug return tracking

The count of the oral drug returned by the patient is recorded on the CCE IRST by the pharmacy operator, referring to the number of tablets returned for each kit previously serialized and assigned. The returned drug is stored in dedicated spaces and available for monitor verification before collection/authorization for disposal. The successful verification, during the monitoring phase, is traced in CCE IRST making the data unchangeable. During 2021, 3,509 kits of experimental oral drug returned by the patient were accounted for.

Disposal/return operations

Pharmacist also has the possibility of electronically recording drug disposal/return operations to the sponsor, reporting the date on which this operation was carried out. During 2021, 133 disposals of experimental drug were organized and 235 drug returns to the sponsor were arranged.

Accountability

Taking advantage of the unique serialization code, all operations are recorded and the CCE IRST itself generates a drug-specific form (Drug Accountability Form) and a patient-specific one (Patient Accountability Form). The computerized system registers the operator who performs the single movement. This is identified with an internal code, the trans-coding of which is available at the pharmacy laboratory.

The **Drugs Accountability Form** generated by the CCE IRST contains the following information:

- Drug Receipt with shipment arrival date, shipment number, quantity of units received, lot, expiration date and, if any, study kit number;
- Drug assignment to patient with patient code, date of assignment, amount of drug assigned;
- Drug returned by the patient (only for oral drug) with date and quantity of the individual units returned (e.g. number of tablets);
- Returned to the sponsor/Disposal drug with relative date.

The **Patient Accountability Form** generated by the CCE IRST contains the following information:

- Drug assignment to patient with patient code, date of assignment, amount of drug assigned;
- Drug administration to the patient with date of administration, lot and expiry date of the drug administered;
- Drug returned by the patient (only for oral drug) with date and quantity of the individual units returned (e.g. number of tablets);
- Return to Sponsor/Disposal drug with relative date.

CCE IRST has been developed offering at the same time the ability to safeguard the specific protocol procedures and to satisfy the ICH GCP principles: adequate IT support and its growing implementation represent an essential standard for such a large amount of activity related to drug management experimental, to guarantee the tracking of all information and to allow for accurate reporting, interpretation and verification.

5. The management of trial products at the Pharmacy of the Agostino Gemelli IRCCS University Hospital Foundation in Rome

E. Laudati, A. Piras, M. Pani

The Pharmacy of Experimental Products (FPS) at the Agostino Gemelli University Hospital Foundation IRCCS (FPG) in Rome, is a centralized system dedicated to the exclusive management of Investigational Medicinal Product and not, used in clinical trials.

FPS is a highly specialized service which, in addition to fulfilling the traditional tasks of managing experimental products, has specific laboratories for the personalized safety preparation of the medicines that make up the experimental therapies.

The difficulties that arise in the trials emerge precisely in the management of the trials themselves and are mostly linked to the preliminary knowledge of the drug, and to following specific methods of storage, handling, rendering, etc.

Among the main activities carried out, the pharmacists are guarantors of the correct conservation of the experimental products, separated from other drugs/medical/nutraceutics or similar devices and divided by protocol, until the time of delivery to the Investigator.

At the same time, specific areas have been set up with continuous temperature monitoring and with limited access to specific personnel. Furthermore, for any need to reallocate resources and experimental materials, certain allocations and backup temperature-controlled equipment have been identified in proximity to the reference areas.

The experimental products are normally requested from the FPS directly by the investigator doctor or his delegate, upon presentation of the appropriate form which differs in case of withdrawal of the prepared or unprepared product. The pharmacists proceed with the evaluation of the accuracy and integrity of the documentation in all its parts, without which it is not possible to proceed with the delivery or any preparation.

The FPS, to date, does not have a support information system in the management of the warehouse and of the experimental preparations. In order to increase the level of safety, requests for preparation of investigational products are double-checked and signed by a second pharmacist. Subsequently, the preparation of the IMP and/or NIMP is carried out by the nursing staff, delegated by the trial, reporting the details of the preparation carried out, the signature and the start/end time of the preparation in the appropriate "Worksheet". At the end of the preparation, the pharmacist

checks the outgoing therapies and gives evidence of this check by signing the form indicated above; only after the check can the therapies be delivered to the centres.

The Laboratories set up for setting up the experimental products in aseptic conditions have two separate areas, one of which is intended for the handling of anti-cancer chemotherapy and one for galenic preparations.

The preparation and quality control of the therapies are carried out for all the departments and presidents of the Healthcare Company and possibly also for the Operating Units of external centres involved in the same trials.

From the moment of delivery, the Investigator is responsible for the correct management of the trial products (transport, storage at the centre, administration, accounting by patient and by trial unless specifically agreed with the Sponsor/CRO, final reconciliation).

In recent years, the increased research activity of the polyclinic has led to a reorganization of the routes, personnel and premises of the FPS.

In 2021, there were approximately 534 active clinical trials involving the pharmacy service, of which 8 were studies with analysis of the use of medical devices. Of these, 30% relate to Oncology Gynaecology, 15% Haematology, 13% Medical Oncology, 9% Surgery, 7% Infectious Diseases, 7% Gastroenterology, 6% Neurology, and the remainder from Dermatology, Paediatrics, etc. centres.

Independent research studies represent approximately 12% of the total number of protocols at the Polyclinic. Non-profit research requires great attention in the Pharmacy's operations in the pre- evaluation processes, and following approval, further processes such as re-labelling, drug supply, possible randomization for blind studies, and transparency on the operating methods of collaboration of the subjects involved.

AIFA Resolution 809/2015 establishes the minimum requirements necessary for the functioning of healthcare facilities that carry out phase I clinical trials, emphasizing the importance of the Clinical Trial Quality Team (CTQT).

The design, coordination and analysis of a clinical trial is carried out through the involvement of a multidisciplinary team represented by Principal Investigators, research coordinators (CRC), pharmacists, Clinical Research Associate (CRA) and other investigators.

In this phase, much information (e.g. toxicity) is not yet available, for these reasons the training and information of personnel is equally delicate (the sponsor of the clinical trial, to avoid possible incompatibilities, can ask to work – both in preparation and in administration – with specific materials, which perhaps you are not used to using in clinical practice).

Eight Phase I studies are underway at the FPG, of which 80% of the protocols require the preparation of an experimental drug. The departments involved are the department of Paediatrics, Pneumology, Medical Oncology, Gynaecology and Haematology.

In the case of experimental products for phase I clinical studies, the delivery is made on a patient-specific basis, upon presentation of the appropriate assignment documentation carefully verified by the pharmacy.

In collaboration with other operators of the phase I Clinical Unit, the pharmacists delegated by the Main Investigator of the study, take care of maintaining the accounts of the experimental product and carry out the complete reconciliation of the same at the end of the study.

Furthermore, the FPS guarantees the availability of the specific antidote relating to the product under study, as per the indications provided by the Sponsor and agreed with the Phase I Pharmacologist.

The Pharmacy of experimental products is made up of a team of four hospital pharmacists, 3 preparatory nurses, two administrative figures and two logistics personnel.

On average, 58 therapies are dispensed daily, of which approximately 27 are investigational treatments that require drug preparation and 31 are unprepared investigational products.

These numbers have shown to have a year-on-year growth trend, leading to a managerial, IT and logistic reorganization of the pharmacy that is still in progress.

The Service of the Pharmacy of Experimental Drugs presents a continuous update directly linked to the high demand for the start of new trials, aimed at a greater availability for patients of therapeutic alternatives, access to innovative drugs and safe and effective assistance.

6. The Management of Clinical Trials at the San Martino Hospital in Genoa

S. Beltramini, F. Trovato

Introduction

The Hospital Policlinico San Martino is located in Genoa and pertains to the organizational typology of Institutes of Hospitalization and scientific care IRCCS - with recognition in the disciplines of Oncology and Neurosciences.

These two specialities are the focus of most clinical studies at the facility. However, being home to many specialty schools and university centres, there are numerous active studies both *Profit* and spontaneous (*Non-Profit*) on many other specializations (Rheumatology, Dermatology, Immunology, Gastroenterology, etc...)

1. Pharmacy involvement in the authorization process

Each clinical trial must be approved in advance by the Liguria Regional Ethics Committee, which is responsible for protecting the rights, safety and well-being of subjects participating in a clinical trial.

For clinical studies in which the Hospital Pharmacy is involved, the validation of the Director of the Pharmacy is required in order to submit the study.

In this phase, the Pharmacy primarily examines the feasibility of the study and, if so, confirms its involvement in one or more of the following activities:

- receiving and sending the drugs directly to the PI;
- set up of drugs according to NBP;
- drug storage at the required temperature and SpyLog monitoring;
- possible management with IWRS system of the IP/placebo and assignment of the ID/vial;
- management of documentation relating to taking charge of the drug, keeping general accounts and per subject;
- management of the medical prescription with the Tera80 IT system;
- collaboration with the Sponsor and the Investigating Centre for the entire duration of the study and support for monitoring visits.

2. Initial Study visit

In the SIV meeting, the pharmacists discuss the following aspects relating to the trial with the study managers:

1. Preliminary information on the drug (pharmaceutical form, preparation method, special information, stability, compatibility with medical devices).

2. Type of study (type of phase, randomization and other information).
3. Medication management (arrival confirmation and assignment).
4. Presentation of the internal form of Drug Accountability managed with the Tera80 computer program.
5. Instructions for disposal.
6. References (email and telephone) of the clinical monitors and possibly of the Data Managers.
7. Contract Information.
8. Pharmacy File (documentation provided by Sponsor) containing protocol synopsis.
9. Common opinion of the Ethics Committee.
10. Corporate approval resolution.
11. Contract (within the resolution).
12. Possible drug reimbursement and supply methods.

3. Choice of the Production Laboratory according to the type of Drug

The specialty medicines sector of the Pharmacy receives all medicines and medical devices from clinical trials.

Upon arrival, three different flows are generated:

- Trials involving drugs with present or future ATC L01 (both oral and injectable) and those involving the use of biological drugs are sent to the blood - oncological and biological drug laboratory.
- Trials that include a galenic set-up that is not part of the above are sent and managed by the Clinical Galenics laboratory.
- All other types of drug are sent directly to the PI

4. Computerized management of the process

The most numerous trials at the Polyclinic concern the studies of Hemato-Oncology and Neurology.

These are all managed by the Blood-oncological and Biological Drugs Laboratory through a completely computerized procedure on the prescriptive program which includes the following steps:

1. Insertion of all the active ingredients present in the trial
2. Creation of the worksheet containing all the information necessary for the preparation of the drug or placebo.
3. Creation of the IT protocol necessary to allow the clinician to insert the computerized prescription.
4. Creation of the IT folder for each trial that generates a code that will be reported on the study folders.

5. Creation of the IT warehouse of experimental drugs, through the loading by lot and number of kits of each single vial or tablet present in the laboratory and punctual unloading at each administration or destruction. For each load, a label with a specific ID is generated.
6. Anonymity of patients included in individual trials.
7. IWRS management where required

Points 4 and 5 together originate the Drug Accountability report for each experimental drug usable by the sponsor companies and in line with the new regulations.

The computer warehouse allows both to monitor the stocks of medicines and to check deadlines.

In fact, a special section called "expiry chronologies" is generated in which it is possible to display expired medicines and medicines due to expire on a monthly basis using a colour caption. For those due to expire in thirty days, the pharmacist coordinates with the monitor or data manager to organize collection by the sponsor.

5. Storage temperature monitoring

The trials require a specific temperature monitoring and recording activity.

For the control and monitoring of the temperature of the medicines stored in the refrigerator, a connection has been set up for the refrigeration equipment with a centralized alarm monitored 24h/24h, a local audible alarm and the recording of the temperature through digital thermometers, through which it is possible to download the temperature detected by creating a pdf file with a graph or with a recording data table.

For the control and monitoring of the temperature of the medicines stored at room temperature, an air conditioning system and a daily recording of the temperature in a special form have been set up.

The temperature data collected is sent monthly by email to all the monitors that have offices at our centre.

6. Documentation

For each prescription, a copy of the administration sheet is printed to which the adhesive labels of the individual experimental drugs used are attached.

In the case of protocols that provide for the use of kits, the confirmation received from the electronic assignment system or the e-mail from the Data Manager is attached.

These documents are stored in the trial binder (identified by a numerical code generated by the program) to be used during monitoring.

The information relating to the set up is entered on the worksheet, this document is always intended for internal archiving of the Antiblastic Laboratory, and is not archived in the trial binder.

7. Disposal of Intact Bottles

Profit trials

The Sponsor is responsible for the disposal of unused or expiring vials of the experimental drug.

The pharmacist coordinates with the monitor to alert, during the experimentation, the presence of expiring vials to activate the re-stocking and disposal of the same which will be borne by the sponsor.

At the conclusion of the trial, the pharmacist coordinates with the monitor to activate the disposal of any remaining unused vials.

Non-Profit trials

Disposal of any bottles of expired drugs used in the trial is carried out according to company guidelines.

7. The Hospital Pharmacy of the European Institute of Oncology of Milan, process and management of the Experimental Drug

C. Jemos, E. Omodeo Salè

The hospital pharmacy of the European Institute of Oncology in Milan is directly involved in the management of drugs and devices in clinical trials at all management levels.

The IEO currently has more than 300 active studies with drugs, of all experimental phases, manages studies with GMOs and advanced therapies, has a "phase one structure" accredited by AIFA and a Molecular Internal Tumor Board (MTB).

The pharmacy participates in the compilation of Implant and Employment Notifications for MOGM trials, is part of the Phase One facility, and has two members officially involved in the MTB and Clinical Trial Quality Team. He is also responsible for the pharmacovigilance process for the clinical trial with the elaboration of the DSURs and for the reporting of the SUSARs through EUDRAVIGILANCE CT.

The pharmacy also manages various multi-centre studies as part of the activities envisaged by articles 8 and 15 of the decree no. 200/2007, both as regards labelling and simple preparation activities, and from a logistical point of view through certified couriers for the transport of experimental drugs.

From an operational point of view, the pharmacy is already involved in the feasibility part of the study and in the qualification process of the centre, it follows both the evaluation process of the CE as a member of the Ethics Committee and the one that leads to the administrative resolution, being one of the Decisional Unit called to evaluate the protocol through the 4D® management system. More than 130 new trials are currently activated at the IEO each year.

After obtaining all the necessary approvals for the activation of the study, the pharmacy is involved in the Site Initiation visit (SIV). This moment is very important and the information collected is transcribed in an internal coded form with the verbal name of SIV.

This form is compared with the protocol and Pharmacy Manual in order to prepare the tools and procedures necessary for carrying out the trial itself.

In particular, the main phases are:

- the construction of the trial database within the APOTECA MANAGER® management system (in the version with extension for trial management);

- the construction of the drug master data within the APOTECA MANAGER® management system (master data including the information necessary for the preparation calculations);
- uploading of the study documents in computer format to the Software Repository (protocol; Pharmacy Manual; SIV report).

Other documents are archived in paper format in the pharmacy study folder (CE authorization, resolution, other specific study documents).

Documents of an administrative nature are available on the 4D® management software (signed agreement, cost sheet, specific study agreements with the pharmacy).

The therapy schemes are now in paper format, since the IT prescription software in use does not allow complete management of the experimental product, but they are being transferred to the new electronic prescription management system, which will replace the current one over the next year.

All drugs and medical devices used in trials arrive at the pharmacy as required by Italian law, then the pharmacy staff checks the material, downloads the transport temperature data and places them in the defined location inside cabinets, refrigerators and specified coolers.

The pharmacy has 9 cabinets, a -80°C freezer, a -20°C freezer, two double-door refrigerators and a cold room entirely dedicated to experimental drugs. All areas and equipment are equipped with data loggers controlled by the SIRIUS® software, in addition to the software control and recording system there is also a remote alarm system independent of the data logger which determines prompt intervention by internal maintenance coordinated with the on-call pharmacist.

Fig. 1 – Example of SIRIUS® layout.

Storage temperatures are shared monthly via a mailing list containing major oncology clinical trial sponsors and CROs.

The drugs arriving at the Pharmacy Division are loaded into the experimental drugs warehouse section of the APOTECA MANAGER® system. The system allows the traceability of the single bottle or vial and allows the insertion of the serial number(also called CID or box identification number).

Fig. 2 – Example of SIRIUS® layout.

Confirmations in IXRS for studies that require an unblended user are made by the pharmacy, while the others are managed by the Data Manager/ Study Coordinator.

The non-automatic resupplies are managed directly by the pharmacy.

The dispensing of the oral drug takes place for each patient on the basis of the medical prescription and the compilation of a specific form for the request 0f the experimental drug.

The dispensing is recorded at the time of delivery using the APOTECA MANAGER® software which allows you to print the dispensing report which is then archived in the pharmacy binder of the practice.

The research nurse double checks with the pharmacist at each dispensing.

The returned drug is accounted for by the research nurse who registers it in their records (the pharmacy does not manage the drug returned by patients), the returned drug is then stored in a dedicated warehouse separate from the hospital pharmacy warehouse.

Drug prescriptions that require preparation are instead received by the pharmacy, checked by the pharmacist and recorded in the APOTECA MANAGER® system, the operations concerning the assignments are divided according to whether or not the study requires a blind figure. All the activities

that require an unblinded figure are carried out by the pharmacy, while the other open activities are conducted by the Study Coordinators of the study.

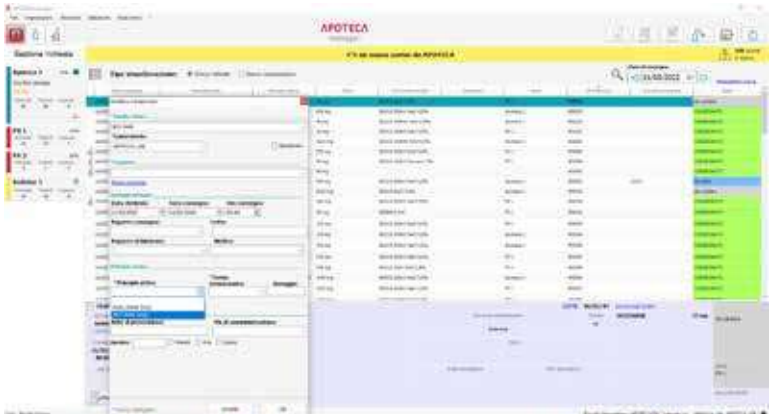


Fig. 3 – Example of prescription mask in APOTECA MANAGER®.

The preparation takes place within the UFA and all the operations are recorded in the APOTECA MANAGER® software, furthermore all the preparations that allow it are managed with the PS, i.e. a preparation assistance system which includes a monitor containing the preparation information, a scale for gravimetric control, a video camera that allows registration of videos and images which are then stored for possible review.

The work sheets of the preparations are also printed through the APOTECA MANAGER® system and are then attached to the assignment sheets and to the labels of the drugs used for the preparation.

The therapies provided are in the order of 10,000/year, of which about 65% are IV preparations, 324 active studies with drugs are currently registered on the APOTECA MANAGER® platform.

Any drug-related electronic CRFs are managed by the pharmacy in studies with unblended staff and only on the basis of specific agreements for other studies.

All loading, dispensing and preparation activities are therefore computerized on the APOTECA MANAGER® software, which then allows the printing of the inventories showing all the data necessary for the traceability required by the sponsors. The inventory forms are then printed, signed and filed in the pharmacy binder so that they can be verified during monitoring in the pharmacy. The pharmacy does not fill in specific sponsor study forms but relies on its own quality system built specifically for study management, thus avoiding unnecessary transcriptions.

Fig. 4 – Immagini derivanti da PS di una preparazione sperimentale (le immagini ed i video catturati dal sistema sono archiviate automaticamente sul server aziendale).

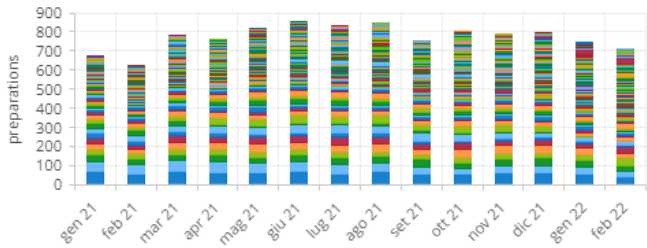


Fig. 5 – Numero di preparazioni sperimentali per mese (ogni colore rappresenta le preparazioni raggruppate per singolo *trial*).

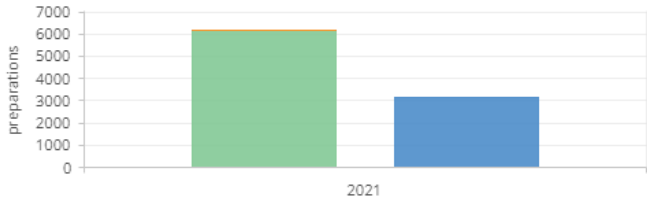


Fig. 6 – numero di preparazioni sperimentali nel 2021 divise tra endovenose (IV) e non endovenose (non IV).

The Monitoring Visits, as Audits in the pharmacy are agreed directly between the Sponsor/CRO and the Pharmacy, according to an agenda based on codified slots, currently the available slots are not sufficient to cover the requests of the sponsors.

8. Ancona University Hospital, SOD Clinical Pharmacy, Management of clinical trial drugs and medical devices

S. Leoni, A. Pompilio

The company

The University Hospital "Ospedali Riuniti of Ancona" (United Hospitals of Ancona) comes from the merger of three Hospital Companies, Umberto I - GM Lancisi and G. Salesi Hospitals and from their integration with the Marche Polytechnic University. The University Hospital is divided into two hospital facilities: Torrette (Umberto I and GM Lancisi) and Salesi (G. Salesi, a highly specialized facility). The Company represents a multi-specialist pole, with both medical and surgical specialties, equipped with 934 beds. The Company adopts the Integrated Activity Department (DAI) as its operational management model for assistance activities, which adopts a unitary management of the economic, human and instrumental resources assigned and guarantees integration with university teaching and research. The Departments are made up of organizational structures called Departmental Organizational Structures (SOD) which have the function of aggregating the homogeneous professional skills pertaining to a specific function. The Company is UNI EN ISO 9001-2015 certified for the design and provision of Diagnostic Therapeutic Assistance Pathways (PDTA) to guarantee the quality of healthcare provided to patients with specific reference to hospitalization and outpatient activities as well as processes relating to transversal services to the PDTA.

The SOD Pharmacy

The Hospital Pharmacy is part of the Services Department and is organized in two locations: Torrette Hospital and G. Salesi Hospital. Since the origins of the hospital, the hospital pharmacy has supported the therapy of admitted or assisted patients by providing drugs, medical devices, dietetics, specialized medical supplies and assisting the doctor in the appropriate use of the same. The staff consists of 14 Pharmacists + 1 Director and 10 Pharmacy Technicians.

The Hospital Pharmacy has been ISO 9001/2008 certified since 2014 for the following activities: procurement, evaluation, storage and distribution of medicines, dietetics and medical devices; preparation of pharmaceuticals, antiblastic drugs, artificial nutrition preparations and quality control of the preparations; information and documentation on drugs, diets and medical

devices; pharmacovigilance, device-vigilance and inspection activities and clinical pharmacy and appropriate use of drugs. The SOD Pharmacy is structured in four Simple Operating Structures (SOS): Clinical Pharmacy, Drugs, Medical Devices and Paediatric Pharmacy (c/o Presidio Salesi). The SOS Drugs and Medical Devices deal with the distribution of drugs, medical and dietetic devices to the various departments and to external users, the SOS Clinical Pharmacy and Paediatric Pharmacy, on the other hand, deal with the production and distribution of immuno-chemotherapy preparations (laboratory U.Ma.CA), total parental nutrients (NPT laboratory and injectable galenics) and galenic (personalized and officinal) and experimental sterile and not sterile preparations and to the various departments and to external users, logistics and drug distribution to the paediatric departments.
The SOD Pharmacy in both locations, depending on the activities mentioned above, also performs a service of pharmacotoxicological documentation and information, surveillance and inspection of pharmaceutical wardobe, quality control of drugs (Regional Laboratory Quality Control, LRCQ) and pharmacovigilance activity. The Pharmacy service is also entrusted with secretarial activities as regards the updating and revision of the Hospital Therapeutic Handbook , the activities assigned by the Regulations for Clinical Trials, the activities of the Committee for Hospital Infections, the didactic and training activities for both internal and external personnel and expenditure control activity. The SOD Pharmacy is characterized by a high degree of computerization and automation of the processes, there are: a software that allows the digitalization of the purchasing processes and the computerized management of the warehouse products (AREAS®, Engineering), an automatic rotating wardrobe and a refrigerator (Kardex ®, Grifols) managed by software (Mercurio®, Grifols) which allow orderly and temperature-controlled storage and accurate identification and selection of the product with the automatic production of warehouse documentations (integration with AREAS), a wireless monitoring alarm system of the humidity and centralized temperature conditions (MySirius ®, JRI), an automatic filling system for the preparation of bags for total parenteral nutrition (Siframix ®, FreseniusKabi) managed by specific software (AbaMix ®, FreseniusKabi), a software for the computerized management of galenic preparations (Magistra ®, Galen) and a platform for the preparation of sterile infusion therapies composed of a robotic system for the preparation of immuno-chemotherapy drugs (APOTECAchemo ®, Loccioni HumanCare), a robotic system for the preparation of non-toxic drugs (APOTECAunit ®, Loccioni HumanCare), a robotic system for setting up paediatric therapies (APOTECAped ®, Loccioni Human Care), a semi-automatic support system

for manual production of therapies (APOTECAps ®, Loccioni HumanCare), a software for managing the entire setting process (APOTECAmanager ®, Loccioni Human Care), a software module for the management of experimental drugs/MD (APOTECA trial ®, Loccioni Human Care) and a statistical analysis and reporting tool (APOTECAm @a ®, Loccioni Human Care).

The management of Clinical Trials

The pharmacist of the Ancona University Hospital is involved in all phases of the clinical trial. In the authorization phase, the pharmacist is present as a member of the Ethics Committee and as a member of the technical-scientific secretariat of the Ethics Committee (EC). In the Marche Regional Ethics Committee there are two Pharmacists of our Hospital, one of which is an expert in medical devices.

The director of the SOD Pharmacy, according to specific forms prepared by the EC, defines in detail the participation of the Pharmacy, in each individual clinical trial, within the application for company authorization (distinguishing whether it concerns a matter of involvement only in logistics or even in preparation activity). With regard to the start-up phase and the subsequent phase of conducting the trial, each Pharmacist of the SOD Pharmacy is the contact person and responsible for the management of the experimental drugs/MDs pertaining to one or more SODs grouped by areas of competence. The activity of the pharmacist who deals with the management of experimental drugs/MDs is supported and assisted by the figure of the "Pharmacist Monitor of clinical trials", a pharmacist holder of a scholarship stipulated by the Hospital using part of the proceeds of the SOD obtained from clinical trials.

Within the SOD Pharmacy, at the site Torrette was identified a sector dedicated to the management of experimental drugs/MD called Un.A.Sper (Clinical Trials Allocation Unit), while at the site Salesi, despite not having a dedicated room, specific wardrobes were identified. Un.A.Sper consists of an office area and a warehouse area. In the first there are computer stations, where administrative-managerial activities are carried out, and shelving where all the documentation is kept; in the second, instead, logistical activities are carried out and therefore there are wardrobes, drawers and refrigerators for the storage of medicines/MDs. Access to these areas is permitted only to authorized personnel. All the drawers and the refrigerator trays are marked with appropriate identification labelling of the clinical study in order to avoid any confusion. Furthermore, a colour code was created to identify the medical area to which the clinical study belongs. In

the warehouse there is an area used for holding incoming parcels, an area used for keeping outgoing (returned) parcels, a wardrobe dedicated to the storage of quarantined medicines/MDs and one for expired medicines/MDs. Similarly, trays dedicated to storing quarantined medicines/MDs and one for expired medicines/MDs have been identified inside the refrigerator. The maintenance of ambient and refrigerated storage conditions is guaranteed through a centralized and alarmed continuous wireless monitoring system (24/24h, 7/7 days). This system has a desktop application that allows the extraction of detailed reports on the specific needs of the user. The complete tracking and traceability of each activity concerning the drug/MD intended for clinical trials is guaranteed through the adoption of a software module called APOTECA trial. The latter, integrated within the APOTECA manager software, against an initial data entry is able to produce supporting documents and reports associated with each single activity concerning the experimental drug/MD. Access to the software takes place via username and password and all the actions performed can be found through the Audit Trail function.

The various activities, roles and responsibilities are described and well defined within a standard operating procedure, the SOP management of clinical trials of drugs and medical devices. The latter is periodically reviewed and updated on the basis of continuous methodological developments and technological implementations.

In the phase preceding the start of the experimentation (Pre-Study Visit – PSV and Site Selection Visit – SSV) until the moment in which the center is opened (Site Initiation Visit – SIV) all information concerning the management of the products being tested (staff involved, equipment, logistics, storage, preparation, etc.) is collected and shared bilaterally (between Sponsor/CRA and the experimental centre). This information is used for the creation, in APOTECA trial, first of the Study records (Eudract Number, Study Code, center number, Sponsor, etc.) and then of the Active Principle records (product name, active principle name, pharmaceutical form, dosage, conditions of conservation and stability, preparation notes, etc.). The information entered is used by the software in the construction of the label and worksheet that accompany the galenic preparation. Subsequently, upon arrival of the experimental product, we proceed with loading and the consequent creation of the electronic warehouse (shipment number and date, unit and kit number, lot and expiry date, etc.). The electronic warehouse is structured like an Excel sheet, it allows a very dynamic and flexible punctual visualization thanks to the presence of numerous filters (available/used/disposed/in quarantine status, product and dosage, pharmaceutical form, lot

and expiry date, etc.) without the constant need for physical visualization. Any qualitative-quantitative discrepancies and temperature excursions regarding drug/MD shipments are managed by interfacing with the CRA/Sponsors, while the experimental products are placed in physical quarantine and within the APOTECA trial application. The documentation regarding the arrival of the drug is archived and kept in the study-specific folder.

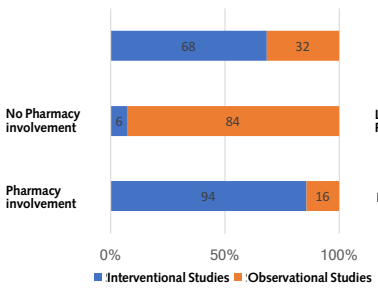
The experimental protocols (only for iv drugs) are inserted by the clinician into the prescriptive software, HUMAN, and subsequently validated by the pharmacist. The patient enrolled in the clinical study is associated with the experimental protocol within HUMAN and therefore the therapeutic cycle becomes prescribable and sendable to the software that manages the sterile galenic preparation of the pharmacy, APOTECAmanager. The communication key between the two software is represented by the EudractNumber, the univocal code of the clinical study. For the inclusion of the patient in the clinical study it is necessary to enter the Patient Code assigned by the study itself, the patient records is then automatically created and the code is used in the various reporting documents for the anonymity of the information. The prescription of the experimental therapy is displayed by the pharmacist in the APOTECAmanager software distinct from conventional therapies by showing an identifying symbol, a small microscope. The validation of the experimental therapy takes place by the pharmacist, thanks to the APOTECAtrial application through which it is possible to directly view the drug kits available in the electronic warehouse of that specific study. Once the assigned drug kits have been selected and the volume of diluent has been established, the pharmacist electronically transfers this information to the semi-automatic device which support the operator in manual preparation, APOTECAps. The Pharmacy technicians following the indications shown on the APOTECAps screen, set up the preparation. The system generates a label, clearly highlighting the wording "experimental drug", to be affixed to the bag before preparation and a worksheet to be archived after preparation, bearing the same wording, in which all the information concerning the preparation (including preparation date and time). Therapies are transferred from the pharmacy to the ward, after being packaged in a photo-protective envelope and placed in special containers, through the personnel who are part of the study staff. The temperature during the transfer is not monitored as the departments involved are located within the same building and the hermetic containers have been suitably validated for maintaining the storage conditions in the two storage hypotheses, ambient and refrigerated. Unlike infusional drugs, experimental drugs that do not require preparation (capsules, tablets, pre-filled syringes, etc.), are prescribed on a paper form,

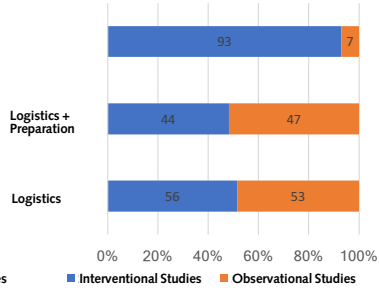
taken from the specific study tray/drawer, packaged and given to the study staff. All documentation relating to the prescription, preparation and dispensing of the drug is archived and kept in the study- specific folder. The reconciliation of the infusional therapy takes place at the same time as the preparation while the reconciliation of the oral therapy takes place through the insertion in the APOTECAtrial application of the units returned by the patient communicated by the medical staff. Any temperature excursions during storage are managed in the Pharmacy by interfacing with the CRA/ Sponsors, while the experimental products are placed in physical quarantine and within the APOTECAtrial application. During the execution or at the end of the trials, in any case before the expiry date, the trial products are returned to the Sponsor. The inclusion of any activity concerning the experimental drug/MD within APOTECAtrial makes possible to automatically produce accounting reports, general and per patient, punctual and consistent with the real situation. Reports that are generated and shared with the CRAs/Sponsors on every occasion for discussion, face-to-face and remote monitoring visits, centre closing visits, etc.

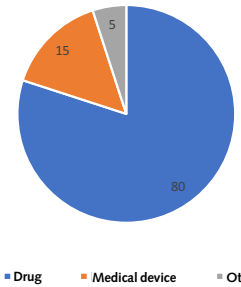
Activities

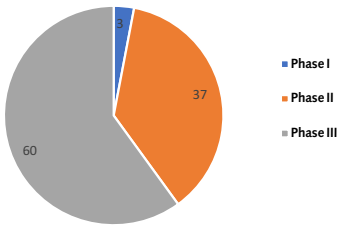
Research activity is strongly present in the corporate mission. A considerable number of trials of varied nature, Profit and No Profit, observational and interventional, concerning drugs or medical devices are managed in the company. Studies of all clinical phases are managed, including Phase I. In particular, the SODs currently certified for Phase I are the Oncology Clinic, the Haematology Clinic and Emergency Medicine. As required by law, the management of this type of experimentation must take place in compliance with more stringent requirements and therefore a series of dedicated SOPs have been drawn up and validated. Currently, a total of 340 clinical trials are actively managed, 232 interventional (68%) and 108 observational (32%). The SOD Pharmacy is involved in 69% of the studies managed, an involvement which rises to 94% if only the interventional studies are considered and which in about 50% of the cases consists of the logistical management combined with the preparation of the experimental drug.

Clinical trials are mostly drugs (80%) and half are Phase III (60%).









9. The logistics of the experimental sample in the S. Croce and Carle Cuneo Hospital (AO)

E. Grande, C. Fruttero

Carle Cuneo Hospital (AO) is a highly specialized national institution. The Hospital Company provides diagnosis, treatment and rehabilitation in hospital and outpatient, both at the expense of the National Health Service and in the liberal profession and carries out its institutional health activities aimed at the public in two facilities:

- S. Croce hospital unit;
- Carle Hospital Presidium

for a total of 700 beds (in the pre-COVID19 era) and is a HUB centre for the territory of the Province of Cuneo (about 700,000 inhabitants).

The Operating Units and the Diagnosis and Treatment Services in which the Company is divided represent all the main medical and surgical specialities. More than 2,300 employees work in the Company, including doctors, nurses, health care operators, technical/professional personnel and administrative sector employees. The two offices located in the city guarantee assistance, hospitalization and services in urgent and emergency situations 24 hours a day through the Emergency Room/AED service (level II).

During 2017, the AO resumed the Quality Certification process according to the UNI EN ISO 9001:2015 standard: the SCs of Haematology, Nuclear Medicine and Immuno-haematology and Transfusion Medicine, SCs of Anatomy and Pathological Histology and Hospital Pharmacy are certified (FO).

The Hospital Pharmacy also carries out its activities in the two facilities:

- S. Croce Hospital – Operating Block Pharmacy where the logistics of Medical Devices and Prostheses are managed, stock management is carried out for the Operating Block Rooms, and there is a Direct Distribution point;
- Carle Hospital – Hospital Pharmacy where the logistics of Medicines are carried out, where the Sterile Clinical Galenic and Traditional Galenic Laboratories are located, and a second point of Direct Distribution.

The Management of Clinical Trials is an important activity mainly focused on onco-haematology and cardiology which joins the standard one.

The FO actively participates in the company's research activity: it manages the logistics of all the experimental samples as required by law. The activity concerns, in addition to the storage of these samples, the delivery to the patient and the preparation of onco-haematological and non-haematological

experimental therapies, which require, by protocol, a preparation in sterile conditions in FO. Furthermore, for the pharmacist's part, data recording and trial monitoring are also carried out. The trials are not managed by a pharmacist dedicated to clinical research activity but by two pharmacists in charge of the Sterile and Traditional Clinical Galenics Laboratories, in addition to the nursing staff/laboratory technicians for the preparation part. In addition, the pharmacist participates in the activity of the company's Clinical Research Unit which evaluates, in collaboration with the Supervisory Health Department, the feasibility, sustainability and relevance of all clinical trials (interventional and observational) which, if deemed relevant and feasible for the Company are submitted to the Ethics Committee for the issue of the opinion.

Logistics of investigational medicines

All the experimental medicines are received in the FO of the Carle Hospital and almost all of the experimental medicines are kept in the FO, in particular:

- all experimental medicinal products that must be prepared in the sterile galenic laboratory (whether they are onco-haematological or not);
- all investigational medicinal products in oral formulation for haematological cancer patients;
- all medicines that require storage temperature monitoring for facilities that do not have the equipment to do so.

The logistics of the experimental medicinal products is supported by a procedure that describes all the various phases and by the use of three software (SW) which allow complete traceability of the path of the experimental medicinal product as required by the Good Clinical Practices.

1. SW for storage and transport temperature monitoring - MySirius

It is a wireless monitoring system of temperature and other parameters such as humidity and pressure, continuously, connected 24/7 to the central alarm. In case of deviation from the storage temperature, the on-call pharmacist is alerted. Also part of the system are mobile probes that allow the monitoring of transport temperatures of experimental drugs when required.

2. SW for the administrative management and setting up of experimental medicines

Two integrated SWs are used: NFS, DEDALUS® (company logistics SW) and HUMAN, BiMind ® (SW for the prescription, preparation and administration of onco-haematological therapies). Human is a multidisciplinary platform for managing the chemotherapy drug cycle and is made up of Human Therapy

medical devices (used for the prescription/report part) and Human Pharmacy used for setup. Both are registered as medical devices, compliant with the essential requirements applicable in Annex I of the European Directive 93/42/EEC concerning medical devices amended by Directive 2007/47/EC transposed by Legislative Decree no. 37 of 25 January 2010. BiMindhas ISO 9001:2015 and ISO 13485:2016 Certifications and complies with JACIE Standards (Joint Accreditation Committee ISCT-Europe & EBMT).

There are two different management methods:

1. If the drug is not prepared by the pharmacy, it is loaded into the FAR warehouse and only loading and delivery handling is carried out with unloading to the department only on NFS.
2. If the medicine is prepared/dispensed, it is loaded into the ATB warehouse and the interface with Human is activated.

The following phases take place on the NFS, DEDALUS® logistics SW:

creation of a registry with pre-established and validated coding rules of all the experimental medicinal products associated with a "fancy" MA code; each item is placed on the income statement which does not create consumption but which allows its management;

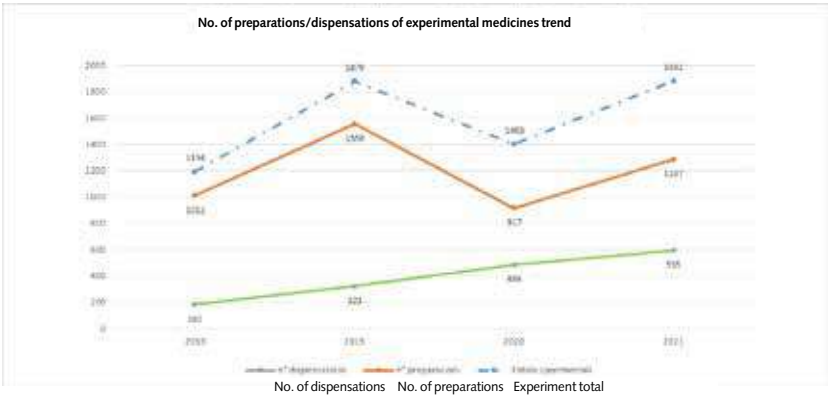
loading/unloading with dedicated movements in order to trace the batch, the expiry date, the shipment identification number and identification number (Medication number) where provided.

On Human, the path of the experimental drug goes through the following stages:

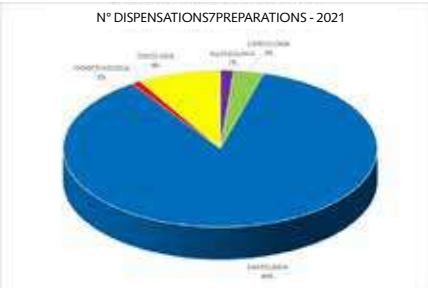
- import of stocks/lots and deadlines from NFS of experimental medicines;
- master data import of drug packs from NFS/DEDALUS to HUMAN through the AIC of the experimental drug and subsequent implementation with detailed preparation methods;
- construction and validation of experimental protocols with the clinician for the purpose of generating the computerized prescription;
- validation of the computerized prescription by the pharmacist;
- generation of a worksheet for the operator who sets up containing all the necessary information;
- picking of the experimental drug by the pharmacist who also combines the drug by reading the barcode with an optical pen; during the matching phase it is also possible to enter the identification number of the investigational medicinal product;
- barcode label printing of the single preparation which then allows administration traceability (operator, patient, administration time);
- unloading of the used packs from the warehouse and attribution of the experimental drug to the single patient and prescribing centre.

This system allows complete traceability of the path of the experimental drug and therefore allows for automated accounting with the possibility of exporting data from both SWs; this determines the enormous advantage of not having to fill in the specific study paper forms and of obtaining both the Drug Accountability that the Subject Real-time accountability.

The number of preparations of investigational medicinal products prepared in the FO in 2021 represents 3.6% of the total number of preparations and 8% of the dispensing of oral onco-haematological therapies. It is an important and continuously growing activity, in the graph below it is possible to see the graphical representation of the activity.



ONCOLOGY 36%
ALLERGY OUTPATIENT 1%
NEPHROLOGY DEPARTMENT 1%
HEMATOLOGY 62%



ENDOCRINOLOGY 1%
ONCOLOGY 9%
ALLERGY 1%
CARDIOLOGY 3%
HEMATOLOGY 86%

10. The Management of Clinical Trials in the City of Health and Science AOU of Turin

E. Buffa, F. Cattel

The AOU Città della Salute e della Scienza (AOU City of Health and Science) of Turin is among the largest healthcare centres at national and European level, has about 9,500 employees and guarantees diagnosis and third-level healthcare assistance in multiple treatment pathways, favouring multidisciplinary approaches that ensure appropriate care highly qualified to best respond to the needs of patients.

The hospital pharmacy inserted in this context has a staff of 25 structured pharmacists and 85 professional figures of other profiles (nurses, administrative employees, warehouse workers, technical operators, social-health workers).

The professional commitment of the pharmacist is aimed at the management of assets (drugs, medical devices, diagnostics) according to efficacy and safety criteria, guaranteeing economic governance, the governance of innovations, to which is added the governance of risk.

The maintenance of the Clinical Governance is carried out through clinical assistance activities (centralized preparation for oncological and/or high-cost drugs, preparation of master galenics and Orphan Drugs), through appropriateness support and monitoring activities (department pharmacist, clinical trials, pharmacovigilance, information to healthcare professionals) and technical-management activities (logistics management of warehouses and administrative activity).

The Pharmacy is open from Monday to Friday from 8 to 18; on Saturdays, Sundays and holidays from 8 to 13 for the distribution of emergencies. In cases of emergency, the night and holiday service availability is active. Direct distribution (clinical discharge pharmacy) is open from Monday to Friday from 9 to 17.

The laboratories and offices cover an area of approximately 2,200 m2, the warehouse an area of approximately 4,200 m^2.

The Complex Structure is divided into 4 simple structures which respectively deal with the logistics management of medicines, direct distribution (hospital continuity), clinical galenics and logistics management of medical devices.

The clinical galenic area includes 5 laboratories dedicated respectively to the preparation of reagents, master galenics (for internal, external, sterile uses), bags for parenteral nutrition, sterile paediatric and adult oncological preparations.

The antiblastic drug preparation laboratories also deal with the preparation of experimental drugs and are equipped with 7 vertical laminar flow hoods in as many negative pressure rooms (5 in the Molinette unit for oncological therapies for adults, 2 in the Oirm Sant' Anna for paediatric therapies).

In 2021, 102 observational studies (11 Profit and 91 Non Profit), 23 pharmacological studies (16 Profit and 7 Non Profit) and 18 studies with medical or other devices were authorized by the Ethics Committee.

The pharmacist participates in the selection visits of the centre and in the SIVs, is a member of the CTQT and deals with pharmacovigilance reports, in the context of the IEC (CEI) evaluates the aspects of competence for the authorization of the study on the company portal, during the reception phase, carries out the qualitative-quantitative control on the imp, deals with the purchase and any refunds of advance products for clinical trials, monitors the storage conditions of the drugs and manages the quarantines.

It also deals with the preparation of parenteral drugs, the training of preparatory nurses and actively participates in monitoring visits.

In the case of Phase I clinical trials (3 Phase I units active in the Hospital) it also deals with the management of the randomization and accounting of medicines as per AIFA Resolution no. 809/2015, as part of a quality system constantly monitored by the company QA and by the Auditor in accordance with the GCP.

All activities are suitably processed and tracked through specific forms which are available for monitoring checks. The correct conservation of medicines is controlled by probes which carry out measurements 24/7, controlled by the surveillance service and available to the pharmacist.

The experimental drug for parenteral use is managed on computer through the Suite Log80 software. The therapy schemes are entered in the SW by the pharmacist, validated by the doctor and the pharmacist and prescribed as needed. All experimental drugs are serialized and labelled in order to guarantee traceability from arrival to patient assignment and to allow expiry history control and inventory management. Synopsis and protocol of the study are always available both in paper form and on computer support.

In 2021, the Molinette unit's cytotoxic laboratory prepared around 60,000 preparations of drugs for parenteral use (antiblastics, biological drugs, antiviral drugs) of which around 2,500 were experimental for the Onco-Haematology Department, around 150 preparations for ophthalmic use, 250 analgesic infusers for pain therapy, about 1,000 preparations for patients affected by Sars-Cov2 (anti-virals, monoclonal antibodies) and was involved in the management and preparation of anti-Covid vaccines.

In 2021, the cytotoxic laboratory of the Oirm Sant'Anna unit prepared

around 10,700 preparations of drugs for parenteral use (antiblastics, biological drugs, anti-virals) of which around 600 are experimental. In addition, 1,600 bags of parenteral nutrition for paediatric use were prepared.

A restructuring and unification plan of the three laboratories is currently underway with a view to rationalizing resources and implementing activities (highly complex therapies, Phase I clinical trials). This project also provides for the automation of the preparations and the introduction of a system based on RFID technologies for tracking the experimental preparations and detecting the temperatures of the drugs during transport, in special certified and temperature-controlled containers, up to the users.

In 2021, the Cytotoxic Oncological Preparation Laboratory for adult patients went through the certification process, fully satisfying the requirements of the ISO9001:2015 standard and obtaining Accredia certification.

11. SC PHARMACY and U.Ma.CA. of the IRCCS "Giovanni Paolo II" (John Paul II) Cancer Institute of Bari

P. Nardulli, M. Laforgia

The IRCCS Cancer Institute "Giovanni Paolo II" (John Paul II) of Bari is located at the centre of a large welfare network, the Oncological Network of Puglia, which offers cancer patients the opportunity of receiving treatment according to the highest welfare standards, both in terms of safety and easy access to innovative treatments. The Institute consists of 5 Operational Units of Oncology (5 outpatient clinics and 3 inpatient), one of Haematology (outpatient and hospitalization), 7 of Oncological Surgery (general, urological, senologic, gynaecological, plastic, thoracic, otolaryngology (ENT)), 5 Operating theatres and a post-operative intensive care unit (TIPO).

The SC Pharmacy and U.Ma.CA. of the Institute is considered HUB in terms of setting up antiblastic chemotherapy, also thanks to an intense activity of regional and national collaborations which sees it involved in a wide range of translational research and professional training projects. The working group is made up of the Director of Pharmacy and 4 Pharmacists Managers, 3 research contract Pharmacists, 9 nursing staff, plus administrative and warehouse logistics staff. The structure is the training centre of the School of Specialization in Hospital Pharmacy and of the Short Master on Oncological Pharmacy by the Faculty of Pharmacy of the University of Bari, it also collaborates with other universities in the field of oncological masters, such as the University of Catania and Camerino.

It has collaborated with ITELpharma in Ruvo di Puglia, a leading company in the production of radiopharmaceuticals and validation of robots and mechanical arms for handling dangerous drugs, as well as with the electro-medical engineering company Masmec in Modugno, with whom it shared the project ERDF "NexMedia" materialized with the creation of a mechanical arm prototype to be placed in a hospital setting for the preparation of antiblastic preparations. Currently, the fruitful collaboration with BIOFOR DRUG, a spin-off of the Faculty of Pharmacy of the University of Bari, has made it possible to evaluate the chemical-physical stability of the preparations set up in the U.Ma.CA. regardless of the data reported by the manufacturer in the technical data sheets of the drugs, confirming the role of the Hospital Pharmacist as a Researcher in the pharmaceutical sector.

The SC Pharmacy and U.Ma.CA. consists of two physically distinct units, of which the U.Ma.CA. is by strategic choice allocated in the areas of most

intense administration of chemotherapy preparations, near the outpatient clinic, in order to give information and technical support also to the administering nurses, as well as for practical logistical choice.

The local U.Ma.CA. consists of a laboratory of about 30 square meters, equipped with three latest generation vertical laminar flow hoods, adjacent to a filter room and a decontamination room and communicating with the other rooms by means of a pass-box through which the prepared therapies are delivered.

The Pharmacy, on the other hand, is located in areas with easier access for the delivery of products, even of large volumes, and consists of a pharmaceutical warehouse and 2 warehouses for medical devices, medical and surgical devices and large volume infusion solutions.

The U.Ma.CA. service for the preparation of parenteral oncological therapies it is active from 08.00-20.00, while the Pharmacy is open to the public from 09.00-13.00, from Monday to Friday and on call at the weekend for both pharmacist and nursing staff.

The prescriptive activities of the doctors of the institute reach the SC Pharmacy and U.Ma.CA. in computerized mode, in fact as early as January 2008, when a pilot project in collaboration with an IT Bioengineering Consortium led to the implementation of a software for the computerized prescription of chemotherapy.

In the first decade of the year 2000, the UMACA software was the first example of management software in central-southern Italy entirely conceived and created by oncologists and hospital pharmacists on the basis of their prescription, clinical and traceability needs. Various software releases have been implemented with periodic upgrades consistent with the evolution of clinical needs, ministerial recommendations and the contingent healthcare reality. In 2021, a computerization process also began for the preparation of parenteral oncological therapies which will lead to the imminent adoption of the CATO system which, through gravimetric analysis and verification of drugs via bar code, will guarantee effective preventive management of the risks associated with manipulation of cytotoxics. The CATO software will give further strength to the U.Ma.CA certification and its Quality Management System which, in November 2021, achieved the third consecutive Certification pursuant to the European Standard ISO9001:2015, which ratifies the great commitment made and the continuity in the will and ability to ensure very high quality standards on the part of all staff involved in the preparation of oncological therapies. The certification is entitled *"Design and development of galenic preparations. Set up of galenic preparations based on antiblastic and biological drugs with anticancer activity"* and

was obtained for the first time in October 2015, constituting the first national case of certification of a U.Ma.CA Laboratory independent of its parent hospital. The Quality Management System consists of 14 Operating Procedures which trace every single moment of the ordinary daily activity, from personnel management to documentation management, from the procurement method (orders, loans) to the traceability operations of the lots in use and the activity of the individual operator, through detailed daily checklists, albeit quick to compile.

Even in the pharmacy, the prescriptions arrive in computerized mode, with a weekly delivery organization for the various requesting departments, display of the pharmaceutical drawers and department stocks, daily dispensing of the first cycle of therapy upon discharge on the regional Edotto computerized platform, dispensing of oncological IMPs for oral administration within the trial experimental protocols.

The planning of the "intelligent cabinets" of the Pharmacy and Ward is in the technical evaluation phase.

The galenic products based on antiblastic drugs for use other than the oral one are all prepared at the U.Ma.CA. In the three-year period 2019-2021, the average number of preparations per year reached 75,000 units of the three product standards set up, i.e. bags, syringes and fixed-flow elastomeric systems, of which 5% is represented by drugs subject to phase II and III clinical trials.

Every year, the Institute's Ethics Committee evaluates about 110-115 clinical trials. For example, 109 trials were evaluated in 2019, including 58 observational and 51 interventional studies, with an approval rate of 93.5%. The 86% of the studies were multicenter, 75% non-profit. In 2020 and 2021, the trend remained comparable and currently between U.Ma.CA. (parenteral preparations) and Pharmacy (drugs for oral use) about 65 interventional studies with drugs are active, which mainly involve the Operating Units of Medical Oncology, Oncology for Thoracic Pathology and Haematology. These data are processed by the Scientific Secretariat of Ethics Committee, followed personally by the Director of Pharmacy with the help of 2 Contracted Pharmacists for all the documentary activities.

The management of Experimental Drugs in the context of Clinical Trials is governed by two separate Operating Procedures between the Pharmacy and the U.Ma.CA., since the arrival of the drug for logistical reasons always takes place in the Pharmacy.

Only the drug for oral use is kept in the Pharmacy together with all the documentation that arrived with the shipment which is archived in the Pharmacy Binder after verification and electronic confirmation of receipt,

according to the methods provided for by the single protocol (dedicated platform, email, fax). The verification consists in the evaluation of the packaging and the packing list, as well as maintaining the correct storage temperature during transit; in general, the latter involves the download of precise temperature data from a USB Temperature Device with final printing of the reports (diagram and data table), which are attached to the packing list documentation. The confirmation of receipt is contextual to the accounting of the drug in the accountability logs provided by the Sponsor or, if not present, in forms locally prepared by the pharmacist.

If the experimental drug must be prepared at the U.Ma.CA. Laboratory, the Pharmacist of the Pharmacy quickly checks the packaging and packing list and immediately sends the drug to the U.Ma.CA., without interrupting the continuous recording of the temperature on the Device. Upon arrival at U.Ma.CA., the drug is checked, stored and accounted for, after checking the temperature conditions during transit, and finally confirmed electronically.

Both in Pharmacy and in U.Ma.CA., depending on the storage methods, the drug is then allocated in a refrigerator or in a temperature-controlled cabinet, both exclusively dedicated to experimental drugs. There is also another fridge, identified as a backup in case of doubts or malfunction of the main equipment.

All refrigerators, including those dedicated to IMPs, are monitored continuously both by means of an internal mechanism (temperature scale display, smart card that records the punctual temperature values, visual alarm, audible alarm) and external, through the centralized software SPYLOG which, through the detection of the temperature indicated by the probes positioned inside all the refrigerators, allows the simultaneous display of the status of all the refrigerators. All equipment, in particular hoods, refrigerators and the SPYLOG system are subject to annual scheduled maintenance in outsourcing.

The computerized prescription of the experimental drug requires the pharmacist to enter into the managerial software and, in parallel, into the platform dedicated to the clinical study and to report on prescription the active ingredient, the number of dosage units in the case of oral therapies, or the method of reconstitution and dilution, the concentration of stock solution and the one intended for administration, the chemical-physical stability and methods of conservation of the final preparation, in the case of therapies for parenteral use.

The manipulation of anticancer drugs for parenteral use at the U.Ma.CA. laboratory takes place through the conscious use of CSTD closed circuit systems to ensure the sterility of the preparation and the safety of

professionally exposed operators (primarily nurses). Conscious use entails for each new operator assigned to the U.Ma.CA. a training period of about two months in support activities for preparation, knowledge of drugs and active ingredients, unloading operations and reconciliation of used vials; at the end of the two months, the operator is accompanied and followed by a tutor nurse as a guidance and is started on the work of setting up in safety, regulated by a specific procedure drawn up with a view to standardizing the various operating steps, medical devices and individual protection, dilutions, storage of residues and even the volumes of syringes to be used for each drug.

Consistently with the need to guarantee the quality of the product to all patients who refer to the Institute's services, the U.Ma.CA. in 2018 began a path certified by a third party for particle and microbiological environmental monitoring of the Laboratory, additional health surveillance to that already envisaged at an institutional level and validation of the preparation process of the preparations (using the MEDIAFILL test) for all manipulator operators. The results of these checks have always been compliant and, despite the fact that the hospital infrastructure is now 12 years old, the U.Ma.CA. of the IRCCS continues to maintain its quality levels high, with the laboratory in class C in operational and B at rest, in compliance with the Standards of Good Preparation of Medicines and the Good Manufacturing Practices.

While the dispensing of oral therapies takes place in the Pharmacy, the dispensing of the preparation set up at the U.Ma.CA. it is traced through an ISO9001:2015 certified therapy delivery form, on which an adhesive label is affixed with the name of the individual patient in the individual ward.

All pharmacists are engaged in periodic meetings with the CROs who follow the experimental studies, participate in the SIVs and monitoring visits, as well as being an active part in the institutional Multidisciplinary Teams, distinguished by pathology and which often refer specific patients to specific trials clinicians.

The Director of Pharmacy is also part of the Molecular Regional Cancer Board, a multidisciplinary group which, in line with the new prescribing trends with reference to single mutations and agnostic drugs, discusses the therapeutic possibilities from the point of view of precision medicine.

The figure of the Researcher Hospital Pharmacist is a great conquest in the healthcare world and has made it possible to overcome the concept of the "dispenser" pharmacist and to elevate the profession to high levels of collaboration with medical healthcare professionals, becoming an active part of therapeutic choices.

12. The ARNAS Garibaldi of Catania ("Garibaldi - Nesima" Presidium and "Garibaldi-Centro" Presidium) and Clinical Trials

G.E. Fassari

The ARNAS Garibaldi of Catania, in its two divisions represented by the "Garibaldi - Nesima" Presidium and the "Garibaldi-Centro" Presidium, has as its main corporate mission *the diagnosis and treatment of cancer pathologies; in a context of complete multidisciplinary integration of the diagnostic-therapeutic pathways of adult oncological and onco-haematological pathologies, it expresses the ability to guarantee the preparation and administration of approximately 30,000 chemotherapy preparations a year for the treatment of several thousand patients, placing itself in this sense as a point of reference in the whole of the regional panorama.*

The full management of the cancer patient is guaranteed thanks to the insistence of an Oncology Department which includes the Operating Units of: Oncology Surgery, Thoracic Surgery, Breast Unit (Breast Surgery), Medical Oncology, Hematologic, Oncological Hospice.

The full functional integration of the activities of the aforementioned Operating Units, achieved through shared and standardized Diagnostic-Therapeutic Pathways (PDTA), has always translated into taking charge of the oncological users belonging to ARNAS Garibaldi which develops be it horizontally (guaranteeing a multidisciplinary approach to the diagnosis and treatment of the oncological pathology), or vertically (ensuring assistance capable of adapting to the different phases of the natural history of the oncological pathology).

An efficient centralized management of oncological therapies has had as a prerequisite the creation of a multidisciplinary team which, through the sharing of issues and critical issues, has allowed the implementation of the best conditions for the production of oncological therapies and treatment management according to the principles of clinical-prescriptive appropriateness and the protection of patient and operator safety. The synergic action between the professionals involved in the therapeutic process, in particular between the oncologist, the haematologist and the pharmacist, represented the humus from which, during 2013, the integrated clinical governance model "UFA -ONCO-EMA" which, in line with the requirements identified in Ministerial Recommendations no. 14 and with the provisions of DA 2092 of 10 October 2012 "Centralization of antiblastic drugs", has contributed to definitively consolidate the functional

integration between the Antiblastic Drugs Unit, Medical Oncology and Hematologic.

This programme, which regulates the implementation of the oncological path with the integration of skills between pharmacist-oncologist-haematologist, was certified in July 2013 by a National Certifying Body and adopted by the Sicilian Region Health Department, as a reference clinical governance model regional, to be adopted in all oncological units prevailing on the regional territory.

The management of Clinical Trials

In 2014, ARNAS Garibaldi of Catania established an interdisciplinary body identified as the Clinical Trial Centre (CTC) with the aim of improving its efficiency in the management of activities related to applied clinical research and guaranteeing the best quality levels in the conduct of controlled clinical trials. The Clinical Trial Centres, in fact, represent a governance model of the management and clinical pathways underlying controlled clinical trials and have as their objectives the development and implementation of assistance paths dedicated to the selection and enrolment of patients, monitoring of quality and of the safety of the courses, their certification, professional growth and updating of the medical and paramedical personnel involved in applied clinical research activities, promotion of the culture of clinical research, acquisition of highly specialized personnel functional to the optimization of the courses (data-managers, quality managers, research nurses).

In 2015, the CTC of ARNAS Garibaldi of Catania achieved a first process certification according to the ISO 9001:2008 standard and in November 2016 it obtained, first in Italy, the ISO 9001:2015 certification of the pathways related to phase I studies in oncology field.

Mission

- Optimize the management of clinical research carried out in the Company, guaranteeing competitiveness and innovation and improving the reliability and efficiency of clinical trials.
- Provide specific training on Good Clinical Practice in the study of new drugs and devices, defining cross-functional and multi disciplinary criteria and standard operating procedures (preliminary to the start of the study, during the development of the trials and at the end of the same).

Increase the interaction between the various stakeholders (Ethics Committee, Hospital Administration, Sponsor, Clinical Trial Centre) standardizing and tracing the process for starting new research activities.

TARGETS

1) Minimize study activation times, by reducing:

- Time between receipt of a Confidential Agreement and its signing (between the investigator and the sponsor):
- Time between receipt of the protocol draft, acceptance by the PI (T1) and remitting the complete documentation to the CE (T2)
- Time between obtaining the favourable opinion of the EC and signing the contract between Sponsor and Experimental Centre
- Time between the start-up visit and the enrolment of the first patient.

2) Improve the following qualitative levels of performance:

- Ratio between patients actually enrolled and the number commissioned
- % of queries that are within the contracted time frame
- Number of serious violations of the protocol
- % drop out of the enrolled patient (lost at follow-up, voluntary desertion).

3) Increase the visibility of the CTC and the presence of the investigators as:

- N° of papers published with the presence of at least one investigator of the centre as co-author
- N° of conference posters with the presence of at least one investigator of the centre as co-author
- N° of national and international congresses on the results of clinical trials with the presence of at least one investigator from the centre as a speaker.

4) Optimize economic indicators:

- Annual volume of funding received from outside
- Savings on patient therapies.

CLINICAL TRIAL CENTER

APPROPRIATENESS
Diagnostic
Therapeutics
Rehabilitative
Welfare

SAFETY
of Path

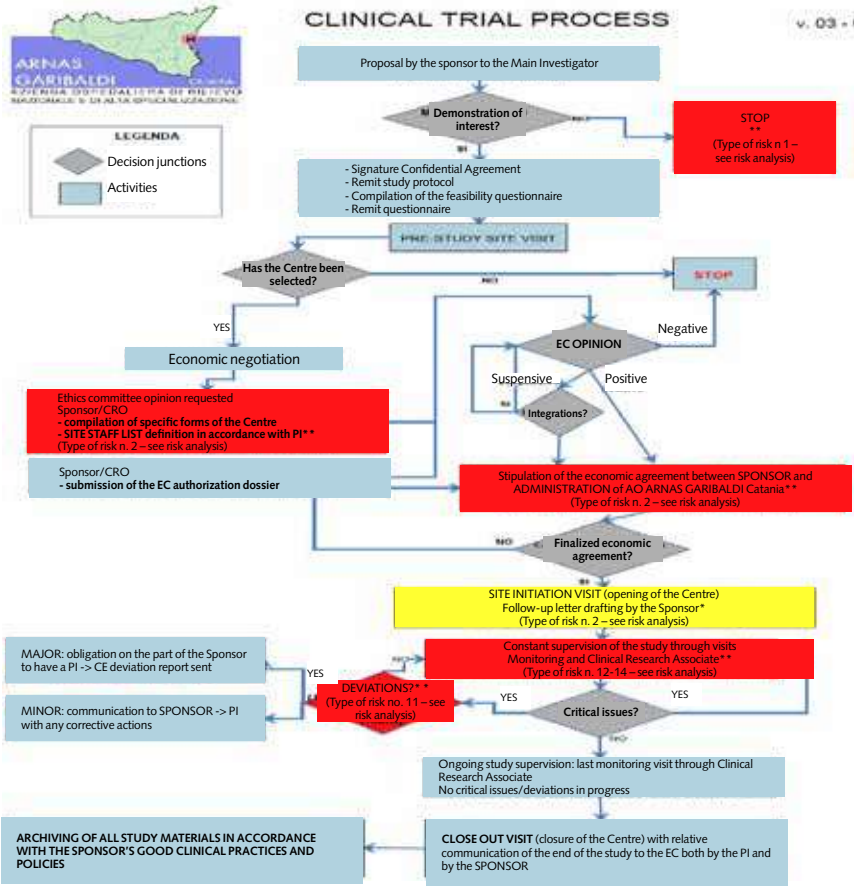
COMMUNICATION
Reporting vs
- Institutions
- Citizen
- …
Equity
Uniformity
of treatment

CLINICAL TRIAL PROCESS

CLINICAL RESEARCH
COMPETITIVE
AND OF QUALITY

EXCELLENCE
SCIENTIFIC

PARTNERSHIPS
EFFECTIVE
PUBLIC-
PRIVATE



Requests for authorization to conduct a clinical study are addressed to the Management of ARNAS Garibaldi, examined and approved by the Ethics Committee. In order to allow the correct and rapid management of the procedural process, the Principal Investigator produces the documentation relating to the opinion of the Ethics Committee, the assumption of responsibility, the duration of the study and the personnel involved and delegated. The pharmacist, who by natural vocation and professional training must be a fundamental component of the operational units dedicated to research in the pharmaceutical field, is fully integrated with clinicians, data managers and research nurses, participates in the coordination of administrative activities related to the activation of controlled clinical studies "Profit" and "No Profit", assists researchers in the collection of clinical data,

participates in the development of databases for the collection of data, in the processing and preparation of scientific material for educational and/or dissemination purposes, supports the activities training of medical and nursing staff and promotes the professional growth of the colleagues involved.

After obtaining the approval of the Ethics Committee and the administrative resolution, a preliminary SIV is planned in the OU involved in the study and at the Pharmacy. During the meeting the responsibilities between the parties are defined.

An archive is set up at the Pharmacy, where the Pharmacy File is kept for each clinical study, containing all the documentation relating to the handling of the experimental drug: DDT accompanying the supply of experimental drugs and any aids, where envisaged, with the registration of the date and time of arrival and the signature of the responsible pharmacist; forms provided by the Sponsor and, if not foreseen, internal forms for loading and unloading the experimental drugs with the indication of lot, expiry date, kit number; documentation certifying the destruction of the experimental drug; documentation relating to the prescription, preparation and dispensing of the experimental drug; other documentation required by the Sponsor. Upon arrival of the experimental drug at the Pharmacy, the pharmacist carries out a qualitative-quantitative check of the drugs and aids received in compliance with what is described on the transport documents, as well as the maintenance of the cold chain, using the appropriate digital detection devices provided by the Sponsor, between 2-8°C. In the event that the DDT is not complete, the drug will be placed in quarantine, until all the required documentation is completed by the Sponsor.

Where there is an IT system (IWRS) for recording the shipment of the drug, the Pharmacist registers the arrival of the experimental drug using a specific personalized password, provided by the Sponsor of the study.

Medicines intended for clinical trials are stored in the Pharmacy premises in special cabinets and refrigerators, separated from other medicines, respectively at temperatures below 25°C and between 2-8°C. Access to these medicines is permitted only to authorized personnel of the Pharmacy. The Pharmacy checks on a daily basis the storage temperature of the medicines using special MySirius digital detection devices. Each refrigerator is equipped with a temperature recording system and is subject to annual calibration by an accredited body. Upon request or periodically, a temperature graph will be printed with an indication of the minimum and maximum value recorded. The refrigerators have an alarm system and in the event of thermal excursion, the on-call pharmacist is contacted who will arrange to move the drugs to a backup refrigerator.

The experimental drug infusion, once received and checked, is recorded in a special computer database.

In compliance with DA no. 586 of 12 April 2018 "*Requirements and standards for the Antiblastic Drug Units (UFA) of the Sicily region*" and in compliance with Recommendation no. 14 of the Ministry of Health, in order to prevent errors during therapy with antineoplastic drugs, the UFA of ARNAS Garibaldi in Catania has equipped itself with software for the IT management of prescriptions, HUMAN, integrated with the departments. In fact, the computerized prescription makes it possible to reduce errors in writing, transcription, interpretation and manual calculation, making it fundamental for the purposes of adequate interaction between the UU.OO. clinics (responsible for the prescription and administration processes) and the Anticancer Drugs Unit-UFA (where prescriptions are validated and the anticancer preparations and experimental drugs are prepared).

This software is able to promote therapeutic and organizational appropriateness, maximize occupational risk management, reduce the risk of therapeutic error and promote the quality of the preparations, ultimately ensuring the complete traceability of the entire therapeutic process.

The centralized computer system is able to electronically govern all phases of management of the experimental protocols; these are processed and approved by the clinician and entered and validated on the HUMAN platform by the pharmacist, after an accurate analysis of all the information contained in the study protocol.

The software also provides for the presence of an archive containing all the drugs in use, including experimental ones, through which it is possible to view the stock and expiry date of the registered lots.

In the event of the first arrival of the experimental drug, it is necessary to carry out the following operations with the help of the IT application:

- creation of the active ingredient of the experimental drug;
- creation of the drug associated with the previously inserted active substance;
- packaging of the drug with attribution of a 9-character AIC, identifying the experimental drug and the reference study (e.g. SPE0000075);
- description of the package with indication of the name of the experimental drug and of the clinical study;
- indication of all the instructions relating to the reconstitution and dilution of the drug to be administered parenterally;
- warnings and possible precautions for use;
- relabeling of the investigational drug;
- loading of the batch and the expiry date of the experimental drug.

Through the use of the electronic prescription, the UU.OO. clinics send the UFA the request for preparation of the experimental drug, deriving from previously shared trial protocols and inserted within the prescription software. If the clinical study provides for randomization for the assignment of drug kits, the data manager dedicated to the clinical study specifies the kit number on the paper prescription received by fax, which can also be viewed by the pharmacist on the platform dedicated to randomization.

Once the pharmacist has detected the doctor's confirmation, he can proceed with the validation of the prescription, i.e. the verification of the correctness and adequacy of the prescription.

After validation by the pharmacist, the doctor will no longer be able to modify the prescription, unless the pharmacist himself returns the prescription to the "to be confirmed" status, maintaining the traceability of the reasons that led to the modification.

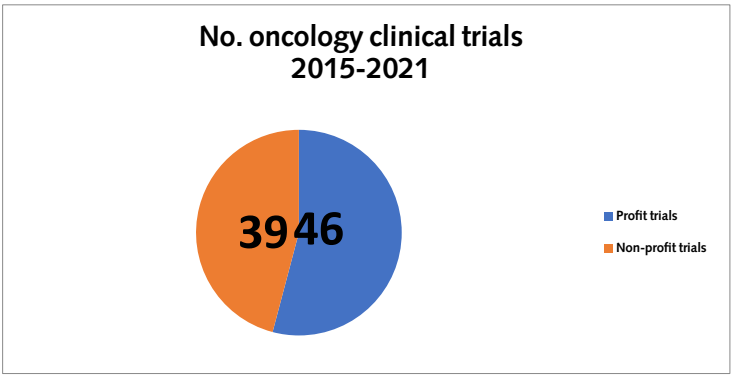
After setting up the therapy, the software generates a worksheet containing the instructions for the personnel in charge of the preparation and two labels: the first is placed on the infusion bag and shows the patient's name, surname, date of birth and information relating to the dosage, drug and diluents volume, stability and storage temperature of the experimental drug; the second is affixed to the bag containing the drug and shows the patient's personal details and the drugs prepared and contained in the bag dedicated to the individual patient. Experimental drugs are transported using containers that guarantee a high standard of safety during the transfer of drugs from the UFA to the administration premises.

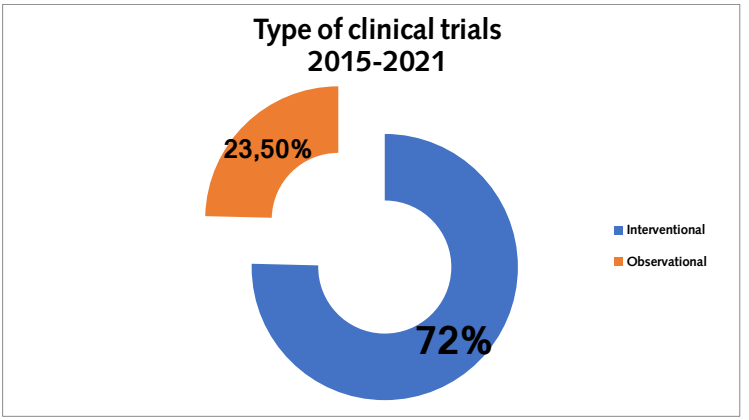
The delivery of the experimental therapies to the department involves the processing by the software of a bubble containing the summary of all the drugs prepared with the initials of the patients; the date and time of delivery; the UU.OO. to whom the therapies are intended; the signature of the UFA employee on delivery; the signature of who collects and who receives the therapies.

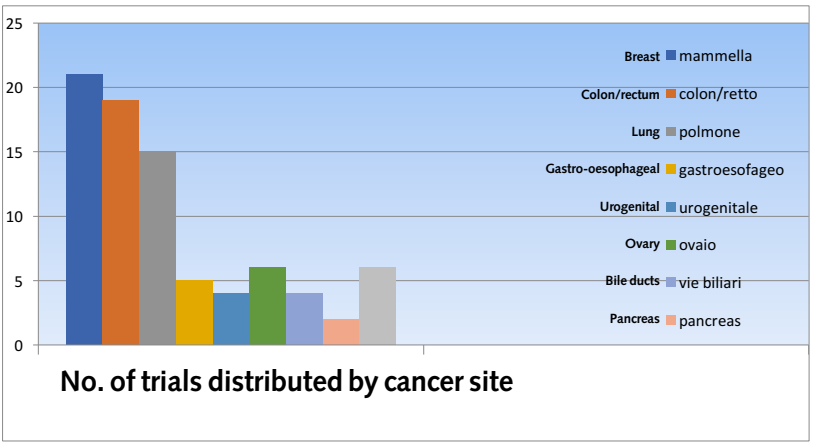
The administration phase represents the completion of the prescribing and preparation phases. The perfect integration of these activities is ensured by an administration form which summarizes the sequence, times and methods of administration of the experimental protocol.

The workflow of oral investigational drugs is analogous to infusion investigational drugs. By going directly to the pharmacy to pick up the therapy, the patient receives detailed information from the clinical pharmacist on how and when to take it, as well as informative material and a clinical diary to be filled in daily to monitor any side effects induced by the treatment.

At the next visit, the patient will take the drug packages to the data manager and any remaining tablets will be counted.


No. oncology clinical trials
2015-2021
39
46
Profit trials
Non-profit trials


Type of clinical trials
2015-2021
23,50%
72%
Interventional
Observational


25
20
15
10
5
0
Breast mammella
Colon/rectum colon/retto
Lung polmone
Gastro-oesophageal gastroesofageo
Urogenital urogenitale
Ovary ovaio
Bile ducts vie biliari
Pancreas pancreas
No. of trials distributed by cancer site

Even for oral drugs, prescription sheets shared by the entire team (doctor, pharmacist, nurse) are used, bearing:

- personal data of the patient (name, surname, date and place of birth, residence);
- telephone numbers of the patient and any caregiver;
- weight, height and body surface area;
- comorbidity;
- complete list of medications taken by the patient;
- dosage of the experimental drug and number of kits to be dispensed, with an indication of the doses to be taken for each single administration, the methods of administration in relation to meals and the time of administration.

The mission of ARNAS Garibaldi of Catania is to guarantee that the management of anticancer therapy – highly complex healthcare services – takes place through a defined and controlled process in the behaviours, with traceability of the activities carried out and the relative responsibilities, in compliance with the safety of the patients and of the operators.

The synergistic integration of the various professional figures together with the efficient organization created, have made it possible to achieve the set objectives:

- Reduction of therapeutic error;
- Increased levels of safety for occupationally exposed workers;
- Increased levels of patient safety;
- Increase in the levels of appropriateness of the treatments provided and improve the sustainability of the system by optimizing resources and containing pharmaceutical expenditure, as demonstrated by the maintenance of the assigned monthly budget (1,500,000 Euros) for the procurement of anticancer drugs, while continuing to ensure patients have access to the best and most innovative cancer therapies;
- Adoption of a management software capable of satisfying the requirements of quality, traceability, monitoring, risk management and creation of the economic flow T for the over 20,000 oncological preparations carried out over the course of a year with a daily average of 110 formulations required;
- Implementation of strategies for optimizing the use of resources massive use of biosimilars, use of residues, organization of drugsday, use where required by law of medicines for compassionate use and of the 5% Fund, use of medicines on CNN supplied by pharmaceutical companies at a symbolic price until obtaining the regional CIG) use of experimental medicines.

- For 2019, with the same volumes of activity, economic and structural resources, we managed to save around 850,000 Euros compared to the same period of 2018 (405,000 Euros in revenues obtained from the use of only two biosimilars, trastuzumab and rituximab, and 450,000 Euros in savings obtained from experimental drugs from ongoing clinical trials).
- Coordination of a multi-regional Active Pharmacovigilance Project, which sees ARNAS Garibaldi as the lead company, financed with the 2012-2013-2014 funds, already approved by the Department of Strategic Planning of the Regional Health Department and by AIFA.

13. The logistics of clinical trials in the Mediterranean Oncological Institute - Viagrande Catania

M.P. Vitale

The Mediterranean Oncological Institute is a highly specialized Institute: one of the three existing III level departments in Sicily and has also received a favourable opinion from the Sicilian regional council for the recognition of Scientific Institute of Hospitalization and Care (IRCCS). In 2019, the Institute, as an oncological research centre, was recognized as a Full member in the Organization of European Cancer Institutes (OECI), an organization that brings together and puts together the most qualified European Oncological Institutes.

It is a centre, complete with all the specialties to treat cancer, where professionals integrate and work together in an interdisciplinary and multidisciplinary way to define the best clinical path for each individual patient. The IOM promotes and governs oncological research as an instrument of knowledge and engine of excellence, innovation and progress both in terms of diagnostic, assistance and therapeutic aspects and for the improvement of organizational processes, in the most advanced areas of clinical research and the treatment of neoplastic pathologies with higher incidence and higher social impact. We believe that synergies, networks and critical mass are essential to achieve levels of excellence and produce important results in translational research. The Oncological Centre of Viagrande, in its entirety, brings together doctors and researchers with the ultimate goal of bringing the patient closer to the research results of "from bench to bedside". For this reason it has created a research centre equipped with the most advanced technologies, and designed it as a Campus open to the settlement of other research realities, public and private, to multiply its potential. It is equipped with molecular biology and cell biology laboratories, an NGS genomic platform, an animal enclosure and laboratories for preclinical research on rodents, a cytofluorescence and cellsorting unit and a service for in vitro and in vivo imaging. The Institute holds the UNI/ISO 9001/2018 quality certification for the clinical processes provided in all branches and services.

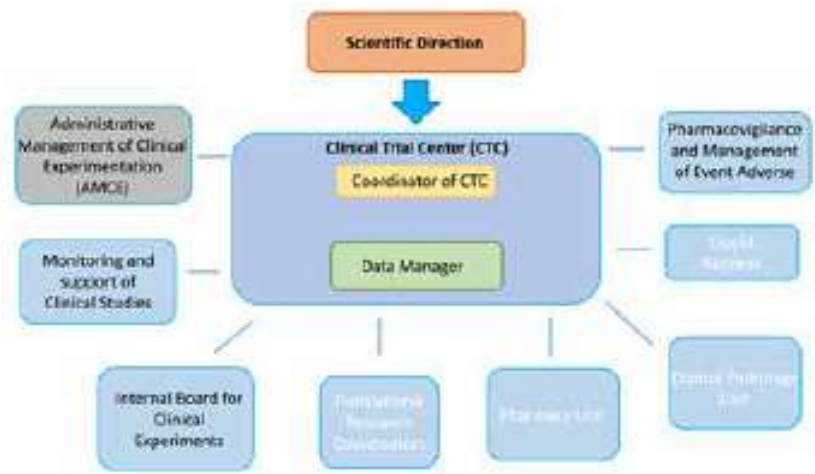
The structure has used the Pharmacovigilance Unit since 2009 coordinated by Dr. Maria Paola Vitale whose objectives can be summarized below:

Mission

- Supporting and promoting reports through meetings of suspected adverse drug reactions (ADR);
- Educating in the production of ADR reporting (doctors, nurses);
- Registration and updating ADR reports in the National Pharmacovigilance Network (RNF: national pharmacovigilance network);
- continuous monitoring of drug safety;
- ADR reporting in research studies;
- knowledge of determined factors and clinical significance of drug interactions;
- knowledge of the dangers associated with the use or abuse of therapeutic drugs.

Clinical Activity

- education and information of patients to the use of medicines (in clinical *trials)*;
- registration of ADR forms in the National Network of Pharmacovigilance (RNF);
- assessment and communication of the risks and benefits of approved drugs;
- Hospital reports, guidelines, and procedures discussed on the weekly Hospital meeting;
- rational and safe use of medicines.



Our Clinical Trial Centre (CTC) was established in 2009, it is an integrated type structure in which various professional figures rotate, the management process is equipped with SOP (internal operating procedures), and coordinated by the supervision of the Scientific Management in the person by Prof. G. Stassi (University of Palermo).

Each member of the CTC has a very clear mission and the paths to be taken in the management of clinical trials, the clinical staff makes use of the following figures:

- a Main Investigator (UOC directors of Oncology and Oncohaematology and directors of the UOC of Breast and Oncological Surgery);
- assisted in patient management by 2 Sub-investigators;
- a Data Manager;
- a research nurse;
- Internal services which include: Radiology, the Analysis Laboratory, Pathological Anatomy, Cardiology, Nuclear Magnetic Resonance and the Pharmacy Service.

All members of the Clinical Research staff currently hold the appropriate GCP training certificates.

Environments

The Institute has a management office dedicated to clinical trials, where the Data manager works and where the archive containing all the folders relating to the various clinical trials is located. It is a closed and exclusive environment. The Pharmacy service is equipped with a cabinet and fridge dedicated to experimental drugs (IMP) which are kept under the supervision of the Pharmacy Service Manager.

All activities relating to the management of clinical trials are supported by an IT application and a computerized medical record.

Our structure has been involved in clinical trials since 2009, considering that it is a relatively young structure initiated in 2005. Over the years we have participated in numerous multi-centre clinical trials both observational (retrospective and prospective) and interventional (phase II, phase III and phase IV), with a good response also in the field of scientific publications deriving from data analysis. The following table shows the experimental studies to which we have participated in recent years, all clinical trials are carried out according to GCP.

Antiblastic Medicines Unit (UFA)

The Antiblastic Medicines Unit (UFA) is part of the Pharmacy Service of the Mediterranean Oncological Institute, equipped with all the technical characteristics and requisites necessary to satisfy the guidelines in force.

The activity of setting up sterile galenic preparations with antiblastic drugs is under the direct responsibility of the Director of the Pharmacy Service, whose work staff includes 2 professional nurses who work in the clean room. The responsible pharmacist coordinates the daily working session by first of all carrying out the control activities on the prescribing appropriateness, the appropriate controls relating to patient access to the DH, the daily supply of the antiblastic drugs necessary for the current day and the relative balancing of the warehouses antiblastic drugs.

Our structure makes use of the computer aid of the HTSAN G program, shared throughout the Institute which has a section completely dedicated to the management of chemotherapy, where there is a part relating to all the protocols used in our structure which are reviewed every six months, the management part shared by the pharmacist, doctors and nurses, and the part relating to the warehouses for the transfer of antiblastic drug vials.

An average of 30 patients access our DH every day, for which on average about 100 preparations of medicated bags with antiblastic drugs are set up in the UFA, which are then transferred to the oncological DH by transport carried out with safety deposit boxes on suitable safety trolleys. Our UFA was definitively adapted to the regional law UFA/ONCO/EMA in 2012 thanks to the project set up by the Sicily region relating to the "*Programme for the implementation and monitoring of the Recommendation for safety in oncological therapy*".

The regional program of "implementation of the UFA-ONCO-EMA integrated clinical governance model" aims to create a regional UFA-ONCO-EMA integrated clinical governance model for the best guarantee of safety, appropriateness and overall management of therapy anticancer.

The realization of the regional project meant that all the 36 UFAs present in the Sicilian Region align themselves with the quality standards disclosed by the regional law in order to have shared characteristics and requirements in all existing public and private hospital, this has meant that the four main areas of the model were standardized:

1. mission and improvement policy;
2. management of human and technological resources;
3. anticancer drug management processes;
4. Tools for verification and monitoring methods.

14. The Paolo Giaccone Polyclinic Company Palermo and clinical trials

A. Pasquale, C. La Seta

As of December 2021, the Paolo Giaccone Palermo Polyclinic Company has 113 active interventional studies, of which 72 with preparation and dispensing of medicines and over 300 observational studies. The Oncohematology CTC manages 103 studies of which 60 are interventional and 53 are observational. The Pharmacy plays a key role in the management of the clinical studies conducted in all the Company's Operating Units involved in the experimentation from internal medicine to General Surgery passing through Hematologic, Neurology, Oncology and other specialist branches.

The Pharmacy manages the trial medicines under investigation in full from their arrival, to delivery to the enlisted subject, until the return to the sponsor or destruction, ensuring traceability and quality of the work. In particular the storage temperatures of the medicines are traced through the use of calibrated temperatures and the data are downloaded on a monthly basis and sent to the sponsor companies or CROs. The Pharmacy takes care of quality and quantity control and registers the arrival of medicines on the IWRS portals dedicated to clinical trials. As regards the dispensing of medicines to enrolled subjects, we proceed directly with the simultaneous confirmation and registration of what has been returned and, if required by the protocol, calculation of compliance. The pharmacy also has the task of proceeding with the destruction of medicines not used or returned by patients after appropriate review and authorization by the Sponsor company.

As regards the set up for each study, specific study preparation sheets are drawn up, with all the information for the preparatory nurses, the information is in any case shared in a briefing at the beginning of the study where the pathology and the study are illustrated and particular attention is paid to the key steps of the set-up itself. The management software for preparing onco-haematological therapies allows you to have dedicated sheets with the same information. These preparation sheets, in addition to containing all the information relating to the patient and the prescriber, keep track of everything that has been used, from the drug to the medical devices and solutions. The times of assignment, the start and the end of preparation are also defined. All the preparations are performed in a sterile environment, validated and checked every three months at the UFA Simple Operating Unit

A separate form allows you to trace the transport and delivery to the

OU where the trial is located, even the time required and the transport temperature are carefully traced and evaluated.

From an administrative point of view, the Pharmacy also takes care of the pre-authorization part, evaluating for itself, the feasibility of the study and its economic repercussions. Particular attention is paid to reporting on the use of medicinal products, especially if these are *Non-Profit studies* or with brackets that are labelled as clinical practice.

During the Monitoring visits by the Sponsors or CRA, a dedicated room is made available and, the day before, the *Pharmacy binders*, the medicines returned by the patients and those still to be dispensed are brought in, provided that they are not medicines to be store below room temperature.

For each of these activities, a specific tariff has been developed which takes into account all the figures who actively work and the time dedicated by each of them. The amounts requested were calculated on the basis of the regular salaries. The activities for which *grants are requested* are the following:

	Activities
1	Investigation Trial
2	SIV
3	Fee for each supply
4	Randomization
5	Assignment of IWRS and Delivery of drugs to the enlisted subject
6	Deliver drugs to enlisted subject
7	Monitoring visit
8	Remote monitoring visit
9	In situ destruction
10	Closing visit
11	Preparation of returns to be sent back
12	Assignment, preparation and delivery of infusion drugs
13	Preparation and delivery of infusion drugs
14	Dispensing to patients by courier

1) Trial Preliminary: collection of information necessary for carrying out the clinical study, provision of curriculum vitae, provision or renewal of GCP certification (course provided by the sponsor or CRO), identification of the pharmacy study staff, sharing existing procedures with Sponsors and Investigators, development of specific study procedures.
   The fee is required only once.

2) SIV (Initiation of Study Visit): assistance to the monitor and CRO for the opening of the centre, evaluation and study of the protocol, synopsis, characteristics of the medicines, creation of the IWRS account and definition of the times and methods of keeping the accounts.
   If done remotely, a surcharge applies.
   The fee is required only once.
3) Fee for each supply: provides for quality and quantity control of each shipment arrived, confirmation of receipt electronically or by fax, compilation of accounts, notification of any thermal excursions during transport, management of quarantine.
   The consideration is required for each shipment.
4) Randomization: assignment of an enrolled subject to a treatment arm.
   The fee is required for each individual randomized patient
5) IWRS assignment and drug delivery to the enrolled subject: assignment of the kits manually or via the IWRS system and dispensing to the enrolled subject. Accounting. Rendered.
   The fee is required for each dispensation.
6) Drug delivery to enrolled subject: dispensing to enrolled subject. Recording render.
   The fee is required for each dispensation
7) Monitoring visit: assistance to the monitor and CRO during a monitoring visit, supply of medicine storage temperature certifications, document control, accounting control, assistance in preparing returns to the company.
   The fee is required for each monitoring visit.
8) Remote monitoring visit: remote assistance to monitors and CROs at each monitoring, document control, accounting control, sending of certifications of medicine storage temperature certifications.
   The fee is required for each remote monitoring visit.
9) *In situ* destruction: destruction of medicines by the AOUP. The cost incurred for the destruction will also be added to the consideration
   The fee is required for each destruction.
10) Closing visit: assistance to monitors and CROs for the closure of the centre, supply of documents and delivery to the Main Investigator of the binders and documents present in the pharmacy.
    If done remotely, a surcharge applies.
    The fee is required only once.
11) Set up of returns to be re-sent: preparation of the return of medicines.
    The fee is required for each return.
12) Assignment, preparation and delivery of infusion drugs: assignment of kits and dispensing of infusion drugs to the department.

The fee is required for each dispensation.

13) Preparation and delivery of infusion drugs: assignment of kits and dispensing of infusion drugs to the department.
The fee is required for each dispensation.

14) Delivery of drugs to the enrolled subject by courier: dispensing to the enlisted subject if the procedure is permitted by the protocol, and accepted by the Sponsor, and accounting for Returns. The costs and the choice of the courier are borne by the sponsor company.
The fee is required for each dispensation.

The dedicated staff consists of:

- a Pharmacist Manager, hired on a permanent basis, who has a series of specific characteristics such as an Advanced Training Course in Clinical Trials, a Masters in Design and Conduction of Clinical Studies in the human environment and a Masters in Preparation of sterile preparations and oncological therapies;
- a support pharmacist who has a specialization in hospital pharmacy and has been trained in the management of sterile preparations;
- 4 Research Nurses and Dressers who have received appropriate technical training on the handling of sterile preparations.

All personnel are in possession of the GCP E6(R2) Certificate.

Pharmacy is taking on an increasingly dynamic role in clinical trials. In fact, the role of simply receiving medicines has moved on to a complete management of the same even beyond normal activities. In addition to the routine workload during the Sars Cov-2 pandemic, it was necessary to develop, in agreement with the sponsoring companies, home delivery systems for medicines and reporting in order to avoid blocking of trials and loss of precious data. In this phase, particular attention was paid to the assessment of patient compliance by asking them to notify the pharmacy of the arrival of the new drugs and by means of photographic documentation verify the returns which were subsequently returned

Expanded/Early Access are borrowed from the sphere of competences relating to clinical trials.

A few numbers (Year 2021):

Sterile set ups	654
Package arrival	456
Close Out Visit	5
Studies configuration (*)	150
Dispensations to patients	523
Billings	30
Study management (**)	568
Monitoring	101
Package preparation	5
Drug request to the sponsor	15
Packages collected by investigators or couriers	394
Site Selection visit	24
Site Initiation visit	20
E-mails received	7.541
E-mails sent	2.342

(*) All budget configurations and negotiations fall into this category.

(**) This category includes stock checks, deadlines and various activities.

15. General aspects of the Logistics of Clinical Trials in the Hospital Pharmacy of the Careggi University Hospital of Florence

M. Pucatti, M. Angileri, M. Cecchi

The governance process of clinical trials at the Hospital Pharmacy of the Careggi University Hospital of Florence, Tuscany, requires expertise of the hospital pharmacist in the field of management of the experimental sample, definition of standard operating procedures and application of current legislation.

In fact, the pharmacist is involved at various levels in the management of the Company's experimental protocols: analysis of local feasibility, evaluation of trials in the Ethics Committee session, participation in initial study visits, management of the experimental product, management of documentation, participation in monitoring visits and closure of the clinical study.

The assessment of the local feasibility of an experimental protocol is essential to verify the organisational, managerial and economic sustainability of the trial, before submitting it to the Ethics Committee. From this point of view, the pharmacist collaborates with the company's *Clinical Trial Centre*, the unit responsible for signing the agreements, and participates in the selection visits of the experimental centre to guarantee the certification of the pathways.

The hospital pharmacist also assumes the institutional role of member of the Ethics Committee as an expert on drugs and medical devices, making his technical and legislative knowledge available. With Regional Resolution no. 418 of 3 June 2013, the Tuscany Region recognizes a single Regional Ethics Committee for clinical trials, as an independent body aimed at guaranteeing the protection of the rights, safety and well-being of people included in the trial programs and to provide a public guarantee of this protection. The organizational model of the Regional Ethics Committee includes four sections:

- Vasta Centro Area Ethics Committee, with location at the Careggi University Hospital and responsibility for AOU Careggi, Local Health Authority Toscana Centro (Florence, Pistoia, Prato, Empoli) and Ispro.
- Wide North West Area Ethics Committee, with location at the Pisan University Hospital and responsibility for AOU Pisana, North West Tuscany Local Health Authority (Massa and Carrara, Lucca, Pisa, Livorno, Viareggio), Fondazione Toscana Gabriele Monasterio (The Gabriele Monasterio Tuscan Foundation) (for trials in non-paediatric field).

- Wide South East Area Ethics Committee, with location at the Siena University Hospital and responsibility for the Sienese AOU, South East Tuscany Local Health Authority (Siena, Arezzo, Grosseto).
- Meyer University Hospital and competence, specifically for paediatric trials, AOU Meyer, IRCCS Stella Maris, Fondazione Toscana Gabriele Monasterio (The Gabriele Monasterio Tuscan Foundation) (only for trials in the paediatric field), Health Trusts of Tuscany (for paediatric trials).

Following the authorization of the study by the Ethics Committee, the pharmacist is called to participate in the activation visits of the experimental centre and/or Study Start necessary for the definition of the processes. All the information collected during the local feasibility analysis of the study and the selection/activation visits of the experimental centre, together with the authorization resolution of the Ethics Committee, are catalogued in the Pharmacy in digital and paper format, accessible only to authorized personnel. A computerized archive has also been defined which collects the main information on clinical trials approved by the Ethics Committee: the study/Protocol code, the EUDRACT code, the date of authorization, the Principal Investigator, the department involved, the experimental products being studied and the contact details of the Investigator or his delegate. This archive ensures correct management of the experimental products in the context of authorized clinical studies. As recalled by the decree of the Ministry of Health of 21 December 2007, the hospital pharmacist, in fact, is called to carry out activities in the field of clinical research concerning the aspects of reception, quality-quantity control, registration, correct storage and forwarding of the experimental sample to the experimenter. The Pharmacy has a computerized archive for loading and unloading experimental products and for compassionate use (Ministerial Decree of 7 September 2017), which guarantees their traceability, from receipt in the Pharmacy to delivery to the Investigator.

The experimental products are stored in special areas of the Pharmacy used for clinical trials, clearly identified and accessible only to authorized personnel. The Pharmacy is equipped with rooms for the conservation of experimental products at temperatures below 25°C, a refrigerator for conservation at 2-8°C, a -20°C freezer and a -80°C freezer. The premises and equipment are equipped with probes for continuous temperature recording, remotely monitored and connected to a 24-hour security service; it is possible to check the temperature and the status of the probes using a special company application, which can only be used by authorized personnel. In the event of a malfunction of the temperature maintenance and/or monitoring systems in these rooms, back-up rooms and equipment have been set up, also

connected to a continuous temperature recording system and to the 24-hour security service 24. Refrigerators and freezers are also equipped with disk and display that allow alternative temperature control. The equipment used is equipped with calibration and correct functioning certifications issued by the competent companies. These certifications are recognized by Accredia, a national accreditation body which ensures the compliance of systems and processes with the requirements set by international standards and norms.

The COU of Hospital Pharmacy is ISO 9001:2015 certified. The ISO 9001 Standard defines the requirements of an organization's quality management system. The purpose of an organization with a certified management system is to continuously supply products/services that comply with statutory and regulatory requirements. Regulatory developments require the Pharmacist to have increasingly specific skills with a view to improving clinical standards in the execution of studies and optimizing all processes for managing the product being tested through the adoption of precise standard operating procedures (SOPs) and Operating Instructions (OI) in accordance with the ICH-GCP (Good Clinical Practices). ISO 9001:2015 certification guarantees that all procedures drawn up are in line with the requirements of the reference quality system.

The UOC Hospital Pharmacy was involved in the corporate self-certification process for the conduct of Phase I studies: the SOPs were drawn up that describe the operating procedures for the management of the Phase I experimental product by the Pharmacy hospital, from reception to transport to the experimental centre, defining the minimum requirements for company self-certification provided for by AIFA Resolution no. 809/2015. In the self-certification process, the pharmacist has made his technical and legislative knowledge available, contributing to the regulation of all the paths and processes envisaged by the regulations relating to clinical research to ensure the quality of the data and the safety of the patients treated, fundamental requirements for the initiation of Phase I clinical trials.

Furthermore, the Careggi University Hospital is authorized to conduct clinical studies involving the use of Genetically Modified Microorganisms (GMMOs) (DL No. 206/2001 - Implementation of Directive 98/81/EC which amends Directive 90/219/EC, concerning the contained use of genetically modified microorganisms); the premises notified to the Ministry of Health include the Pharmacy's Clinical and Traditional Galenics laboratories, authorized for the possession and manipulation of GMOs.

To ensure the conduct of a clinical study and the traceability of the processes, the Pharmacy, on the basis of a contract stipulated between the Company and the Sponsor/Promoter, makes itself available for the

procurement of drugs and/or medical devices to support the clinical trial, if the Sponsor/Promoter cannot guarantee its supply. The Pharmacy also defines the disposal process for unused, deteriorated, close to expiry or expired trial products, agreeing on remote collection with the Sponsor/Promoter or proceeding with disposal in the Company, where provided for in the contract. Disposal is also regulated by a special form which authorizes the Pharmacist to request the disposal of the products from the competent corporate entity and guarantees the traceability of the products. In fact, the competent body is required to produce a specific disposal certification shared with the experimental centre and the Sponsor/Promoter.

As at 31 December 2021, approximately 318 clinical studies were active: 15% in the haematological field, 20% in the oncological field, 9% in the radiotherapy field. 47% of the studies conducted in the Company are Phase III; are around 33% of Phase II studies, 15% of Phase IV and 5% of Phase I, and increasing. 40% of active studies require preparation of drugs in the Pharmacy laboratories; in particular, the pharmacist is required to prepare the drugs subject in the clinical study, labelling of the products set up according to the rules established by the Sponsor/Promoter, in line with current legislation (Annex 13 eudralex Volume 4), management of the blind and possible preparation of the placebo, accounting management of medicines and dispensation to patients.

Phase I studies provide for a greater involvement of the hospital pharmacist: the Pharmacy is responsible for storing the experimental products for the entire duration of the study and for managing the accounts; the medicines are set up in the Pharmacy laboratories in order to ensure the quality and safety of the preparation; the maintenance of the storage temperature is guaranteed even during the transport of the experimental products. On the day of the clinical trial, in fact, the experimental products are transported from the Pharmacy to the Phase I unit, the unit responsible for conducting the Phase I clinical trials, with the aid of an isothermal bag which guarantees the constant maintenance of the temperature. The bag has a temperature detection device, equipped with RFID technology, capable of connecting to a smartphone for recording the temperature during transport. The smartphone also allows you to record the date and time of start and end of transport, any deviations from the established storage temperature range and for how long these deviations have occurred. The device for detecting the temperature is calibrated annually by the manufacturer, guaranteeing the reliability of the data detected.

The hospital pharmacist, therefore, is called upon to carry out activities in the context of clinical research which do not only concern the aspects

of receiving, recording, correctly storing and forwarding the experimental sample to the investigator, but is a professional support figure for the investigator and all corporate structures involved in clinical research, Sponsors and Contract Research Organizations (CROs).

16. The experience of the Siena University Hospital in the field of Clinical Trials

D. Paoletti, S. Giorgi

The Siena Hospital-University company is very active in the field of clinical trials.

The departments most involved are the onco-haematological departments (Immunotherapy Oncology, Haematologic Medical Oncology) followed by Rheumatology, Respiratory Diseases and Internal Medicine followed by the other medical specialties. In the management of clinical trials, the company is made up of various players, each of which contributes to the development of new studies and to making the company attractive so that clinical trials are increased and thus always offer patients more innovative treatments. Starting from the evaluation phase of the study, we have a Clinical Trial Office (CTO) and the Technical-Scientific Secretariat (STS) of the Ethics Committee of the Vast Tuscany South East Area (CEAVSE) which respectively have the task of validating the clinical study; specifically, the CTO deals with the part concerning the business feasibility of the study and the contract between the sponsor and the clinical centre; the STS takes care of the more strictly scientific part, therefore verifies and validates the documentation presented by the sponsor and requests any additions or modifications. All the activities of the CTO and STS are managed by the CINECA software which integrates in the various parts with the Regional Ethics Committee (CER), with the Clinical Centres, STS, CTO, Hospital Pharmacy for taking charge and managing the drug. Following the approval of the study, the drug is taken over by the hospital pharmacy according to the established operating procedures and this management is computerized with an easily traceable electronic archive of the experimental files. This step is essential as the computerized management of the documentation relating to experimental drugs starting from the transport document ending with the traces relating to temperature monitoring, dispensing carried out, etc.

Most of the operating units involved in clinical trials have *Study Coordinators in-house* who are in close correlation with sponsors, clinical hospital pharmacy and enrolled patients. In the event that there is a delivery of infusion therapies, the pharmaceutical laboratory is involved, and using the log 80 software manages the experimental sample in its path from receipt, storage, to the setting up and monitoring of the study. The part of the hospital pharmacy regarding the management of clinical trials has the ISO:9001 quality certification. The staff involved in the various areas in

CTO and STS are hospital pharmacists and administrative staff. The STS coordinator is a hospital pharmacist. In the pharmacy we have hospital pharmacists and hospital pharmacy trainees, administrative staff, biomedical laboratory technicians and professional nurses. Let us specifically analyze the organization and function of the subjects involved: what is described below has been incorporated into the standard operating procedures of the Ethics Committee and the Hospital Pharmacy, each in relation to the activities they perform.

The Clinical Trials Office

Specifically, the CTO carries out the following activities:

- promotes clinical research in the company, proposing itself as a qualified point of reference for investigators and sponsors;
- guarantees the Company Management greater control of the processes concerning clinical trials, preliminarily assessing their feasibility (assessments of company impact, negotiation and closure of the study contract, management of relations with the Sponsors, request for invoicing to companies or institutions sponsor for *Profit* studies);
- interfaces with the various Company structures for a better and faster management of the administrative processes necessary for the conduct of clinical trials;
- provides services of an administrative, managerial, methodological and ethical nature to the Company's researchers so that clinical studies are carried out in compliance with current legislation;
- collaborates independently but jointly with the sections of the Regional Ethics Committee, the Ethics Committee of the Tuscany Region Vast South East Area (CEAVSE) and the Paediatric Ethics Committee (CEP), to ensure the finalization of the authorization processes for clinical trials.
- supplies the regional *Clinical platform Research Management System* (CRMS), in compliance with the established deadlines, and specifically the modules "Feasibility", "Budget" and "Contract".

Technical-Scientific Secretariat Ethics Committee

The Secretariat, composed of at least five full-time units in addition to the Head of the Office, shall:

a) having heard the opinion of the President and the members, prepare an annual calendar of meetings;
b) receive, record and verify the formal correctness of the request for an opinion and the completeness of the documentation submitted by the sponsor in copy to the section of the Ethics Committee and the

directorates management of the peripheral centres in which it intends to conduct the study;

c) on the indication of the President prepares the convocation of the meetings of the section and take care of the agenda, taking care that the convocation, including the agenda, is sent to the members of the section at least 5 calendar days before the date scheduled date of the session.
d) draw up the minutes of the sections' meetings;
e) takes care of the settlement of attendance fees due to external members and reimbursement of expenses;
f) files all the documentation relating to the activity of the CERT section, including the minutes and opinions;
g) enters the data relating to the opinions expressed by the section in the National Observatory on Clinical Trials and in the Register of Observational Studies, maintained by AIFA (Italian Medicines Agency). To this purpose, and for any need connected to the Observatory, a contact person is identified within the Secretariat Office;
h) in the case of issuing the single opinion, verifies that the information notified to the Observatory by the applicant is consistent with the documentation provided;
i) take care of relations with the health departments and with the *Clinical Trial Offices* and the *Task Forces* for clinical trials of the companies of the Vast Area under its competence, pursuant to DGRT 553/2014, as well as with the investigators and with the sponsors for as pertaining;
l) make available to the components all the documentation necessary for the evaluation of requests for opinions;
m) collect and manage, as far as it is appropriate, the activation and closure reports of the centres participating in the studies and all reports relating to pharmacovigilance;
n) supports the monitoring activity pursuant to art. 21;
o) verifies that the data relating to the studies carried out in the institutions of its competence are made public by the sponsor, according to the procedures established by current legislation;
p) organizes training activities promoted by the CERT section

Ethics Committee

Even the management of the meetings of the Ethics Committee starting from the convening of the session, to the consultation of documents up to the drafting of the final report are managed by the Cineca Platform that allows t0 manage the evaluation process of a clinical smoothly and quickly.

Abbreviations

CEAVSE = Wide South East Area Ethics Committee
RFO = Head of UOSA Oncological Pharmacy
FRL = Pharmacist in charge of the Galenic area laboratories
FRQ = Pharmacist in charge of Quality
FDFO = Pharmacist Director of Oncological Pharmacy AOUS
FSFO = Pharmacist specializing in Hospital Pharmacy
IP = Registered Nurse
TLB = Biomedical laboratory technician

Hospital Pharmacy: Example of Standard Operating Procedures

- **Phase 1: Receipt and confirmation**

No.	*Phases*	*Function Manager*	*Involved function*	*Description of the phases*
1	Results of the CE	RFO	RFO; FDFO; FSFO	The Secretariat of EC communicates to the RFO the results of the meeting with the trials and/or therapeutic uses approved by the EC through the regional platform for the management of clinical trials.
2	Opening Dossier	RFO	RFO; FDFO; FSFO	RFO, FDFO and/or FSFO for each incoming shipment of experimental drug and therapeutic use a shall open a FSUT reporting on the title page all the data referredisted in Annex 2.
3	Reception of medicines	RFO	RFO; FDFO; FSFO; AM	1. The Oncological Pharmacy receives the trial at the following times: Monday-Friday 8.00-13.00 as indicated in the attached document in OSsC http://Oss-sper- clin. agenziafarmaco.it/ ethics Committee (data, ethics committee Siena, bulletin board) It will be the task of the RFO, FDFO, FSFO, AM; arrange for the collection of packages containing investigational medicinal products and/or medicinal products for therapeutic use; 2. RFO and/or FDFO and/or FSFO verify the qualitative-quantitative correspondence of the material sent with respect to what is reported in the transportdocument, Packing list or accompanying document, check the integrity of the package, the conditions of correct storage through temperature recording systems associated with experimental drugs, maintenance of the cold chain; 3. FDFO and/or FSFO enter all the documentation received in the specific FSUT in the "trial to be delivered" folder following the numerical progression of the FSUT files. 4. AM and/or FSFO update the Fex with the medicines that have arrived and with the corresponding FSUT file number.

4	Storage	RFO	RFO; FDFO; FSFO	1. Medicines are stored by FDFO, FSFO, as required by the storage conditions; 2. Monitoring of storage temperatures (refrigerator/t. Amb.) is carried out by an automatic detection system (Spy log SIRIUS) and remote alarm on the mobile of the pharmacists. The storage temperature (ambient or fridge) is constantly monitored through the Sirius monitoringsystem connected to the fridge and to the experimentation room.
5	Communication to the investigator and sponsor/ CRO	RFO	RFO; FDFO; FSFO	Where FDFO, FSFO, AM are properly stored, they shall send notices of compliant arrival and storage of the investigational medicinal products and/or therapeutic use to the investigator, with the form all. 4 by telephone and e-mail; in the event of incorrect storage, FDFO and/or FSFO send notices of non-conforming arrival and storage of the investigational medicinal products and/or therapeutic use to the investigator and the sponsor/CRO according to the specific models foreseen by the sponsors. Temperature excursion alarm: in the event of a non-compliant temperature (2-8°C and 15-25°) and/or fridge alarm, FDFO and/or FSFO send a notice to the sponsor/CRO using the specific forms for excursion communication provided by the sponsor. In both cases, the shipment is placed in quarantine pending formal communication by the sponsor/CRO stating the instructions for the use or not of the medicinal products, or their possible withdrawal and reintegration.
6	Medicine delivery	RFO	FDFO; FSFO; AM	Medicinal products shall be collected by the investigator or referent identified by the investigator himself every day from 12 to 13 within 30 days from the date of receipt in the pharmacy. The medicinal products shall be delivered to the Investigator or to the contact person identified by the Investigator, who will sign the appropriate withdrawal form at. 5 The AM or FSFO, file the collected FSUT in the special "trials archive" folder following the numerical progression.

- **Phase 2: Preparation; management of master galenic preparations intended for clinical trials**

For trials where the involvement of the pharmacist is expected for the preparation of the experimental samples, following the reception and control operations of Phase 1, the preparation and management operations of the master galenic preparations for clinical trials are reported. These phases include the use of a Log 80 IT management system and the forms used for the set-ups generated by the system replace the *formats* and forms prepared by the individual Sponsors for these operations.

No.	*Phases*	*Function Manager*	*Involved function*	*Description of the phases*
1	Reception and labelling and loading of the experimental drug into the warehouse	RFO	FDFO; FSFO	FDFO and FSFO using the software log 80 experimental studies section (operating instruction manual Annex 6) registers the load of the experimental drug reporting quantity, lot, expiry date and identification number of the vials; connects the drug to the therapy scheme envisaged by the experimental protocol and subsequently prints the serialization labels. Following the registration of the load, it is possible to view through screen the log 80 in "Situation", the warehouse of the experimental drugs where all the accounting data of the incoming drug based on the study protocol are reported. For incoming and outgoing accountingit is possible to view all the movements in the "Experimental studies screen" in the section "print form" in this way The software automatically generates the study accountingform (Annex 7 Experimental Studies Drug Accounting).
2	Validation of the Prescription for preparation of the experimental drug	RFO, FRL	FDFO; FSFO	FDFO, FSFO through the software log 80 validates the doctor's prescription by confirming the data and uses the vials of the experimental protocol indicated on the prescription sheet (Annex 8 prescription sheet) possibly awaiting confirmation from the contact person of the department of lot numbers/id of the vials assigned, where foreseen (randomization/ double blind)
3	Formulation processing	RFO, FRL	FDFO, FSFO	FDFO, FSFO processes the worksheets (Annex 9 Technical Worksheet), administration forms (Annex 10 patient administration form), labels (Annex 11 preparation labels). In the FDFO worksheet, the FSFO must write clinical trial and attach the labels of the bottles assigned or used for the preparation. At the end of the session, archive the worksheet with the possible assignment of vials in the dedicated Pharmacy Binder (specific to the sponsor).
4	Preparation of the set-up box	RFO, FRL, FDFO	FDFO, FSFO	FDFO, FSFO prepares the CA by putting in: • Administration sheets • Worksheets with set-up operating instructions • Labels The patient box will be completed, according to the data provided during the prescription phase by the doctor/dataM of the study, with the following products: • Medicines necessary for the preparation taken as indicated by the medical investigator/data manager; • Any particular DM necessary for the set up of the preparation indicated on the worksheet; • Any particular DM necessary for the administration of the drug indicated on the worksheet; • Diluents indicated in the worksheet.

5	Incoming quality control	RFO, FRL, FDFO	FDFO, FSFO	FDFO, FSFO will check, in the patient boxes, the experimental drugs necessary for the preparation, taken as indicated by the medical investigator/data manager (where applicable, check the assignment of the experimental vials to the patient, according to IVRS) At this time the first check on the correspondence between the experimental drug and the protocol associated with the patient is carried out; dosage, lot and expiry date are also checked.
6	Set up preparations	RFO, FRL	FDFO, FSFO, IP, TLB	After having carried out the incoming quality controls, the patient box will go into preparation. Before materially performing the set up FDFO, FSFO, IP, TLB, read with an optical pen the serial code of the log 80 carrying out the second safety check on the preparation (Annex 6 operating instructions Log 80 Experimental studies - new version). In fact, the optical pen reads the serial code log 80 assigned to each vials during loading and connects the following information: identification number of the experimental vials, study protocol and patient; it also records the drug discharge movement to the patient allowing the outgoing accounting of the experimental drug (Annex 7 Experimental Drug Studies Accounting). After having carried out all the checks, proceed with the set-up following the operating instructions given in the technical worksheet. At the end of the preparation on the worksheet, the volume of residual drug contained in the vials is reported, as a final control on the volume of drug taken during preparation (Mass balance).
7	Management of experimental drug production residues	RFO, FRL	FDFO, FSFO	The production residues of the experimental vials, for organizational reasons of space and for justified safety reasons, are disposed of as non-experimental antiblastic chemotherapeutics, according to current legislation and with reference to the current Company Operating Procedure for Waste Disposal.
				(Annex 12 waste management), simultaneously with the setting up of the experimental therapy, at the end of the production cycle.
8	Documentation registration	RFO	FDFO, FSFO	All withdrawals and entry and exit movements of experimental drugs are highlighted in the "Experimental drugs" menu by selecting the reference study under the "Print form" item. In this section, the following data are recorded for each individual study protocol: type of experimental drug (drug/placebo); lot, expiry date, incoming drug quantity, loading date, unloading date quantity of vials downloaded to the patient and vials identification number where applicable (Annex 7 Experimental Drug Studies Accounting).

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- Phase 3: Total management

Based on the needs and requests of the sponsor, in addition to Phases 1 and 2 of the FDFO, FSFO manages the IVRS (double blind randomisation, assignment, *resupply*) the methods of which vary according to the IT platform provided by the sponsor.

17. The Management of Clinical Trials in the AOU of Perugia

E. Murrja, A. D'Arpino

The Perugia hospital, in agreement with the University of Perugia, is a health centre of high specialty that, due to the specific professionalism present, the complex of innovative technologies and the type of services offered, is a point of excellence for both Umbrian and national healthcare.

The Company is structured according to the departmental organization, currently in existence ten Health Departments with the Operating Units that constitute them. The Company represents a polyspecialistic pole, with medical and surgical specialties, equipped with 817 beds.

S.C. Hospital Pharmacy

The Hospital Pharmacy Complex Structure is organized into areas, as listed below:

- Medicinal Specialties Area
- Devices and Diagnostics Area
- Narcotics Area - Dialysis
- Radiopharmaceuticals Area
- Clinical Galenic Area

The Pharmacy's staff includes 9 structured pharmacists and 20 other professional figures (administrative employees, warehouse workers, technical operators, social and health operators, biomedical laboratory technicians).

The professional figure of the hospital pharmacist within our Company is involved in clinical assistance activities (centralized preparation for oncological and/or high-cost drugs, preparation of sterile and non-sterile master galenics); support activities for appropriateness and monitoring (clinical pharmacist, clinical trials, pharmacovigilance, information to healthcare professionals) and technical-management activities (logistics management of warehouses and administrative activity).

The sectors of the SC Hospital Pharmacy are represented in Fig. 1.

Below are the various activities involving the pharmacist within our Company.

The clinical galenic area includes four laboratories dedicated respectively to the preparation of reagents, master galenics (for internal, external, sterile uses), bags for paediatric parenteral nutrition, sterile paediatric and adult oncological preparations (UFA Antiblastic Drugs Unit). Four structured

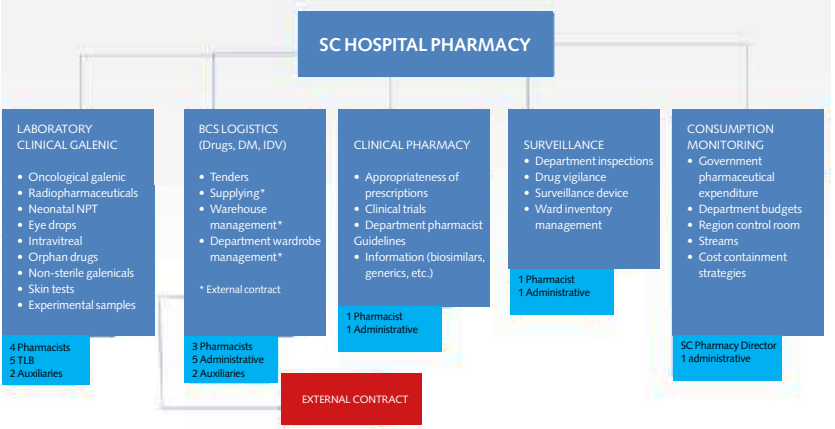


Fig. 1 – The sectors of the S.C. Hospital Pharmacy.

pharmacists are involved in the activities listed above and to support the activities carried out we have the following computerization and automation systems in our SC Pharmacy: SAP management software that allows the computerized management of drug orders, medical and diagnostic orders; the automatic filling system for preparing bags for total parenteral nutrition (Siframix®), managed by specific software (AbaMix®); the software for the computerized management of galenic preparations (Magistra®) and the automated platform for the preparation of sterile infusion therapies composed of a robotic system for the preparation of immune –chemotherapy drugs (APOTECAchemo®) and the semi-automatic support system for manual preparation of oncological therapies. The clinical galenic preparation laboratory also deals with the preparation of experimental medicines, and is equipped with 2 vertical laminar flow hoods.

Our UFA laboratory is a centralized laboratory and prepares oncological preparations for three other neighbouring hospitals in the city of Perugia.

Specifically, in the clinical galenical laboratory, injectable and oral personalized dose therapies, injectable and infusion clinical trials, injectable personalized dose therapies of oncological treatment protocols, and experimental ones for the Perugia Hospital are set up.

The activities of prescription, validation, preparation, delivery of therapies are supported by the management system (log 80), as required by national and regional legislation.

To guarantee the safety and quality of the sterile preparations set up in our UFA Unit, process qualification and validation tests are carried out, including periodic environmental and technological checks (particulate

and microbiological), checks on preparations (sterility test) and operators (mediafill test).

The volumes of activity are represented below:

Preparations	No. of set up (yearly)
NPT	1,825
Oncological	36,000
Eye drops	291
Non sterile	825
Total	38,941

Five pharmacists of our staff are instead involved in the procurement of appropriate and safe use of conventional and experimental drugs, medical devices, diagnostics, infusion solutions, dialysis material, prosthetic material, vaccines, nutritional products, disinfectants, radiopharmaceuticals, narcotics, medical gases, contrast media and blood products. They collaborate in tenders, contribute to the planning of hospital needs for drugs and medical devices, the correct management of stocks and the verification of the handling of relevant products in the various departments of our hospital. It's the pharmacist's activity the issuing of drug orders and DMs, stock management, request management and fulfilment after careful evaluation of the prescribing appropriateness, taking into account the importance of resource allocation in order to optimize pharmaceutical expenses.

The Hospital of Perugia, with a view to rationalizing and optimizing costs, decided to outsource in 2003 the warehouse of the Hospital Pharmacy by *outsourcing it* to an External Cooperative, which makes its storage facilities available and takes care of deliveries to 216 collection centres (CDP).

The consumption monitoring sector is a crucial aspect that sees the pharmacist increasingly involved in our reality and it is precisely in the context of Pharmaceutical Governance that the Umbria Region Control Room has been established, which has as its main objective that of planning and monitoring, in order to identify the opportunities and needs for consolidating the unitary *governance* at regional level on the materials/products/services that fall within the pharmacy's sphere of competence.

The management of Clinical Trials

The various activities, roles and responsibilities listed here are described and well defined within a standard operating procedure, the "Clinical Trials Drug Management" which is subject to periodic reviews and updates.

Clinical Trials AO Perugia	
Departments	**Number of Trials**
Hematology Transplantation	10
Oncology	30
Neurology	15
Neurophysiopathology	2
Internal Medicine	13
Psychiatry	8
Gerontology	10
Anesthesiology	8
Ophthalmology	15
Infectious diseases	10
Paediatrics	10

Initiation of the study: activity of the pharmacist

Experimental and observational trials with drugs can only begin after approval by the Regional Ethics Committee, the DMO Hospital Medical Directorate and a resolution by the Company Management. The resolutions are published in the Praetorian Register and downloaded by the Pharmacy which in any case receives a copy from the DMO.

In the phase preceding the start of the experimentation (Pre-Study visit – PSV and Site Selection visit – SSV) until the moment in which the center is opened (Site Initiation visit – SIV) all information relating to the management of the products being tested is collected and shared bilaterally (between the Sponsor/CRA and the experimental centre). The pharmacist participates in the start-up visit, reads the protocol and builds the computer archives; validates the therapeutic schemes in agreement with the doctors and

according to the indications present in the *Pharmacy Manual* of the clinical trial and finally informs the laboratory technicians on the challenges of setting up the drugs belonging to the clinical trial.

Operating procedures: Reception, control and registration of experimental drugs

The technical staff operating at the Hospital Pharmacy:

- Receives the medicines from the Courier and verifies that there is an exact correspondence between the bill and the packages delivered (heading, address, number of packages, etc.);
- Visually inspect the box which shouldn't show signs of dents and shouldn't be wet;
- Notes in the annual trial register; the following information is noted in the annual register: progressive number, which is shown both in the package viewed and in the documentation; name of the carrier courier; number of packages and mark with an asterisk if the material is refrigerated; date and time of receipt of the parcel; investigator's name; clinical study name/ protocol; shipping company; Delivery date; name and signature of the person collecting the goods; signature of the person delivering the drugs related to the trial.
- Proceed to notify the contact Pharmacist.

The Hospital Pharmacist:

- Gives directions for storage;
- Check the transport temperature recording and download the data (temperature recording for Phase 1 studies mandatory by AIFA Determination 809/2015 also for drugs to be stored at room temperature);
- Verify qualitative-quantitative correspondence with the transport note;
- Check for proper labelling;
- Archive the documentation (authorization resolution, transport documents, communications to the investigators, disposal declarations);
- Notify the experimenter of the arrival by e-mail;
- In case of non-compliance, it places the samples in quarantine and notifies PI.

Control and storage of the experimental drug

The Hospital Pharmacist is responsible for the correct storage of the drug until delivery to the Investigator or the CRC. The experimental drugs are kept according to the indications of the Sponsor and/or the AIC in spaces identified and separate from the other drugs. In particular for experimental medicines

that must be stored between 2 and 8°C, there is a dedicated refrigerator. The refrigerator registers the temperature electronically (eviSENSE®) in 24 hours and is equipped with an alarm system connected to the Company switchboard which calls the pharmacist on call in case of temperature deviation.

Operating procedures: Delivery and archiving of documents

- Medicines are left in their original packaging.
- Together with the FS, a copy of the delivery note and the documents present in the delivery package are delivered to the investigator.
- The Investigator and the Company are advised of receipt of the drug:
- In the event of evidence of non-compliance, the samples must be placed in quarantine, storage takes place in the pharmacy, in a special environment and correlated with specific forms that highlight the nature of the non-compliance found upon receipt. The sponsor is notified and communications are awaited.

Preparation of the experimental drug in the Galenic Laboratory

- For investigational drugs not yet on the market: the sponsor/promoter must provide the IB (summary of existing preclinical and clinical data) and the Preparation Manual (*Pharmacy manual*) and the preparation of the experimental samples is carried out in sterile conditions in the UFA laboratory where they are handled in septic conditions by technical personnel trained according to procedures validated by the pharmacist.
  The medicines are prepared on the same day as they are administered or in any case according to the indications specified in the pharmacy manual and in compliance with the Good Set up Standards.
  For Phase 1 clinical trials for which we have approval from AIFA and activation of an ongoing Phase 1 trial, the prepared drugs are collected from the laboratory by the investigator or his delegate in suitable containers and transport temperatures.
- Clinical galenic activity: UFA
  The fittings are carried out according to Good Standards Clinical Practice GCP, which specifies the need to implement systems with procedures that ensure the quality of every single aspect of the trial.
  The preparation takes place with the same procedures already in place for all oncological galenic preparations, using the same management system (LOG80).

Collection, disposal and distribution of experimental drugs
The investigational drug may be collected and disposed of or sent to external warehouses in the event of:

- Expired product;
- non-use;
- Product not stored correctly;
- Withdrawal upon request by the sponsor.

Profit studies: paid by the Sponsor
Studies Non Profit: charged to the FO
The Documentation of successful disposal or return is archived in FO.

Volumes of experimental activity
The Perugia Hospital Pharmacy is involved in the management of no. 188 receipts of experimental drugs (verification of congruity with the DDT, compliance with controlled temperatures, dispatch to experimental centers, return of any residues), trials which mainly concern therapeutic areas of Onco-Hematology. In the last two years, however, there have been a total of no. 207 clinical trials.

18. Organization of the Pharmacy in the IOV IRCCS Veneto Oncological Institute and logistics of the trial sample

M. Coppola

The Pharmacy Complex Operating Unit of the Veneto Oncological Institute is headed by the Hospital Medical Directorate. It has offices in Padua and one in Castelfranco Veneto for complete coverage of the territories of the two provinces in which the Institute operates (Padua and Treviso). Two Simple Operating Units belong to the UOC of Pharmacy (Clinical Oncological Galenics and Management of Medical Devices). In the pharmacy, the organization contemplates the figure of QM (quality referent), of the clinical risk referent and referent for the activities of the Hospital Infections Committee, both in the coordination and in the operational group. The pharmacy is responsible for the technical-scientific secretariats of the Company Therapeutic Commission, of the Company Evaluation Unit of Medical Devices, of the Ethics Committee for Clinical Trials and of the Ethics Committee for Clinical Practice. The pharmacy also actively participates in the GOM activities envisaged by the Intercompany Functional Oncology Department and in the mapping of PDTA.

The Pharmacy has the Structural Department of Translational Oncology and Services which has 4 Complex Operative Units, 2 Simple Departmental Operative Units, 4 Simple Operative Units, for a total of 146 structured employees. The Operating Units that belong to the department provide complementary services to the processes of diagnosis and treatment: pathological anatomy, pharmacy, pain therapy and palliative care, radiopharmacy, oncological molecular diagnostic immunology, basic experimental and translational oncology. These are Operating Units with contents and with very different purposes, but it is precisely from the diversity of contributions that the cultural humus for translational research derives, which covers and includes all aspects of neoplastic pathology, from prevention to diagnosis and from treatment to monitoring. In particular, the activities of the Department support the path of each individual patient in the characterization of the neoplasm at a morphological and molecular level, and in the identification of innovative and highly targeted pharmacological treatments, aimed at ever greater personalization of care. To complement and support these activities, the Department is heavily involved in numerous research projects on the pathogenetic mechanisms of neoplasms, on the identification of biomarkers useful both for prevention and diagnosis and for prognosis and response prediction, and on the development of innovative therapies and their

implementation at clinical level. Studies related to pharmacodinamics of the drugs, drug genetics, genomics, kinetics, are fundamental contributions to the development of precision medicine, which is the antechamber of the transition from a fixed-dose therapeutic approach to an approach with a dose that can be modulated on the basis of the individual profile drug concercing exposure and toxicity.

In the field of Medical Devices, studies are underway on new market technologies which are now approaching a stricter registration process very similar to that of drugs; this opens up scenarios for the development of translational research on medical devices, an innovative approach that will see the interest of manufacturers grow in retaining research centres that have the qualifications to support this new method of translational research. Last but not least, the importance of technological and IT development aimed at the declination and monitoring of PDTA, with a view to homogeneity and safety of treatments, traceability/retraceability of all operations, taking charge of the patient to the subsequent phases of prescription, preparation, administration, discharge. In line with the institute's *mission*, high technology in the development and application of treatment tools are always combined with a strong focus on the suffering individual, implemented through simultaneous treatments, pain therapy and palliative care included in the activities of department.

Accreditations

The Pharmacy is accredited:

- ISO9001;
- IRCCS instance,
- OECI;
- ESMO;
- Regional operating authorization;
- Regional excellence accreditation.

Pharmacy activity

The Pharmacy Complex Operating Unit of the Veneto Oncological Institute works in synergy with the Strategic Management, contributing to the achievement of health objectives for the pharmaceutical sector.

It guarantees the appropriate and safe use of conventional and experimental drugs, medical devices, in vivo and in vitro diagnostics, infusion solutions, dialysis material, prosthetic material, vaccines, nutritional products, disinfectants, radiopharmaceuticals, narcotics, medical gases, contrast agents and blood products.

It is responsible for planning hospital requirements for drugs and medical devices, for supplying, correct management of stocks and for verifying the movement of products within the Institute's Operating Units.

The Pharmacy Unit ensures the supply of pharmaceutical material to the operating units of the Padua and Castelfranco Veneto sites by providing requirements, managing personal data, issuing order proposals, managing stocks, evaluating the appropriateness of requests in order to carefully control pharmaceutical expenses. The pharmacy is responsible for maintaining the profiles, validating and checking the health goods that are supplied to all the UUOOs of the IOV headquarters; the function of DEC (Executive Director of the Contract) of the company logistics is in charge of the coordinator.

Garantees continuity of hospital/territorial care through the distribution of drugs to patients on hospital discharge from ordinary hospitalization, day care and after specialist outpatient visits; ensures the supply of class H drugs to patients treated at the Institute, guaranteeing the patient structured advice with adequate information material relating to the management of oral therapy in order to improve adherence to drug therapy and *outcomes*; in this context he takes charge of the *counselling* and of the *patient education*.

It manages the home delivery of oral therapies in order to guarantee continuity of care and pharmacological adhesion to all patients who are loyal to the Institute.

The service also guarantees the recovery of intact medicines returned by patients in accordance with DGR 2311/2014.

Through the oncological clinical galenic laboratories, it prepares the injectable and oral personalized dose therapies, codified by oncological treatment protocols, conventional (LEA) and experimental treatment protocols, the supportive/ancillary therapies and the preparations for analgesic therapy prescribed to outpatient and recovery.

Under the agreement, injectable personalized dose therapies of the oncological, conventional (LEA) and experimental treatment protocols are also set up for the University Hospital of Padua.

The activities of prescription, validation, preparation, delivery of therapies (infusion, oral, support, experimental) are supported by the management system (computerized oncological medical record), as required by national and regional legislation.

To guarantee safety and quality in the preparation of sterile therapies, the quality assurance system contemplates a qualification and validation system with periodic environmental and technological controls (particle and microbiological), on preparations (sterility test) and on operators (mediafill test).

The Pharmacy monitors pharmaceutical expenditure through the processing of monthly reports, governs it with assiduous Horizon Scanning activity and focuses on the areas subject to regional monitoring in order to ensure the achievement of health objectives and compliance with the cost limits established by the Region.

It governs the prescriptive appropriateness through the validation of the treatment protocols, the monitoring of the levels of adhesion to the Innovative Medicines Recommendations, the management of the Treatment Plans, the secretarial activity of the CTA and UVAD.M., the authorization of the Centres, the correct keeping of AIFA registers and the management of conditional reimbursements for prescriptions generated by clinicians of the IOV operating units of the Padua and Castelfranco Veneto offices.

It supports management control and budgeting in the activities related to correctness and completeness of pharmaceutical flows, preparation of budgets, analysis and justifications of overruns in quarterly reports; it coordinates with Azienda Zero and the region for the purpose of correctly calculating the expenditure thresholds assigned by council decree.

Oversees supervisory activities, understood as Supervision of the pharmaceutical cabinets of the operating units, Pharmacovigilance, Supervisory device, according to Ministerial and Regional indications; collaborations are active with the Region and with the National Pharmacovigilance Network for the development of projects of regional and national value.

Promotes independent information on drugs and medical devices, according to criteria based on *Health Technology Assessment*; provides advice to healthcare professionals on pharmaceutical legislation, referring to international databases, independent journals and guidelines of international scientific societies, which are methodologically based on *Evidence Based Medicine* (EBM).

It supports the designated structures in the phases of authorization to operate, institutional accreditation, IRCCS applications, OECI and ISO 9001 accreditation by promoting a quality-oriented culture, preparing the necessary documentary evidence (management procedures, operating instructions, functional organization chart, information material), activating training projects in the field, setting up joint actions for the management of clinical risk and putting in place the necessary measures for the declination of the procedural contents.

The IOV Pharmacy is a reference centre for carrying out pre and post-graduate internships, specialization internships at the Specialty School of Hospital Pharmacy of the University of Padua and in the Specialization Schools of the most renowned universities in Italy.

Volumes of activity and economic LEA therapies

At the clinical galenic laboratories, the prescriptions of the clinicians are validated and galenic formulations of magistral infusion and oral therapies are prepared in personalized dosages that cannot be found on the market. The volumes of activity are around 105,000 annual preparations based on antiblastic chemotherapy and 70,000 preparations per year as premedication therapies, corresponding to approximately 4,500 patients in IV therapy per year at the Padua site and 1,000 for the Castelfranco Veneto site.

The economic volumes relating to the internal production of infusion therapies are around 30,000,000 Euros per year.

The activity of distributing drugs to patients in hospital discharge from ordinary hospitalization, day care and after specialist outpatient visits sees access by around 5,000 patients/year at the Padua site; the same activity is also guaranteed in the Castelfranco Veneto site for a number of accesses equal to approximately 1,000 patients per year. The economic volumes relating to direct distribution are around 38,000,000 Euros per year.

With regard to home deliveries of medicines, an activity launched in the Covid period, in 2020 medicines were supplied to 194 patients for a total of 311 prescriptions, in 2021 (January-September) 160 patients for 232 prescriptions.

The recovery of intact drugs returned by patients pursuant to DGR 2311/2014 generates annual savings of around 65,000 Euros.

The management of medical devices sees a volume of operations equal to 23,000 validations/unloads from the warehouse per year and a total expense for Padua and Castelfranco that is around 8,000,000 Euros per year, of which 1,700,000 Euros for robotic surgery.

The keeping of the AIFA registers and the management of conditional reimbursements for the prescriptions generated by the clinicians of the IOV operating units of the Padua and Castelfranco Veneto offices see a number of treatments that is around 1,500, of which more than half are subject to reimbursements, and a payback income of around 2,600,000 Euros per year.

Activities (patients)	number of patients 2020 non experimental	Number of patients 2021 non experimental
Direct distribution	4,875	6.049
Galenic preparations	4.206	4,521

Activity (expense)	Expenditure 2020 (euros)	Expenditure 2021 (euros)	Expenditure per patient 2020 (euros)	Expenditure per patient 2021 (euros)
Direct distribution	28,691,248	32.515.015	5,885	5,375
Galenic preparations (mag. 10C)	24,509,482	25,163,778	5,827	5,566

Radiopharmacy Organization

The Radiopharmacy is strongly involved in the radioligand therapy sector (Radio Ligand therapy– RLT), which represents an added and innovative value in the most advanced therapeutic choices

The Radiopharmacy belongs to the Pharmacy and is organized into 3 production sites where the following activities are carried out:

In Castelfranco Veneto (c/o nuclear medicine):

- Conventional activity with radiopharmaceuticals Technethiates, alpha emitters, beta (–) emitters;
- PET radiopharmacy activity officinal galenic radiopharmaceutical preparations labelled with 18F, 11C, 13N, 15O, 68Ga;
- radiopharmacy and PET document management.

In Padua (c/o nuclear medicine):

- Conventional activity with radiopharmaceuticals Technethiates, alpha emitters, beta (–) emitters;
- Management of PET radiopharmaceuticals (with and without AIC) supplied from outside 18F FDG, 18F Choline, 18F DOPA;
- Experimental radiopharmaceuticals;
- radiopharmacy and PET document management.

In Padua (c/o Radiotherapy):

- Collaboration in the management of the radiopharmaceutical 177 Lutetium -DotaTate (Lutathera).

The Radiopharmacy in the three locations is responsible for the maintenance and development plan which includes:

- Maintenance and development of the Standard Operating Procedures and implementation of the Quality Assurance System (SAQ);
- Maintenance of the specifications of the set up environments (radiopharmacies) and related controls;
- Continuous training and education of the personnel involved (TSRM, Nurses, Hospital Pharmacists);
- Clinical risk analysis; Introduction of new registered radiopharmaceuticals, innovative or experimental, for diagnostic or therapeutic use; Pharmacovigilance (radiopharmaceutical -vigilance);
- Evaluation of drug- radiopharmaceutical drug interactions.

Collaborations are also active with Health Physics (radioprotection for operators and patients, sharing of radiopharmaceutical procedures), with Nuclear Medicine (drafting and sharing of POS, study of drug interactions, research, study of new diagnostic procedures with radiopharmaceuticals), with Radiotherapy: drafting and sharing of POS, management of the receptor radiopharmaceutical 177 Lutezio Lutathera in the therapy of NETs.

With regard to the activity relating to the Quality Assurance functions of radiopharmaceuticals, the Radiopharmacy provides the maintenance and implementation of the Quality Assurance System (SAQ) required by the Standards of Good Preparation of Radiopharmaceuticals for Nuclear Medicine NBP-RF (I suppl FU XI ed. 03/30/2005); in particular, all the methods provided for by the law are applied to guarantee the quality, efficacy and safety requirements of radiopharmaceuticals to patients undergoing diagnostic/therapeutic investigations.

As regards the activity concerning the function of "Responsible for the release for clinical use", the function in question provides precise responsibilities for the Pharmacist, with regard to the release for clinical use of radiopharmaceutical medicinal preparations to patients. The functions of the Manager of the release for clinical use are envisaged both for the part of conventional nuclear medicine, diagnosis and therapy, as well as the part of positron emitting radiopharmaceuticals.

Volumes of Radio pharmacy activity

- Batch Record Radiopharmaceuticals Technethiates: 1,100 annually.
- Batch Record radiopharmaceuticals P.E.T. IOV internal use: 528 annually.
- Batch Record radiopharmaceuticals P.E.T. distributed to other centres: 320 annually.
- Drug interaction study: 63 DatScan studies per year.

Grant for Clinical Research activities

The management of clinical trials is centralized at the IOV IRCCS pharmacy in all phases of the process from procurement to delivery of the drug to the patient, both in the case of a drug set up in the clinical galenic laboratory and for the delivery directed to the patient of oral experimental drugs. The Pharmacy is in fact in the delegation log for all the activities concerning the management of the experimental sample, with particular reference to logistics, re-supply, opening of the blinds, provision of oral therapies, preparation of infusion therapies, management of returns and expired products, accounting, monitoring; actively participates in *audits*, initial study visits and site visits. Participates in the local feasibility coordinated by the Clinical Research Unit and coordinates the technical-scientific Secretariat of Clinical Trials Ethics Committee, supporting the latter in the approval process with particular reference to the evaluation of the scientific and ethical nature of the study proposals through the analysis of the scientific-methodological aspects and the verification of ethical requirements. The Pharmacy also contributes to the development of translational clinical research both in the

field of drugs and in the field of medical devices, through direct and indirect contributions and active participation as investigator or co-investigator in retrospective/prospective observational interventional clinical studies. It contributes to the IF of the Institute with scientific works related to the research areas of interest: pharmacology, pharmacokinetics, pharmaceutical technology, pharmacoeconomics, pharmacovigilance. Participates in scientific congresses through active contributions (Abstracts, posters, oral communications). Collaborates with Universities and Scientific Institutions in the development of thesis, experimental projects, training and tutoring for professional activity.

Volumes of Experimental activity

The management of clinical trials receives access to the pharmacy of about 400 patients per year in experimental oral therapy and the production of experimental infusion therapies for about 600 patients per year.

Table 1 shows the number of *Profit,* nominal therapeutic uses and *Non-Profit incident studies* activated in 2020 and 2021, broken down by operating unit and by type of study.

Table 1

	Profit Study		Nominal Therapeutic Use		No Profit Study		TOTAL	
Department	2020	2021	2020	2021	2020	2021	2020	2021
Castelfranco ONCOHAEMATOLOGY			1			1	1	1
CFV Oncology 3				3		3	0	6
Oncology of melanoma and oesophagus	3		1		1	1	5	1
UOC of Medical Oncology 1	8	21	4	8	4	6	16	35
UOC of Radiotherapy						1	0	1
UOC of Medical Oncology 2	12	8	6	13	2	3	20	24
							42	68

Table 2 shows the number of patients enrolled in clinical trials with provided drug in 2021 compared to the entire year 2020, broken down by department and by type of trial.

Table 3 shows the prevalence of 2021 compared to 2020.

There are 200 prevalent studies with active patients in 2021, compared to 174 studies managed in 2022.

Table 2 – Incidence of patients enrolled 2021.

Department	Profit Study	Nominal Therapeutic Use	No Profit Study	TOTAL
Castelfranco ONCOHAEMATOLOGY			1	1
CFV Oncology 3		10	5	15
Oncology of melanoma and oesophagus			3	3
UOC of Medical Oncology 1	55	33	31	119
UOC of Radiotherapy			3	3
UOC of Medical Oncology 2	17	53	8	78
TOTAL	72	96	51	219

Table 3.

Department	N. PATIENTS (January - 21 December 2021)				TOTAL year 2020
	Profit Study	Nominal Therapeutic Use	No Profit Study	TOTAL	
Castelfranco ONCOHAEMATOLOGY		2	1	3	2
CFV Oncology 3		21	6	27	15
Oncology of melanoma and oesophagus	64	8	23	95	148
UOC of Medical Oncology 1	293	72	115	480	426
UOC of Radiotherapy			3	3	0
UOC of Medical Oncology 2	104	127	30	261	248
Hereditary Tumors Unit	1			1	2
TOTAL PATIENTS	462	230	178	870	828

Secretarial activity of the Ethics Committee for Clinical Trials

The scientific-technical secretarial office of the CESC is housed at the Pharmacy.

In 2021, it supported the CESC, to the extent of its competence, for a total of 163 clinical studies, 440 amendments and 276 nominal therapeutic uses.

In Table 4 the details of the clinical studies by type and funding with date of first evaluation in the year 2021.

Table 4

Study typology	Profit	No profit	Total	
	no.	no.	no.	%
Interventional with medication	60	21	81 (4 PU)	49
Interventional with medical device	0	0	0	0
Interventional without drug and device	0	14	14	9
Subtotal interventional studies	60	35	95	58
Observational with medication	3	21	24	15
Observational with medical device	0	0	0	0

Traceability of trials

The pharmacy plays a key role in all stages of the trial by ensuring the correct traceability of the trial sample:

- insertion of the therapy schemes after comparison with the clinicians on the study designs;
- elaboration of specific operating instructions and procedures for the correct management of the experimental samples;
- document management through computer and physical archive classified by study code assigned to each trial;
- generation of specific reports to be provided during the monitoring arranged by the Sponsors/Promoters;
- storage temperature monitoring;
- deadline control through warehouse reports and disposals on site or at the Sponsors;
- document archiving following the closure of the trial, through computerized archives for rapid traceability in the event of an audit.

The traceability of the experimental sample is guaranteed in all its states through the integration of the systems, specifically the accounting management system and the computerized medical record. The experimental sample is identified in the same way as a commercial drug: the pharmacist assigns, through the management of an internal database, all the information necessary for coding and movement through the warehouse management system. They are therefore encoded:

- internal code: unique identification code in the Integrated Accounting System, warehouse management system in use;
- AIC code: 9-digit fictitious code, progressive according to the order of arrival of new experimental samples;
- supplier code: corresponding to the Sponsor/Promoter of the trial;
- type of experimentation, location of the pathology, phase of the experimentation, packaging.

All drugs and devices received by the sponsor are then loaded into separate physical and accounting depots. The rooms are equipped with cabinets, refrigerating columns and freezers, equipped with a probe for temperature monitoring; there is also an environmental probe that controls the entire room. The probes are connected to a remote assistance system and set to detect the temperature every 5 minutes and immediately forward a warning report to the pharmacy email and to the technician for a timely intervention.

The contents of the experimental material is highlighted by means of signs on the doors, accompanied by lists with the progressive codes of the trials to

facilitate identification during the preparation of the kits to be dispensed to the patient.

The accounting deposit is integrated with the medical record for assignment to the patient following a medical prescription.

During the validation of the therapy, the pharmacist therefore has the possibility of viewing from the single patient's prescription the warehouse stock corresponding to the prescribed drug, including lot and expiry date; has the option of indicating the kit identification number of the dispensed experimental sample; the system then automatically unloads the indicated quantity from the warehouse.

Information tracked in the medical record is only partially visible to clinicians to ensure blinding in the case of placebo trials.

The deliveries are then transmitted from the medical record to the management system which generates phase 3 of the direct administration of drugs, both in the case of infusion drugs and in the case of oral. Following a partition and a differentiated system on specific reasons, the information relating to the experimental drugs dispensed is excluded from the regional health information flows, but also allows the traceability of any commercial drugs used which must subsequently be reimbursed by the Sponsor/ Promoter depending on the contract conditions of the trial.

A structured dashboard allows you to make a direct connection to the various data sources (medical record, accounting management and phase 3 management), providing traces containing drug information accountability; these records have been approved by all the Sponsors of Profit trials to replace the paper forms required by individual clinical trials, allowing for complete computerization of the traceability of drugs dispensed and returned to the pharmacy, as well as an important reduction in time and errors in manual compilation.

Infusion therapies are set up in the sterile galenic laboratory next to the warehouse of the experimental samples, allowing a minimum latency time from the withdrawal of the drugs to the preparation of the therapies to be administered.

At the pharmacy there is also an outpatient clinic dedicated to patients undergoing clinical trials with oral drugs, where the pharmacist carries out information and education activities for patients at each cycle and where the accounting of the residual drug is carried out and the assessment of adherence to the therapy in close contact with clinicians. The information relating to the returned drug is reported in the folder and available in the tracings elaborated with the available IT tools.

16. Risk Assessment of Laboratories and Clinical Trials: regulatory aspects and general considerations

E. Rossin, C. Donati

Clinical Risk Management in Health Care represents the set of actions put in place to improve the quality of health care services while guaranteeing safety for patients and is one of the dimensions of Clinical Governance, which aims to foster actions that are able to control risks, to promote and enhance the role and responsibility of health care professionals and operators in order to induce system changes with a view to the continuous improvement of the quality and safety of care.

Clinical risk management approaches change the way errors are interpreted at the source of adverse events, that is understood as a system error rather than an individual error and as an opportunity for improvement.

Risk management, however, cannot be separated from quality management in pharmacy, which is essentially based on three tools: '**responsibility, planning and documentation of activities**' (cit. NBP).

In order for processes to function properly, it is necessary to identify the knowledge required to correctly carry out activities that have an impact on quality and at the same time, to foster operators' understanding of their role within the organisation.

Managing risk means acting with a view to permanent improvement, and staff skills are a key element in this respect.

Clinical Galenic Laboratories, which deal in particular with the preparation of galenic and experimental drugs, find themselves more and more often, also due to the ongoing reorganisations of companies and hospital networks, to interface with areas that are not always known and to undertake paths that have a significant impact both from an organisational point of view and from the point of view of legal responsibilities.

The Standards of Good Preparation (NBP) have the force of law and are published in the Official Pharmacopoeia (FU), therefore it is to them that the pharmacist and the preparatory nurse must comply.

To underline its importance, we refer to an extract from the Official Pharmacopoeia Ethical considerations and guidance in the preparation of pharmaceutical preparations without authorisation:

"**An appropriate level of risk assessment is adopted** when considering the preparation of an unlicensed pharmaceutical preparation.

The risk assessment identifies:

- *the criticality of various parameters (foe example, quality of the active substances, excipients and containers; preparation process diagram; extent and significance of testing; preparation stability) which may affect the quality of the preparation;*
- *the risk that the preparation may present for a certain group of patients.*

Based on the risk assessment, *the person responsible for the preparation must ensure, with an adequate level of safety, that the pharmaceutical preparation, during its shelf-life, is of an appropriate, adequate and fit-for- purpose quality. For stocks of preparations, the storage conditions and shelf life must be justified on the basis of, for example, analytical data or professional judgement that can be based on literature references"*.

In this context, therefore, error risk reduction must include the identification and removal of the root causes, which have produced it and the development of corrective/improvement actions for its compression, using multidimensional process analysis tools for the construction of safe and reliable systems.

To further support this, the new version of ISO 9001:2015 in fact makes risk management an explicit requirement, embedding it in every part of the document to ensure that organisations learn risk-based thinking right from the start.

For all hospital processes, therefore, the analysis of risks and opportunities based on internal and external factors and conditions that can affect the achievement of expected results becomes indispensable.

Managing risk also means acting for permanent improvement and personnel skills represent a key element in this sense; therefore, the objective of improving the practice of managing drugs safely can be pursued by experimenting with the risk assessment system, in order to increase operators' awareness of their work and evaluate any obstacles encountered which, in some cases, prevent the achievement of optimal performance.

Finally, we would like to recall some highlights of the European declarations of hospital pharmacy which, in representing the profession, can help to achieve better results for patients and which can be found at the following link: https://statements.eahp.eu/statements/final-statements#final_statement-block_1-4.

Now focusing the attention in the various sections and some important aspects in the sections themselves we have:

Section 5 https://statements.eahp.eu/statements/final-statements#final_statement-block_1-4

Patient safety and quality assurance

Section 5

Patient Safety and Quality Assurance

Statement 5.1

"The "seven rights" (the right patient, right medicine, right dose, right route, right time, right information and right documentation) should be fulfilled in all medicines-related activities in the hospital."

This is not an exhaustive list of 'rights' and with the increase in use of personalised medicines the 'right patient' has an additional meaning beyond just identification of the individual, it is also now whether the medicine is genetically appropriate for that individ- ual patient

Statement 5.2

"Hospital pharmacists should ensure the development of appropriate quality assurance strategies for medicines use processes to detect errors and identify priorities for improvement."

Statement 5.3

"Hospital pharmacists should ensure their hospitals seek review of their medicines use processes by an external quality assessment accreditation programme, and act on reports to improve the quality and safety of these processes."

Statement 5.4
"Hospital pharmacists should ensure the reporting of adverse drug reactions and medication errors to regional or national pharmacovigilance programmes or patient safety programmes."

Statement 5.5
"Hospital pharmacists should help to decrease the risk of medication errors by disseminating evidence-based approaches to error reduction including computerised decision support.."

Statement 5.6
"Hospital pharmacists should identify high-risk medicines and ensure appropriate procedures are implemented in procurement, prescribing, preparing, dispensing, administration and monitoring processes to minimise risk."

Statement 5.7
"Hospital pharmacists should ensure that the medicines administration process is designed such that transcription steps between the original prescription and the medicines administration record are eliminated."

Statement 5.8
"Hospital pharmacists should ensure accurate recording of all allergy and other relevant medicine-related information in the patient's health record. This information should be accessible and evaluated prior to prescription and administration of medicines.."

Ensuring there is comprehensive record- ing of allergies is a responsibility of all professionals within the multidisciplinary team. Hospital pharmacists should share this responsibility where there is no aller- gy record for a patient.

Statement 5.9
"Hospital pharmacists should ensure that the information needed for safe medicines use, including both preparation and administration, is accessible at the point of care."

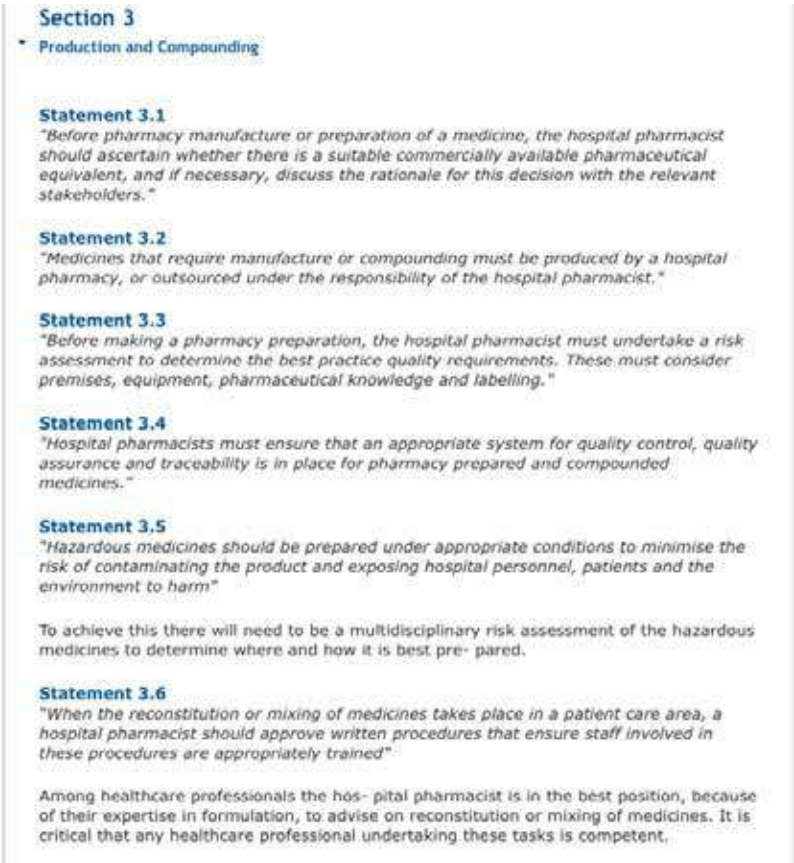
Statement 5.10
"Hospital pharmacists should ensure that medicines stored throughout the hospital are packaged and labelled so to assure identification, maintain integrity until immediately prior to use and permit correct administration."

Statement 5.11
"Hospital pharmacists should support and implement systems that allow traceability of all medicines dispensed by the pharmacy."

Declaration 5.2
"Hospital pharmacists should ensure the development of appropriate quality assurance strategies for medicines using processes **to detect errors and identify priorities for improvement**".

Section 3 https://statements.eahp.eu/statements/final-statements#final_statement-block_1-4

Production and Compounding



Section 3

Production and Compounding

Statement 3.1
"Before pharmacy manufacture or preparation of a medicine, the hospital pharmacist should ascertain whether there is a suitable commercially available pharmaceutical equivalent, and if necessary, discuss the rationale for this decision with the relevant stakeholders."

Statement 3.2
"Medicines that require manufacture or compounding must be produced by a hospital pharmacy, or outsourced under the responsibility of the hospital pharmacist."

Statement 3.3
"Before making a pharmacy preparation, the hospital pharmacist must undertake a risk assessment to determine the best practice quality requirements. These must consider premises, equipment, pharmaceutical knowledge and labelling."

Statement 3.4
"Hospital pharmacists must ensure that an appropriate system for quality control, quality assurance and traceability is in place for pharmacy prepared and compounded medicines."

Statement 3.5
"Hazardous medicines should be prepared under appropriate conditions to minimise the risk of contaminating the product and exposing hospital personnel, patients and the environment to harm"

To achieve this there will need to be a multidisciplinary risk assessment of the hazardous medicines to determine where and how it is best pre- pared.

Statement 3.6
"When the reconstitution or mixing of medicines takes place in a patient care area, a hospital pharmacist should approve written procedures that ensure staff involved in these procedures are appropriately trained"

Among healthcare professionals the hos- pital pharmacist is in the best position, because of their expertise in formulation, to advise on reconstitution or mixing of medicines. It is critical that any healthcare professional undertaking these tasks is competent.

Statement 3.1
"Before manufacturing in a pharmacy or preparing a medicine, the hospital pharmacist should ascertain whether there is a suitable commercially available pharmaceutical equivalent and, if necessary, discuss the rationale for this decision with the interested parties".

Statement 3.3
"Before preparing a pharmacy, the hospital pharmacist must undertake a **risk assessment** to determine the quality requirements for best practices.

These must consider premises, equipment, pharmaceutical knowledge and labelling".

Statement 3.4
"Hospital pharmacists need to ensure that an appropriate system is in place for **quality control, quality assurance** and traceability for prepared drugs and pharmacy-prepared drugs.

Section 6 https://statements.eahp.eu/statements/final-statements#final_statement-block_1-4

Education and Research


Section 6

Education and Research

Statement 6.1
"Undergraduate pharmacy curricula should include an introduction to hospital pharmacy practice. The role of hospital pharmacists should be promoted in the curricula of other health professionals."

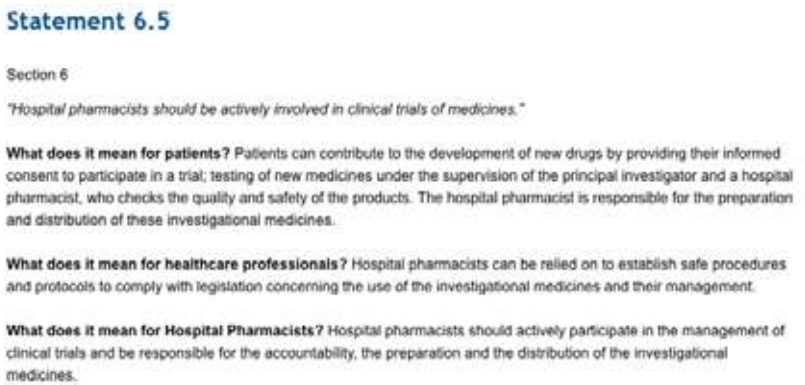
Statement 6.2
"All those involved in medicines use processes must be able to demonstrate their competency in their roles. Hospital pharmacists should participate in the development of European-wide competency frameworks to ensure standards of best practice are met."

Statement 6.3
"A European-wide framework for initial post graduate education and training in hospital pharmacy with an assessment of individual competence is essential. In addition, hospital pharmacists should engage in relevant educational opportunities at all stages of their career."

Statement 6.4
"Hospital pharmacists should actively engage in and publish research, particularly on hospital pharmacy practice. Research methods should be part of undergraduate and postgraduate training programmes for hospital pharmacists."

Statement 6.5
"Hospital pharmacists should be actively involved in clinical trials of medicines."

Statement 6.5
"Hospital pharmacists should **actively participate in clinical trials** of medicines".



Statement 6.5

Section 6

"Hospital pharmacists should be actively involved in clinical trials of medicines."

What does it mean for patients? Patients can contribute to the development of new drugs by providing their informed consent to participate in a trial; testing of new medicines under the supervision of the principal investigator and a hospital pharmacist, who checks the quality and safety of the products. The hospital pharmacist is responsible for the preparation and distribution of these investigational medicines.

What does it mean for healthcare professionals? Hospital pharmacists can be relied on to establish safe procedures and protocols to comply with legislation concerning the use of the investigational medicines and their management.

What does it mean for Hospital Pharmacists? Hospital pharmacists should actively participate in the management of clinical trials and be responsible for the accountability, the preparation and the distribution of the investigational medicines.

There are several factors that influence risk in Oncological Galenical Laboratories and for which a risk assessment can be strategic.

In the field of clinical trials, and in particular the management of the experimental drug, there are, for example, various aspects that make the process more complicated than in clinical practice (lack of drug information, poorly differentiated packaging, procedures required often complex and redundant).

In this field, it can be very important to analyse risks and hypothesise solutions to strengthen the weakest points. Unfortunately, however, the pharmacist's field of action in this context is limited to possible changes in internal procedures, but he is hardly ever able to address changes in procedures requested by the sponsor.

Another relevant aspect in galenic laboratories is the microbiological aspect of the preparations.

The variables that impact on the quality of the productions set up are many and are both of a technical, organisational and structural nature. The organisation of an effective and efficient management system, which guarantees the continuous control and traceability of the work performed, responds to the fundamental need to safeguard the health of the patient and also of the operator who sets up.

Only a systemic vision in which the pharmacist plays a proactive and conscious role enables the healthcare organisation to assess the quality of the preparation process, providing guidance to Pharmacist, prescribing physician, Company Health Management and other stakeholders in the quality of the products prepared and distributed.

The punctual application of the NBPs is also increasingly crucial in view of the growing focus on the centralisation of set-ups with a view to process

efficiency, cost containment and risk management. As already mentioned, risk management is an element required by the various certification and accreditation models.

Processing sterile products requires special techniques to minimise the risk of contamination from microbial agents, pyrogens or particles. To guarantee quality, in this type of preparation, it is necessary not only to strictly adhere to carefully defined and validated procedures and work methods, but also to pay particular attention to the preparation rooms, skills and behaviour of the personnel involved.

In the Galenic Laboratories, a Self Assessment with respect to the Standards of Good Preparation (NBP) is therefore desirable where the tools include "Guidelines, best practices, recommendations (for example, in the case of oncology, Ministerial Recommendation No. 14 "Recommendation for the prevention of errors in therapy with antineoplastic drugs", check lists and other safety tools" and standards of scientific societies such as the Technical Standards of Oncological Galenics - National Oncological Area of SIFO 2012-2016.

In some Italian realities, where a multidisciplinary operational project on the management and reduction of clinical risk in Oncology-Haematology has already been conducted, certain goals have been objectively achieved, such as:

- developing compliance withISO9001:2015 and accreditation requirements on operational risk management;
- applying a methodological approach to conduct a self-assessment on the application of NPBs and assess operational sustainability;
- identifying priority areas for improvement on which to develop shared actions and/or practices for risk reduction.

This made it possible to **identify the priority areas of intervention**, often already known to the professionals involved in the process, but with a systemic vision within the institution. The priorities for intervention concerned: qualifications, skills and responsibilities; procedures and instructions; equipment; periodic environmental controls; instructions, controls; transport; procedures in the event of a technological emergency; reception and take-over in the care unit; self- inspections.

The purpose of the work was not to provide the premises for making comparisons between structures but to provide an overview of the results within the organisation in order to have a "participatory snapshot" as it emerged from the multi-professional work team. Moreover, the experience could be developed in different regional and/or national contexts and could provide useful indications regarding the priority themes of intervention

common to several organisations in order to define/codify unique effective and sustainable response methods.

Below are two slides illustrating both a schematic and graphical representation of a Self Assessment that was carried out in a typical facility-laboratory, which allowed corrective and improvement actions to be set up, based on the points and findings that were below average as a rating.

The results of the assessment

Overall average: 3.6

Macro requirements	Average
1. Quality Management in Pharmacy	3.9
2. Personnel	3.5
3. Personnel	3.3
4. Documentation in the Pharmacy	4.0
5. Raw materials	4.0
6. Preparation operations	3.2
7. Quality control of the preparation	3.7
8. Packaging and labelling	4.0
9. Reconciliation, Distribution and Delivery	3.4
10. Closing operations	4.0
11. Stability of the preparation	4.0
12. Microbiological aspects of preparations	3.5
13. Prescribing and Formulation Software	4.0
14. External Contracts	na
15. Self-inspections	2.0
16. Complaints and Defects	4.0
	3.6

In red text the priority macro-requirements (below average)

The possibility of including this testimony in this Manual of High Specialisation in Clinical Trials constitutes evidence of how one can align oneself with good organisational practice with a view to guaranteeing the quality and safety of care and defining the responsibilities of the multidisciplinary team that will have to work for the patient in full respect of the principle of reliance, that is, the legitimate trust that each member of the team places in the diligent and competent performance of the others.

Normative requirements

- Official Pharmacopoeia current edition and related updates.
- StandardISO9001:2015.
- Ministerial Recommendations on drugs.
- Technical Standards of Oncological Galenics - SIFO National Oncology Area 2012-2016

Module II: Research Pharmacist

Preface

Edited by the Scientific Tutors A. Filippelli, C. Polidori, P. Abrate, M.E. Faggiano, B. Meini, A. Costantin, B. Rebesco

European Regulation (EU) no. 536/2014 on clinical trials for medicines of human use came into force on 31 January 2022. Now is the time to fill it with content, to make the reality of Clinical Research in Italy, adhere to it, recognize the criticalities contained in it so that the transition to this new rules would it be simple and useful as possible to our National Health Service (SSN).

In this context it becomes very important to adapt quickly and, as always, SIFO was ahead of its time and – involving many personalities from the world of clinical research in Italy – allowed the creation of this module within the manual which will certainly help hospital pharmacists and territorial pharmaceutical services to move towards the "new" figure, at least for the Italian scientific panorama, of the "Research Pharmacist".

The main objective of the regulation is to ensure safety of those participating in clinical trials in a context of harmonization of clinical trials procedures in Europe. Who more than the pharmacist, therefore, who has always been involved in the promotion of prescribing appropriateness, therapeutic adherence, pharmacovigilance, pharmacoeconomics, etc. can promote clinical studies by organizing the so-called Real World Data (RWD)?

The International Society for Pharmacoeconomics and Outcomes Research, defines RWDs as data "that are collected outside of traditional interventional controlled clinical trials under real-life circumstances". The various sources of RWD include the flows of territorial pharmaceuticals prescriptions; the provision of pharmaceutical assistance in direct distribution; the AIFA monitoring registers of innovative and/or high-cost drugs; hospital discharge forms; patient access to the emergency room; outpatient services; the ISTAT (Italian institute of Statistic) and Istituto Superiore di Sanità (Higher Institute for Health) surveys and noninstitutional sources. Collecting RWDs brings Real World Evidence to life (RWE) which does not contradict, but complements the Evidence Based Medicine (EBM).

The AIFA monitoring registers represent an important example source of RWD/RWE. Over the years they have assumed a dual value; first becoming not only an instrument of prescriptive appropriateness and second as regulatory and economic instrument, representing a methodological revolution in the reimbursement of new drugs by the Italian NHS: they allow the effectiveness of the drug to be assessed (real effectiveness), make

possible the comparison between the efficacy found during the registration studies and that evaluated in a real world, focusing also on cost/ effectiveness assessments necessary to ensure sustainability of the Italian NHS. The possibilities that the pharmacist can seek in this area of pharmacoeconomic results are many and useful for the actions implemented by the regulatory structures.

Analysis of suspected adverse drug reaction (ADR) reporting streams also generates RWD/RWE, and this too is a field that can and should be update. Indeed, it is essential that the risk "signal" for a particular treatment does not derive solely from spontaneous reports collected in the National Pharmacovigilance Network, but that it can come from a careful analysis of the data deriving from the many administrative flows that are collected every day, taking advantage of the possibilities that Mission 6 of the PNRR (EU funds for next generations dedicated to health measures) brings to life. "Proximity networks, new patient facilities, telemedicine for national health care", should also offer to pharmacists new opportunities for the NHS. Pharmacovigilance activities aim to evaluate the risk/benefit ratio of drugs in the general population, after their placing on the market. This ratio can change over time. Identifing the existence of risk factors help us to recognize ADRs, to estimate the incidence of an already known and/or rare ADRs; to improve knowledge on ADRs and communicate information to both healthcare professionals and citizens. Therefore, the NHS pharmacist can intervene, qualitatively and quantitatively improving ADR reporting, as promoter of ad hoc studies due to the privileged position he occupies both in hospital direct distribution meeting patients and by interacting with healthcare professionals.

Moreover, the registration studies bear by themselves different biases during drug evaluation. The selected population is not always representative of the general population because some groups are generally excluded (women, children, the elderly, etc.) and for a matter of small sample size. For this reason, RWDs, collected only after a drug has been placed on the market, when it is used by the general population, can be an essential source of clinical research.

Furthermore, the health emergency from Covid-19 has made it necessary to rethink the organization of the NHS, for which telemedicine and the use of digital health tools have had a strong influence in the management of health. RWDs were therefore conducted for post-marketing research, or with clinical outcomes, using some digital tools (also wearable) for the recording and archiving of patient data and the subsequent possibility of integration and connection to the various databases. With these assumptions it will be

possible for the Pharmacist of Research to develop Decentralized Clinical Trial (DCT) with the involvement also of general practitioners.

The task of the Research Pharmacist, in interfacing with all these sources, will be to know how to analyze the many sources and help design a clinical study in order to obtain RWE useful for improving clinical-therapeutic practice for an increasingly effective use of medicines and for proper pharmaceutical governance.

Over the last twenty years, the training of the resident in Hospital Pharmacy has undergone constant changes which have made it possible to outline, among other things, the potential of the resident as a future Pharmacist of Research.

Among the multiple areas of expertise of the hospital pharmacist, clinical research occupies a consolidated role and requires a constant contribution of resources especially in the field of specialistic training innovations.

The current specialized training in Hospital Pharmacy starts from an initial basic training of trainees on the management and structural organization of hospitals and local pharmaceutical services. It occurs through structured and professionalizing teachers that allow trainees to access the clinical pharmacy experience. The "clinical area" is a way of maturing the skills to interact with various healthcare professionals in order to acquire the ability to independently plan critical evaluations of data analysis and preparing them for a scientific publication.

The specialist training in the clinical field is developed across the entire training course in order to make the trainee acquire awareness of the responsibility he will have to assume in synergy with other healthcare professionals and in particular on the appropriateness of the pharmacological treatment of patients and in therapeutic monitoring useful for dosage adjustment aimed at improving the quality of therapy. The skills in this area can be acquired through courses that address the main clinical therapeutic areas of the most common pathologies such as the related laboratory diagnostic, pharmacokinetics, pharmacotherapy, pharmacogenetics and biostatistics data. The resulting gain in terms of pharmaceutical patient care involves the acquisition of personal communication skills in order to be able to carry out a proper effective patient pharmacological history, identifying the patient's real need of informations on the prescribed drug.

In the context of training in the clinical field, the acquisition of pharmacoepidemiology and consumption analysis skills oriented towards the monitoring of prescriptions in terms of appropriateness and analysis of consumption data points to at defining the annual budget for the hospital departments and appears to be essential for hospital and general practitioners.

The synergistic development of the training disciplines is aimed at laying the foundations for acquiring skills for the implementation of clinical trials of medicines and medical devices, such as the methodology for evaluate and authorize clinical research protocols in an application context of the rules of good clinical practice.

The acquisition of skills in the economic evaluation of the rational use of drugs and medical devices and of the principles of Health Technology Assessment, associated with that Risk-Assessment judgement is another important resource in clinical education. In particular, in the field of clinical risk management, the pharmacist plays an indispensable role in the recognition, prevention and monitoring of errors in therapy, as he is trained in the preventive and retrospective analysis of the types of error and their consequences.

The training framework outlined up to now bears witness to the potential of the specialist pharmacist in carrying out research activities institutionally envisaged by the training plan of the School of Specialization in Hospital Pharmacy.

The vast training in the clinical field is aimed at the maturation of the trainees being aware that each professional step is possible to qualify one's own assistance intervention. That occurs through an interdisciplinary evaluation process shared with other healthcare operators of the situations faced, from which it can emerge not only the hypothesis but the need to participate in targeted research programs and projects. In summary, this clinical care training course is aimed at creating a scientific mentality needed for doing clinical research. It is a guideline for the constant improvement of the hospital pharmacist in the management of patients, for the evaluation of the safety and efficacy of medicines and for the quality of pharmacoepidemiology and Pharmacoeconomics studies that he will be doing.

1. The point of view of the Schools of Specialization in Hospital Pharmacy on the Research Pharmacist, potential and prospects: data and performance indicators in Clinical Pharmacy

N. Realdon, C. Cifani, F. Bartolini, G. Scroccaro

Over the last 20 years, the specialist training ship in hospital pharmacy has undergone constant changes which have made it possible to outline, among others, the potential of the trainee as a future Research Pharmacist.

Among the many areas of competence of the hospital pharmacist, research, especially clinical research, has a consolidated role and requires a constant supply of resources and innovation in the field of specialist training ship.

The current specialist training course in Hospital Pharmacy moves from an initial basic training on the management and functional organization of hospitals and territorial pharmaceutical services, passes through structured and professionalizing courses that allow them to access clinical pharmacy, and then definitively arrives at the clinical area developing the ability to interact with various healthcare professionals in order to acquire the ability to autonomously plan critical evaluations and analyzes of data, preparing them for scientific publication.

Specialist training in the clinical field is developed throughout the entire training course to make the trainee aware of the responsibility he will have to assume, in synergy with other healthcare professionals, in terms of the appropriateness of the pharmacological treatment of patients and in therapeutic monitoring useful for dosage adjustment aimed at improving the quality of therapy. Skills in this area can be acquired through courses that address the main clinical therapeutic areas of the most common pathologies, the related laboratory diagnostic data, biopharmaceuticals and pharmacokinetics, pharmacotherapy, pharmacogenetics, and biostatistics. The consequent fallout in terms of pharmaceutical assistance for patients involves the acquisition of personal communication and interaction skills in order to be able to carry out a correct and effective pharmacological history by identifying the patient's real need for information on the drug.

In the context of clinical field, the acquisition of pharmacoepidemiological and consumption analysis skills appears to be aimed at monitoring

prescriptions in terms of appropriateness and analyzing consumption data from a clinical-epidemiological point of view, also oriented towards the definition of budget of hospital departments and general practitioners.

The synergistic development of the training disciplines is aimed at acquiring skills for the implementation of clinical trials of medicines and medical devices, such as the methodology for testing, evaluation, and authorization of clinical research protocols in a context of application of the rules of good clinical practice.

The acquisition of skills in the economic evaluation of the rational use of drugs and medical devices and the principles of Health Technology Assessment, associated with the Risk Assessment, represents another important resource in clinical training. In particular, in the field of clinical risk management, the pharmacist plays an indispensable role in the recognition, prevention, and monitoring of errors in therapy, as he is trained in the preventive and retrospective analysis of the types of error and its consequences.

The training framework outlined until now bears witness to the potential of the specialist pharmacist in carrying out research activities institutionally envisaged by the training plan of the School of Specialization in Hospital Pharmacy.

The wide training in the clinical field is aimed at the maturation by the specialists of the awareness that in each professional step it is possible to qualify one's own assistance intervention through an interdisciplinary evaluation process shared with other healthcare operators of the situations faced, from which it can emerge not only the hypothesis but the need to participate in targeted research programs and projects. In summary, the clinical care training course is aimed at creating a scientific mentality aimed at clinical research, as a guideline for the constant improvement of patient management, the evaluation of the safety and efficacy of medicines, and the quality of pharmacoepidemiology and pharmacological economics.

Creating a common and shared culture between the various health professions has always been a fundamental principle that fits into the various activities of the National Health System.

It is at least appropriate if not essential that, in the light of the new condition of the National Health Service (SSN) (NHS), the training path of the SSN (NHS) pharmacist includes specific professional paths which allow the acquisition of a sectorial and specialized competence such as to offer, in each sector, a very high degree of professionalism.

In this regard, new experiences are and must be created, new professional paths but above all strategic experiences for the future, where the concept

of the pharmacist who simultaneously deals with several sectors must be overcome and instead the specialization in specific areas is strengthened. Continuous training and innovative projects focus on the pharmacist, highly trained thanks to new professional paths, able to form multidisciplinary groups aimed at developing new innovative projects within healthcare companies.

Among these sectors we find the interpretation of data, monitoring, evaluation of outcomes and evaluations on how the various health technologies (from drugs to medical devices) impact the care process. The simple evaluation of the use of the various healthcare assets is no longer enough but data and outcomes need to be analyzed in depth, and in this process the NHS pharmacist will have to place himself at the centre, as a point of reference.

In order to do this, the pharmacist must increasingly specialize in the various fields of specific competence. It is precisely from this ambition that the need arises to establish training courses and consequent projects to be implemented at a national or at least regional level.

The high specialization deriving from the different national and regional realities, through a path of communication and sharing of the different sectors dealt with, allows, through this network of experiences, to obtain a unitary value which each Region can use.

All this ideally goes to generate internal structures with dedicated personnel, also external and/or private.

It was therefore intended to build on the one hand a specific training path and on the other the development of a project where to concretize what the National Health Service requests, that is, the pharmacist trained to coordinate this revolutionary process of growth.

An initial opportunity for training and discussion between the Regions was thanks to the two Theoretical-Practical Courses held in Assisi in 2020 and 2021, where the professional figures at the centre of patient care were involved and in which the foundations have been laid for the project of prescribing appropriateness and therapeutic adherence.

A path has been proposed with the monitoring of prescriptive appropriateness at the centre, involving the top national experts in the sector in the two theoretical-practical courses held in Assisi, with the aim, in the future, of going beyond the monitoring of drugs alone, i.e. measuring the performance of all health technologies.

The idea of the Theoretical-Practical Course in Clinical Pharmacy was intended to create a valuable opportunity for discussion between NHS pharmacists (SIFO) and the Regions, through the exchange of experiences

and the elaboration of proposals, in order to identify performance indicators valid and usable at national level.

Prescriptive appropriateness and therapeutic adherence are indispensable for the safety and efficacy of pharmacological treatments, determining an efficient allocation of resources by the National Health Service. The conception and implementation of the theoretical-practical course of Assisi, started from the need to identify and analyze data and performance indicators in Clinical Pharmacy, discovering a shared path that can be implemented at a national level. Any monitoring of the consumption of medicinal products cannot disregard the analysis of the profiles of appropriateness of use, through the identification of suitable indicators to synthesize the prescriptive choices of the doctor and the methods of use of the drug by the patient.

Prescribing appropriateness indicators are specific and measurable elements of clinical practice, developed on the basis of solid scientific evidence and used as a unit of measurement of the quality of care. Among the indicators of adherence to the prescribing methods are those relating to the modalities of use and to the therapeutic indications of the drugs. They are aimed at identifying as inappropriate a use of medicines carried out outside the recommendations for which their efficacy has been tested or reimbursed, in order to bring about a change of perspective in the measurement and evaluation of the prescribing appropriateness with respect to the indicators of consumption. For this reason, an approach based on Real World Evidence (RWE) and Health Technology Assessment (HTA) is essential, where health data is the protagonist of the new pharmaceutical governance.

A drug prescription can be considered appropriate if made within the clinical indications for which the drug has been demonstrated to be effective and, more generally, within the indications for use (dose and duration of treatment), so as to avoid overuse and lack of therapeutic adhesion, especially in elderly patients and/or undergoing polypharmacy. There are currently several tools for the government of prescriptive appropriateness:

- Application of the contractual agreements (Managed Entry Agreements);
- Drug Monitoring Registries;
- Therapeutic Plans and related management tools (IT platforms);
- AIFA notes on the appropriate use of medicines;
- Information and training (prescribers, patients);
- Processing of data and indicators;
- Systematic audits with prescribers.

In this panorama, the figure of the NHS pharmacist is central in monitoring the appropriateness of prescribing through the search for solid, usable and comparable data which today represent a key tool in healthcare planning.

Specializing in specific areas, this is what the pharmacist must do, with the help of a multidisciplinary team, in order to be able to enter the world of appropriateness monitoring and evaluation of the outcome. Close collaboration with the IT personnel is also necessary, essential for correct data processing, but also with professionals with statistical and clinical skills to share the interpretation of the data.

During the two courses held in Assisi, a model for the analysis and management of prescriptive appropriateness was developed and shared. A project has been defined which leads to the activation of a data evaluation cycle and the definition of interventions aimed at promoting appropriateness.

The Process has been defined as:

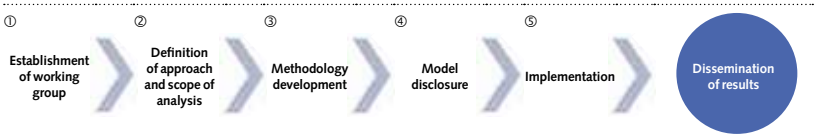
1. Data collection;
2. Methodology application;
3. Input of a regional/company dashboard and data evaluation
4. Indications for clinicians, payers and institutions.

This model allows you to:

- Measure the adequacy of drug therapies used to treat a specific pathological state, based on clinical and economic criteria;
- Increase awareness of regional institutions and prescribers about the relevance of active policies for prescribing appropriateness;
- Promote a better use of the economic resources available in the NHS;
- Promote information to patients on the relevance of adhesion to therapies.

The development path of the model involved 5 phases:

- Creation of a multidisciplinary working group, at regional or company level;
- Definition of approach and scope of analysis:
- Development of methodology for data analysis and assessment of prescriptive appropriateness and definition of organizational requirements;
- Divulgation of the theoretical model and requirements for implementation;
- Regions/ASL for implementation of the model in a pilot context.



1. Constitution of the working group

The first phase of the model developed involved the formation of multidisciplinary working groups where the following were involved:

- Coordinators of GP groupings (AFT), if referring to non-specialized drugs;
- the Director of the Department or of a Clinical specialist for departmental area (medical area, surgical area...) if referring to prescriptions of drugs that require a therapeutic plan or prescription of the specialist;

At this point, in the various working groups, the professional figures necessary for carrying out the activities were defined (e.g. pharmacist, HTA experts, statistician, etc.), involving scientific societies when necessary. For the analysis and processing of data, the collaboration of external companies/institutions may be required, but also a team of experts in setting up the board.

2. Definition of approach and scope of analysis

In the second phase, the working group evaluated the analysis method and approach, such as the choice between applying a bottom-up or top-down approach. The Bottom-up method involves choosing a therapeutic area in which to define an analysis methodology and then defining a general analysis model to be replicated on the other therapeutic areas. On the contrary, the Top-down methodology defines a general theoretical model of analysis to be calibrated and applied to each therapeutic area.

3. Development of methodology for data analysis and evaluation of prescriptive appropriateness

In this part of the process it was essential to define the analysis criteria and the correlation with the various indications of use and/or clinical outcomes. To do this, it was necessary to identify the right reference flows from which to obtain what is necessary to feed the analysis model.

The flow of the agreement provides us with information relating to the prescriptions of general practitioners, while that of the DPC, direct distribution and hospital consumption, data on specialist prescriptions are obtained. You also need to define the frequency and depth of analysis.

At this point, the indicators for monitoring the appropriateness depending on the flow considered were identified, as well as the organizational requirements and the skills necessary for the establishment of the regional/company unit for the evaluation of the prescriptive appropriateness were evaluated.

During these two Courses mentioned above, some indicators were developed for monitoring the appropriateness of the prescriptions of general practitioners in relation to:

◊ **antihypertensives:**

- Percentage of patients started on treatment with antihypertensive drugs in fixed combination with calcium channel blocker that do not come from the same active ingredients in extemporaneous combination;
- Percentage of patients treated with antihypertensive drugs in extemporary combination with a calcium channel blocker who are not switched to the fixed combination.

◊ **COPD:**

- Percentage of patients with exacerbations on ICS treatment;
- Percentage of patients on ICS LABA fixed combinations treatment who do not result from adequate LABA therapy;
- Percentage of patients receiving ICS without exacerbations;
- Percentage of patients on treatment with drugs for obstructive airway syndromes adhering to treatment;
- Percentage of patients on COPD medications without spirometry confirmation.

◊ **Drugs acting on lipids:**

- Percentage of patients initiated on ezetimibe monotherapy who are not intolerant to statins;
- Percentage of patients started on Ezetimibe combination treatment who are not off adequate statin therapy;
- Percentage of patients on statin treatment adhering to treatment
- Percentage of patients with previous cardiovascular event treated with statins;
- Percentage of patients over 80 on statin treatment without a previous CV event or diabetes.

Wanting to analyze the flow of DPC and direct distribution, in relation to the prescriptions of specialist doctors regarding rheumatology, gastroenterology and dermatology, the following indicators are:

- Percentage of patients started on treatment with biological drugs that do not come from adequate therapy with DMARDS (excluding patients with contraindications to the use of DMARDS);
- Percentage of patients started on biologics with an anti-TNF alpha;
- Percentage of patients treated with off-patent anti-TNF alpha in biosimilar or lower cost formulation;
- Percentage of patients started on treatment with off-patent anti-TNF-alpha.

4. Model Disclosure

We have therefore arrived at the dissemination of the model which can take place through workshops with Regions/ASL (Local Health Company) and with central institutions and the publication of the same after the collection of feedback.

5. Implementation of the pilot model

What was developed during the courses was a starting point to then define a path to be shared with the Local Health Authorities/Hospitals and therefore with the Regions, in order to ensure its implementation. Being a first model, it was applied in a pilot context in order to test the results and possibly update the methodologies.

It is useless to reiterate the importance of arriving at an integrated work between the various experiences developed in the various Regions/ Companies.

Once the key points of this project had been analysed, it was necessary to identify the operational and organizational methods at regional/company level to define the timing and methods of the audits with the prescribing clinicians. Also in this case it was essential to find the critical success factors, which are clear and easily assessable.

At the centre of the whole process there is always the sharing of the various regional experiences for the purpose of a comparison aimed at the exchange of experiences and the elaboration of proposals to identify valid and usable performance indicators at national level and the possibility of implementing methods of collaboration interregional networks (network system).

Once again the pharmacist will be able to seize the opportunities that the new frontiers of medicine will offer him, among these, of particular interest is the sector relating to Oncology and Hematology.

In this, the pharmacist will be able to make his professional skills available in an organizational model for gene therapies and precision oncology: the Molecular Tumor Board (TMB), the Next Generation Sequencing Centres (NGS) and the genomic platform.

In relation to this, it is essential to build specific multidisciplinary and highly specialized training courses, and it is desirable that some Regions take charge of them.

2. Biostatistical bases for the realization of an Experimental Clinical Study

F. Carle, M. Iommi

Introduction

The purpose of the chapter is to introduce the reader to biostatistical and epidemiological methods in a study protocol for drug evaluation, with particular emphasis on the characteristics and critical aspects of the experimental study design when the unit of observation is the human subject.

Clinical research is ethical only if the Human Society derives a health gain from the results it produced [1]. In order for this to be possible, it is necessary for the studies to be conducted according to a strict scientific methodology, i.e. according to criteria and rules that are declared, clear and shared by the scientific community which make possible the inter-subjective control of the results and conclusions of the study, thus guaranteeing their scientific objectivity [2].

Several authors, including the English statistician DG Altman [3], have reiterated that it is unethical to conduct a study that does not have solid scientific basis because:

- It exposes patients to unnecessary risks and inconveniences;
- It wastes resources and time that could be spent on more useful activities in the health sector;
- It publishes results that could be erroneous and misleading, and which may direct research towards subsequent unnecessary studies.

Statistical methodology is an integral part of scientific methodology, applied in clinical research and, more generally, in healthcare. The phenomena being studied in these fields are in fact complex phenomena (such as the natural history of a certain disease and the efficacy and the effectiveness of a certain therapeutic treatment), for whose analysis and understanding a single observation is not sufficient. The finding of death in a patient with an influenza infection, for example, certainly cannot lead to affirming that this pathology is lethal every time it occurs.

Furthermore, the true nature of these phenomena can only be hypothesized, since it is not possible to observe them in their entirety. The efficacy of a hypotensive drug cannot be assessed by considering all hypertensive subjects (the target population of the study), but only by administering the drug to a certain number of hypertensive subjects (a sample of the target population). The results obtained from the analysis of the sample will then be used to draw

indications about the treatment of all hypertensive subjects, even if it was not possible to study them individually.

The study of complex phenomena, the object of clinical research, therefore requires the observation and analysis of a number of simple phenomena: the signs and symptoms that repeat in a similar way in different subjects allow to identify diagnostic categories through which the disease is defined; it is also necessary to be able to make inferences, i.e. to extend the results obtained on small groups of individuals to all subjects with the same characteristics.

Statistics provides the methods for appropriately detecting and analyzing individual observations and for, from partial data, evaluating and generalizing hypotheses and making predictions [4].

Uncertainty control: precision and accuracy of sample results

All studies evaluating a therapeutic treatment are conducted by considering a group of individuals (sample) and generalizing the results obtained to all patients with similar characteristics to those of the subjects analyzed (population).

In reality, the result observed by analyzing the sample represents only an estimate of the phenomenon being studied (e.g. the effectiveness of a new drug compared to conventional therapy) which will be closer to the real phenomenon the more accurate the estimation process is, that is, i.e. the more errors that make the efficacy observed in the sample different from the real efficacy of the drug will be reduced.

Figure 1 reports the summary results of 24 randomized trials that estimated the efficacy of fibrinolytic therapy in acute myocardial infarction in reducing the risk of death [5]. The measure of association used is the odds ratio (OR) and its 95% confidence interval (95% CI). The OR can be interpreted as a relative risk: if the OR value is less than 1 (represented in the figure by the vertical solid line) then the administration of the drug reduces the risk of death; conversely, if it is greater than 1, administration of the drug increases the risk of death.

For each study, the value of the point estimate, i.e. the value of the odds ratio measured in the sample of treated patients (fibrinolytic group) and in the control group (control group), is shown with a small square, larger or smaller depending on the number of patients enrolled in the study.

The 95% confidence interval, represented by the horizontal bars for each study, is the measure of precision of the point estimate, i.e. how close the point estimate of efficacy is to the unknown true efficacy value of the drug in the population from which the sample was taken. The wider the confidence interval bar, the lower the precision of the estimate.

It is evident that the answer to the question "*can the therapy be considered effective?*" is characterized by great uncertainty. Medical statistics help us not to eliminate this uncertainty but to recognize its sources, measure it and control it.

The sources of uncertainty deviates the sample estimate from the real value, thus decreasing its precision and accuracy and can be classified into two types of error: random error and systematic error.

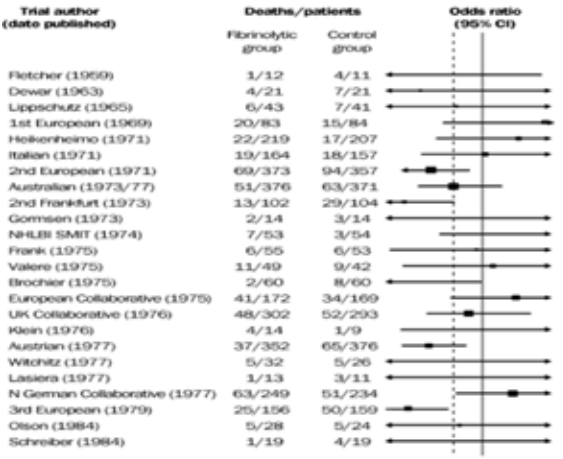


Fig. 1 – Efficacy of fibrinolytic therapy in acute myocardial infarction: results of 24 randomized experimental studies.

Precision of the estimate

The precision of a sample estimate indicates how much the values obtained with the same methodology in different studies converge towards the true value, for example the true efficacy of the drug.

The accuracy of the estimate depends on the control of the random error (Fig. 2). By random error we mean the measurement error resulting from unknown sources of variation that produce distortions in any direction and is substantially due to the fact that there is a part of the observed phenomenon that the researcher cannot expect to observe based on knowledge of the initials conditions [6].

Random error is also called sampling error, as it is the error that arises when a sample survey is carried out to describe a characteristic or a phenomenon of the population that cannot be directly observed.

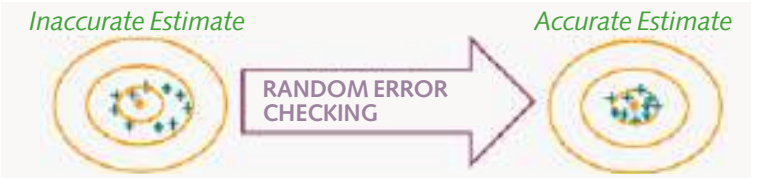


Fig. 2 – The precision of the estimate depends on the control of the random error (*the crosses represent the values of the sample estimates, the centre of the target represents the true value in the population*).

In figure 3, the population is represented by 100 deliveries (•) in the hospitals of the Marche region. The objective of the study is to estimate the percentage of induced deliveries (•); in the example it is assumed that the true value of the percentage of induced deliveries is known and equal to 20%.

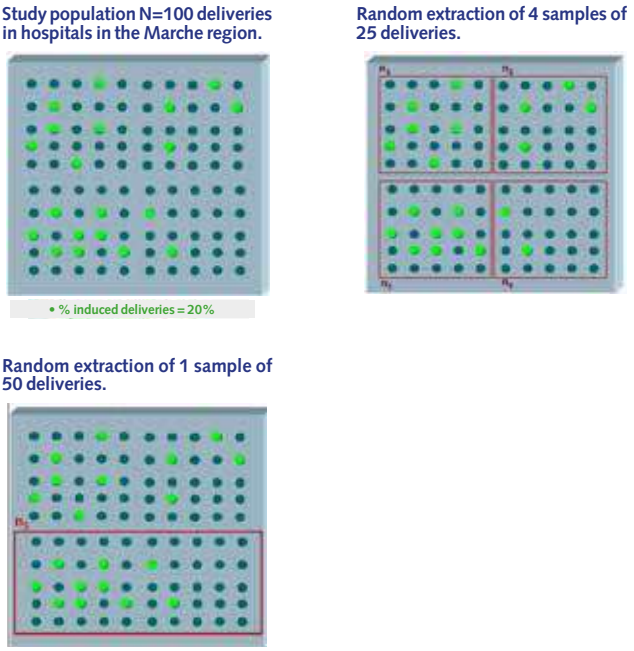


Fig. 3 – Estimation of the true value of the percentage of induced deliveries in the Marche Region through the random extraction of 4 samples of 25 deliveries.

To estimate the percentage of induced deliveries, 4 samples of size n=25 deliveries each are randomly selected. The estimate of the percentage of induced deliveries is 24% (6/25) in sample n_1, 16% (4/25) in sample n_2, 32%

(8/25) in sample n_3, and 8% (2/25) in sample n_4. The results are different from each other and different from the true value.

These differences are due to the non-homogeneity of the distribution of the phenomenon (induced deliveries) in the population (the green dots are concentrated in some areas of the space in the figure) and to the fact that the sample can be randomly be drawn from any point of the space representing the population, thus obtaining different results.

Considering a larger sample ($n_5 = 50$), the sample estimate coincides with the true value (20%, 10/50). The example aims to highlight that the random error depends on the variability of the phenomenon and on the sample size and can be controlled by defining the latter with an appropriate statistical methodology [7].

Accuracy of the estimate

The accuracy of a sample estimate indicates the ability of the study to measure the real phenomenon (e.g. drug efficacy) and depends on controlling for systematic errors that produce biased estimates of the phenomenon.

Estimation bias is generated by sources of variation that produce bias in only one direction; in the left target of figure 4, estimates produced with the same methodology in different studies are similar to each other but systematically far from the true value (centre of the target).

Fig. 4 – Estimation bias is reduced by controlling for systematic error (*the crosses represent the values of the sample estimates, the centre of the target represents the true value in the population*).

In the previous example (Fig. 2), whose objective was to estimate the percentage of induced deliveries in the Marche region, it was decided to extract the sample considering only the obstetric-gynaecological and paediatric hospital unit of Ancona (G. Salesi Hospital), since it comprises 40% of the deliveries in the Marche region (Fig. 5, blue triangle). By extracting a sample of $n_1 = 25$ parts, the % of induced parts is 32% and by increasing the sample size ($n_2 = 38$), the estimate is further away from the real value (34%). This is caused by the introduction of a selection bias, due to the fact that the G. Salesi hospital, being a regional reference hospital, attracts the most

complex pregnancy cases and therefore performs more induced deliveries than other hospitals in the region (31%).

Systematic errors are caused by the effect of factors associated with the study design, conduct, analysis and evaluation of the results of a study; this effect produces results and/or conclusions that are systematically different from reality [8]. These factors may consist of bias evaluations or personal choices of both those conducting the study and those participating in it. For example, the efficacy of a treatment may be underestimated if patients with lower risk of death are systematically assigned to the control group [9].

Systematic error is controlled in the design of the study, identifying possible selection bias and potential confounding factors, applying reliable methodologies for the collection of information, and appropriate data analysis methods for the control of bias.

The definition of the methodology for uncertainty control in experimental and non-experimental studies is an integral part of **the study protocol,** which is drawn up prior to the beginning of the study and guides its entire conduct.

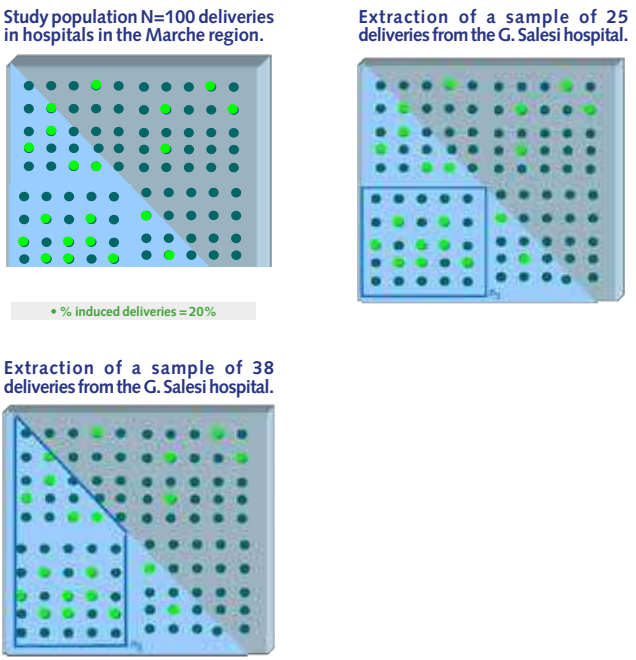


Fig. 5 – Estimate of the true value of the percentage of induced deliveries in the Marche Region, selecting the sample only from the G. Salesi Hospital of Ancona (.).

Experimental study design in the evaluation of drugs

In experimental studies to evaluate the efficacy of a treatment, the therapy is administered according to the objectives of the study in order to achieve them: if the study was not conducted, patients would not receive that particular therapy. In observational studies, on the other hand, the decision to prescribe a treatment (or exposure to a certain factor) is completely independent of the decision to include the patient in the study and is part of clinical practice. In these studies, the natural course of phenomena is observed without any intervention on the part of the researchers.

In the search for evidence of efficacy on which to base decisions in clinical practice, the design of the randomized controlled trial (RCT), which characterizes phase III trials in the process of evaluating the efficacy of a drug, represents the reference method for the efficacy of a treatment (Fig. 6).

This is due to the fact that this is the design that provides the most reliable estimates of a phenomenon since it allows the greatest possible control for systematic errors.

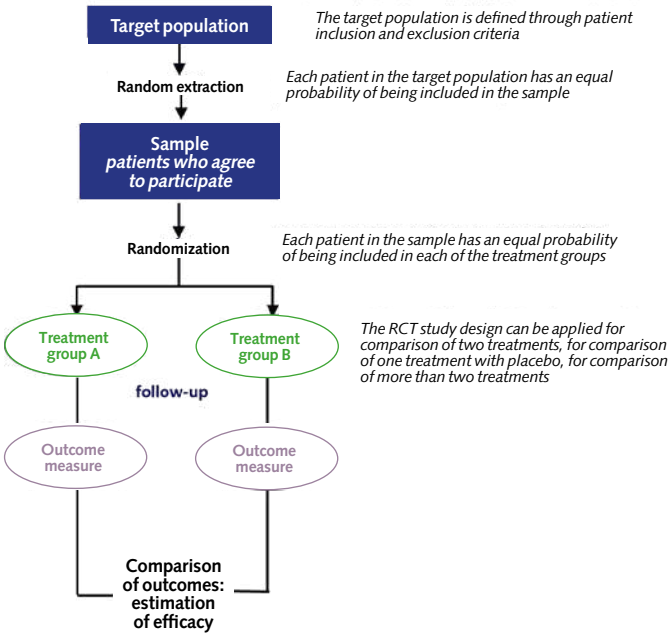


Fig. 6 – Schematic representation of the randomized controlled trial design (RCT).

In RCT studies, randomization, i.e. the random assignment of treatment, makes the groups of subjects comparable at the beginning of the study by distributing the baseline characteristics of the patients, known and unknown, independently of the treatments administered. The most important aspect of this procedure is that it allows to control the effect of the innumerable causes that may influence the study results without the need to know their nature [10].

It is important to note, however, that randomization does not completely eliminate systematic errors within the study, but only those due to the effect of factors present before the treatment is administered; it is necessary that factors that may act between the administration of the treatment and the measurement of the outcome variable are also taken into account in the drafting of the study protocol. The effect of these factors may produce an overestimation or an underestimation of the efficacy of treatment due, for example, to a different application of the clinical and instrumental controls and to a different detection of the outcome variable in the groups of patients examined [11].

Some of these factors can be controlled by masking treatment assignment (blinded study) and maintaining this masking throughout the study period. This procedure, the modalities of which must be explained in the study protocol, allows to control the bias due to the voluntary and involuntary influence of the subjects involved in the study (patients and researchers) on the information necessary to estimate the efficacy of the treatment.

The control of the effect of factors other than the treatment on the outcome variable can be carried out by identifying the prognostic variables on the basis of the knowledge already acquired, e.g. through the phase II studies, and stratifying patients into homogeneous subgroups with respect to the prognostic variable of interest. The study protocol must report the number and type of these variables and it must be indicated whether the objectives also include the analysis of this effect, such as the estimation of drug activity in each subgroup of patients homogeneous by disease stage.

It is important to underline that to achieve this objective it is necessary to adjust the number of subjects to be recruited so that it is sufficient to estimate the phenomenon in each of the identified subgroups; it is expected that the number of patients will be greater than the size sufficient for the analysis performed on the total number of subjects.

It should be noted that the analysis of the effect of the prognostic variables assumes more of a meaning of identification of the prognostic factors rather than of controlling of systematic errors.

Main limitations of the experimental study design in drug evaluation

The demonstration of efficacy obtained through the conduct of the RCT studies does not conclude the process of evaluating the benefit of a therapy. It is necessary to add other information that cannot be found by applying an RCT study design, but is equally important and can be acquired by conducting an observational study with an appropriate study design [12].

In fact, although RCT studies are the best tool to provide solid evidence for treatment efficacy, the conclusions of these studies are often not reproducible in clinical practice, where a much lower efficacy of the therapy can be observed. This limited external validity of RCT studies is due to of the study design and protocol, such as the strict patient recruitment criteria that often make the groups of subjects in the study different (by age, gender, health conditions, etc.) from the patients being treated in clinical practice [13].

Furthermore, RCT studies are often conducted in highly specialized clinical facilities, where the level of quality of healthcare may be very different from that of small health centres where the new therapy will then be used [14].

Information on rare and long-term adverse events attributable to a therapy is also not achievable with an RCT study design. In this case it would in fact be essential to recruit a larger number of subjects and to extend the study over a much longer period of time than the number and time required to evaluate the efficacy of the treatment alone; this would mean shifting the results regarding the latter over time with obvious detriment for patients.

On the contrary, an observational study can be conducted over a long time and on a large number of subjects without changing the conditions in which they receive the treatment necessary to improve their state of health.

For similar reasons, the RCT study design is not appropriate when the study duration required to record the outcome of interest is very long, as in the case of studies evaluating hormone replacement therapy in the prevention of hip fracture or for the evaluation of the durability of hip prostheses, for which a study period of 10-15 years is necessary.

In addition to the above, there are situations in which the RCT study design is not feasible, such as when the therapeutic advantage was so striking in clinical practice that it would not have been ethical to deprive the control group of this therapy; an example is the use of penicillin for bacterial infections and insulin in the treatment of type 1 diabetes.

In other conditions it is then impossible to apply the RCT study design due to the refusal of the doctors' and/or patients' refusal to randomise the treatment, as often happens when the aim of the study involves the comparison between admission to intensive care unit and admission to

the ward of ordinary hospitalization, or the comparison between cardiac transplantation and medical therapy.

In conclusion, in the study of drug evaluation, the first step is to estimate the *efficacy* by conducting randomized controlled clinical trials; the next step is to confirm the efficacy in clinical practice *effectiveness* and to evaluate the safety of the treatment, through observational studies able to generate evidence from the real world (*Real World Evidence*).

The observational study design in the evaluation of treatments is complementary and not alternative to the experimental design, and sets goals that cannot be achieved with RCT study design (see the next chapter).

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3. Focus on Observational Studies: Type, Statistical Methodology and Applications/Developments

R. Gesuita, M. Iommi

Study design in drug evaluation

To properly evaluate therapeutic interventions, the first step is to conduct a controlled clinical trial. Once efficacy and short-term tolerability have been demonstrated, it is essential to monitor and observe drug efficacy outside the experimental setting (aseptic conditions) which does not fully represent clinical practice.

Observation becomes complementary to experimentation by setting goals that are not reachable with the experimental approach.

Definitions

Observational studies represent a broad range of clinical studies and are an important primary source in the development of clinical evidence.

In the observational study the natural course of the phenomena is studied; changes or differences in one or more variables are studied in relation to changes or differences in other variables without the direct intervention of the researcher in the study context.

In the particular case of drug evaluation, the inclusion of a patient in a given therapeutic strategy is part of normal clinical practice and the decision to prescribe a treatment is completely independent of the condition under study.

The key feature of observational studies is that exposure is not assigned by the researcher on the basis of the study objectives and, since everything occurs in the normal routine of clinical practice, no further diagnostic or follow-up procedures are foreseen. Observational studies analyze real-world/real-life conditions.

Areas and applications

The fields of application are wide, some examples are:

- assessment of the natural history of the disease, identifying the factors that contribute to determining its onset, and of the dynamics of diffusion of the diseases themselves;
- validation of diagnostic and screening procedures;

- evaluation of public health programmes, management and organization of health systems in relation to economic and social aspects;
- genetic evaluation to identify the hereditary mechanisms of pathologies, resistance and susceptibility to drugs.

In the field of drug evaluation, the observational study design allows to evaluate the efficacy in clinical practice, i.e. the one closest to the real condition.

Efficacy in clinical practice is different from experimental efficacy, in fact the Anglo-Saxon literature to highlight these substantial differences uses two terms *Efficacy* (measurement of efficacy in experimental conditions) and *Effectiveness* (measurement of efficacy in clinical practice).

Observational studies also make it possible to monitor the onset of rare adverse events in the long term, possibly linked to interactions with other drugs or lifestyles.

They are applied to evaluate the risk/benefit profile of the treatment in care conditions other than the experimental ones. In this way it is possible to guarantee the transferability of the knowledge produced by a research to clinical practice as the benefits and risks attributable to the therapeutic procedures are measured.

Approach

Observational studies can be classified according to two approaches:

- *Observational descriptive studies:* examples are studies of prevalence, incidence, description of the use of resources to treat a specific disease or description of the diagnostic therapeutic care pathways experienced by the patients taken care of for a specific condition. Descriptive studies are not designed to test a hypothesis but to explore and monitor a phenomenon of interest.
- *Analytical observational studies*: examples are studies of *Effectiveness*, safety, sustainability and/or cost-effectiveness. These studies are aimed at testing hypotheses and generating evidence by comparing categories of patients subjected to a different quality/intensity of medical care.

The choice of study design depends on the research objective. Descriptive observational studies answer questions such as measuring exposure to medical treatments in clinical practice, evaluating adherence to recommendations, evaluating persistence in drug therapies, highlighting the differences with respect to treatments that are appropriately prescribed and followed.

Studies with analytical purposes are aimed at measuring the degree of association observed in clinical practice between exposure to treatments and clinical or economic outcomes.

Analytical observational studies are aimed at verifying both associations and causal associations between individual characteristics or factors of exposure and morbid phenomena. There are three types of observational studies: cross-sectional study, longitudinal cohort study, and longitudinal case-control study.

Cross-sectional study

The target population is considered according to the presence of a condition of interest, also detecting some characteristics of the population itself. This can be done both for subjects who present the condition of interest and for subjects who do not present it.

The direction of the observation is transversal since both the outcome and the exposure factors (those characteristics that can determine the onset of a given condition of interest) are detected simultaneously. This study design highlights an association between the condition of interest and exposure but not a causal association.

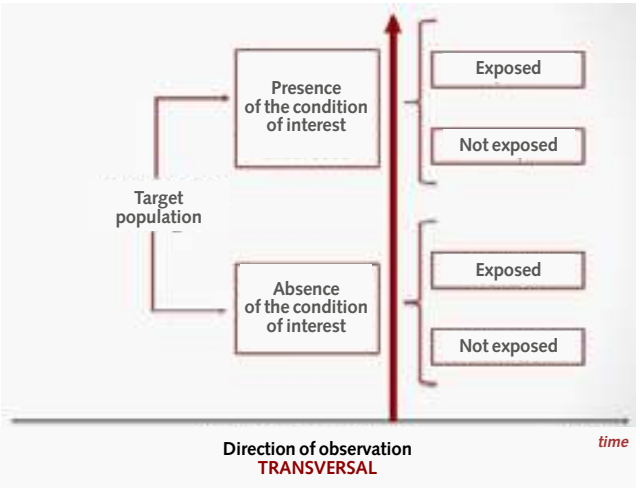

Fig. 1 – The design of the cross-sectional observational study.

Longitudinal cohort study

The target population is assessed according to the risk of developing the outcome; those who are not at risk or have already developed the outcome are excluded from the enrolment.

Eligible subjects are classified according to exposure and followed up for a long-enough time for the outcome to occur. In this exposure is detected at the beginning and then, prospectively, the onset of the outcome,

allowing to highlight a causal association between exposure and condition of interest.

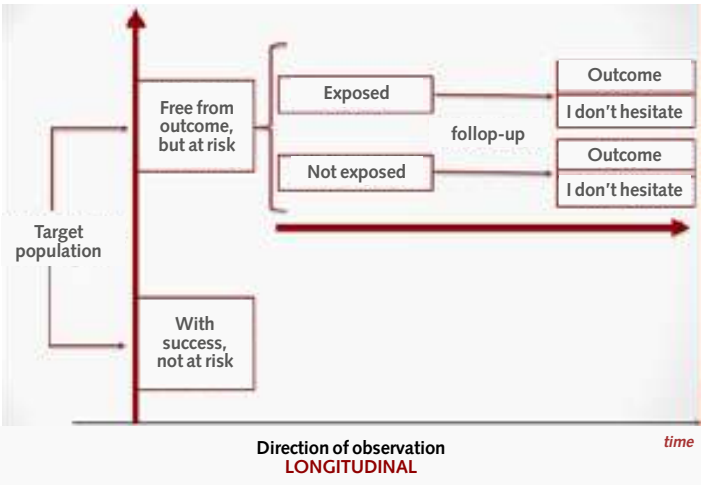

Fig. 2 – Design of the longitudinal observational cohort study.

Longitudinal case-control study

The target population is divided according to the presence of the outcome of interest, distinguishing between cases (subjects who present the outcome of interest; generated from the population) and controls (subjects who do not present the outcome of interest; sample of the population).

Exposure is detected/measured for both cases and controls, then the two groups are subdivided according to the presence of exposure. The observation is retrospective, it starts from the presence of the outcome of interest and then the exposure is retrospectively detected (Fig. 3).

In observational drug evaluation studies, exposure is the drug treatment and the outcomes are the occurrence of adverse events (safety studies) or of a clinical manifestation that should be avoided (*Effectiveness studies*).

Other outcomes of interest are the evaluation of cost-effectiveness or sustainability of the entire therapeutic process with respect to available therapeutic alternatives (estimate of direct costs, estimate of avoidable costs).

In the evaluation process of the outcomes of interest it is necessary to characterize subjects according to some demographic and clinical characteristics (age, sex, comorbidities, therapeutic treatments, previous hospitalizations) called covariates. Controlling these variables, which are external to the relationship of interest, is essential to ensure correct

interpretation of the results of the exposure-outcome causal model since they could act as confounders, effect modifiers or mediators.

The study should include the collection of information on exposure and outcome and covariates with the same level of detail and completeness. The collection of all this information over time also allows the evolution of the clinical and therapeutic assistance profile of the subject to be adequately outlined.

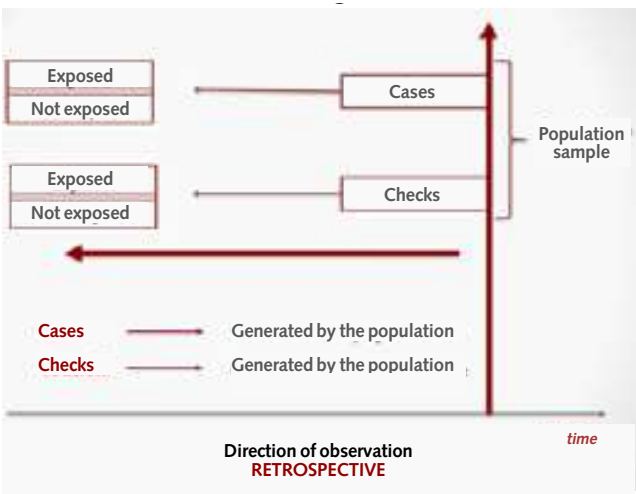

Fig. 3 – The design of the case-control longitudinal observational study.

Data sources

The collection of information can be carried out through *ad hoc* surveys, then through clinical observations, instrumental surveys or by the administration of questionnaires. These sources are defined as **primary sources** with respect to the purpose of the data collection, they are prospective with respect to the beginning of the study that is being conducted, and refer to samples of selected patients and of a number defined on the basis of the objective of the study.

In the context of observational studies of pharmaco-epidemiology and pharmaco-economics, medical records are widely used. Examples are administrative healthcare databases, population surveys carried out by national institutes, pathology registers, drug monitoring registers, biobanks, as well as computerized medical records. These sources are defined as **secondary sources** with respect to the purpose of the data collection, are retrospective with respect to the beginning of the study, concern large

defined and unselected populations, and can be potentially linked to each other.

Limits

Observational studies are not free from limitations, including the poor comparability of the groups, as it is not possible to carry out a randomization of the subjects to the groups, and the heterogeneity of the treatments under study which makes it difficult to attribute the effect to the therapeutic intervention investigated.

Selection Bias

Selection Bias occurs when the probability of inclusion in the study sample depends on exposure and outcome making the sample not representative of the population.

Example

In an observational study aimed at evaluating the association between hormone replacement therapy and the risk of cardiovascular disease (CVD) in women, it was found that women who underwent replacement therapy tended to be more attentive to their health and therefore at a lower risk of developing cardiovascular disease, compared to women not receiving hormone therapy. In this case the observation is biased by the *Healthy - User Effect* and therefore there is an underestimation of the association.

Confounding Bias

Confounding Bias occurs when a third variable (or groups of variables) intervenes between the exposure-outcome association, usually called the confounding variable – or confounder – associated with both the outcome and the exposure of interest.

Example

In evaluating the association between exposure to antibiotic therapy and the risk of developing asthma in children, it is necessary to consider viral infections, which are very frequent in children. Viral infection is a known risk factor for asthma and can be treated with antibiotic therapy as there are difficulties in the differential diagnosis between bacterial and viral respiratory tract infection in clinical practice. Therefore, the viral infection acts as a confounder, producing a bias of the association between antibiotic therapy and asthma (*Confounding-by-Indication*).

Misclassification Bias

Exposure misclassification, typical of studies based on secondary sources and known as *Immortal Time Bias*, refers to a period of time in the follow-up of a cohort during which the study outcome could not have occurred. Misclassification of this period as an observation period leads to distortion of the study result.

Example

A study carried out to evaluate the association between the use of proton pump inhibitors for at least one year and mortality in patients with idiopathic pulmonary fibrosis.

Patients are classified according to the use of antacids, as patients who have been users for at least one year and patients who are non-users, and followed up to the outcome of interest.

Distortion is introduced precisely through the definition of exposure: in fact, all user patients who did not survive 12 months were excluded from the recruitment, while the recruited users had a survival time advantage of 12 months more than the non-users. The person-years of user patients are higher, even if in fact in the first 12 months the subjects were not at risk of developing the event.

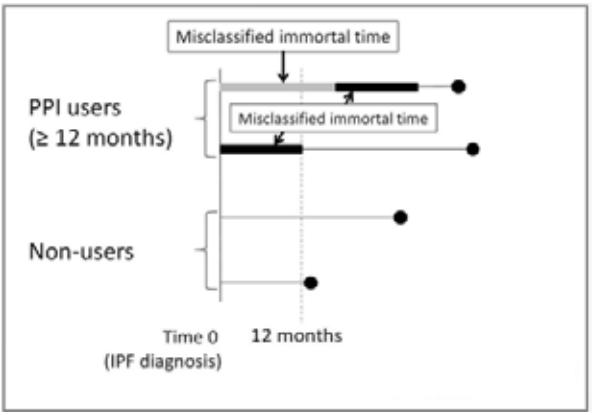

Fig. 4 – Association between the use of antacid therapy and all-cause mortality in patients with idiopathic pulmonary fibrosis [1]. (PPI = proton pump inhibitor).

Sources of uncertainty

Random error and systematic error always represent sources of uncertainty in the observational study which can be controlled through an adequate sample size, study design and data analysis appropriate to the objectives that the study sets.

The observational study, like the experimental study, must be understood as a planned procedure. The drafting of the study protocol before carrying out the study itself is fundamental, describing in detail the starting scientific basis, i.e. the objectives, the design of the study, the variables to be detected, the methods for controlling the distortions, the estimation of the sample size, the plan of statistical analyzes and the expected results.

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4. Quality of the experimental data

C. Polidori

In supporting decisions to be made in terms of patient health policy, evidence-based medicine and randomized clinical trials represent the highest level of evidence to draw on by the decision-maker [1]. Recently, moreover, many medical practices find their reason for existing after a careful analysis of the electronic databases of performed treatments [2]. In fact, these databases, collecting a very large number of case histories, are having an enormous weight on the design of pragmatic clinical trials, in the reimbursement decisions given by regional authorities, in the diagnostic and clinical pathways and in particular in the prescriptions errors of medicines in the elderly [3].

It is commonly understood that the quality of a clinical research is identified and developed through two main concepts: the first in the formulation of an hypothesis on a clinical theme and the second the context where this question will be evaluated [4]. The formulation of a clinical research hypothesis is often prompted by a real-life observation, experience or considerations of the researcher. Hypothesis formulation begins as a clinical problem describing the relationship between certain concepts, such as patient behaviour, and the observed experience. Initially the hypothesis can be of wide range and vague but can still be focused through a greater understanding of what surrounds us.

Some criteria have been prepared by researchers which are certainly very important in declining the quality of the research:

- Clarity of the hypothesis with a good supporting rationale;
- Adequate preparation of the researcher with good knowledge of the literature and work previously carried out on the matter under study;
- Appropriate methods for answering the research hypothesis;
- Significant results in terms of advancement of knowledge in that specific field;
- Effective presentation of results so that other researchers can replicate them or advance on those reported;
- Critical reflection so as to learn from and during the research process.

At this point, it is appropriate to define what is meant by "quality". Quality is a measure of the characteristics of a product (clinical research) in comparison with what is expected of that entity for a given use. Therefore, a good quality of the experimental data will also include a good quality of the research results and consequently a good clinical practice.

With the aim of managing risk and making therapeutic appropriateness,

the hospital pharmacist needs excellent clinical bibliographic data especially in the selection of drugs to be included in the hospital clinical handbook and in the approval of protocols for their use in comparing therapeutic solutions. In these types of comparisons, the hospital pharmacist must evaluate the efficacy in trials presented in scientific papers which must have a very important requirement, i.e. have trials which must be reliable for efficacy of that particular therapeutic intervention.

Scientific works that report evidence of effectiveness can come from clinical studies, also referred to as "primary sources", from supplementary studies (secondary sources) and finally important experiences obtained in the field and described by specialists in that sector reported in editorials (tertiary sources). Primary studies are represented by randomized clinical trials and cohort studies while integrative studies are represented by systematic reviews and guidelines. Finally, general editorial articles and expert opinions represent the "tertiary sources". In these passages, occasionally, distortions of the original results can occur.

The approach to the scientific article is now computerised. In fact, these are found in the universally recognized and most accredited international virtual libraries such as "PubMed" and the "Cochrane Library". These are freely available on the internet. Both require knowledge of the English language and some computer command to find the scientific work to refer to both in the reading and in the comparison processes.

Primary sources	Secondary sources	Tertiary sources
Primary studies	*Integrated studies*	*Opinion- based studies*
	Economic analyses	Treated
RCT	Systematic reviews	Editorials
	Guidelines	Expert Opinions
Cohort	Decision analysis	

Distortion of original search results

An important step in reading a scientific article is the PICO process (Patient, problem or population; Intervention; Comparer; Outcome) [5]. It is a careful way of reading and therefore judging the authority of the considerations made by the authors. This process must identify the Population taken into consideration in the clinical trial, the Intervention carried out, the Control or comparer used in the study and finally the Outcome or the observations that have been made (e.g. type of pain observed, infection or other) and finally, then the results of the study.

Evidence-based medicine rests on some philosophical assumptions such as: there is only one truth, it is recognizable through an empirical study, there is a logical linearity of causality in the efficacy of the treatment and finally, methodological rigor is necessary in order to avoid distorted or biased results. In the event of a pandemic, these assumptions hardly hold. Indeed, in implementing public health interventions in a population (e.g. protective measures against Covid-19) one must not only persuade the population to change their behaviour but also to adapt the environment in such a way that these changes are easier to make and to support. In fact, in these cases, interventions on public health of a large population is generally iterative, initially of local vision and dependent on the paths undertaken, with a methodology of rapid evaluation and adaptation. Evidence-based medicine has therefore classified this type of approach as having "low methodological quality". Although this statement is certainly true, when it comes to studies at the level of large populations, researchers suggest having an epistemological approach and using methods that are better suited to phenomena with large uncertainties, unpredictability and non-linear causality [6].

In an evidence-based approach it is sufficiently clear that the number of evidences has a clear specific weight. The more evidence, the easier it will be to make a decision. Obviously you don't need much evidence but you certainly need to identify the most important questions or the most controversial issues.

For a controlled study: Assessment of methodological quality
1) Adequate design (e.g. *randomization, appropriate comparer, and appropriate use*)
2) Study hypothesis (*superiority, equivalence, non-inferiority*)
3) Appropriate, clinically relevant, objective and reliably measurable outcome measures, combined/not combined
4) Sample size calculation
5) Adequate follow-up duration
6) Statistical analysis (*intention to treat analysis, per protocol analysis*)

In these types of scientific works, the type of patients taken into consideration represents the first detail to be observed for a comparison with the type of patients that will be managed in the hospital setting. The careful observation of the type of diagnostic-therapeutic intervention is of vital importance together with the reference control taken by the authors and the Outcome observed at the end of the study period. Outcome that must be rational with our expectations.

As noted previously, the best source of reasonable outcomes are

randomized clinical trials. Obviously, we reiterate that the question underlying the clinical trial must be essential from a clinical point of view and that it must give rise to an improvement in the already standard therapy. Methodological quality remains an important requirement to establish whether the data are reliable and whether there really was a benefit to the patient and consequently whether the data are clinically relevant.

Evidence-based medicine has recently landed in the development of systematic reviews of data available in the literature and in the production of meta-analyses, methods through which researchers identify the best studies on a medical-pharmacological issue criticizing them and reaching a conclusion as the best evidence.

In the research field, the data presented can be either quantitative or qualitative. Both have their advantages and disadvantages. An appropriate statistical test is applied to each of these, which the Research Pharmacist concisely must know. Particular attention while reading a scientific article must be done in discovering the biases. In fact, these are essentially of four types and can be found in a randomized clinical trial. The first is the "selection of patients" to be included in the experimental group or in the control group. Randomization is important and must follow certain mathematical rules. The second is the "performance" which comes from the inclusion of additional treatments in the various groups studied. The third is "attrition" or when the patient abandons the clinical trial. Finally, the last is of "outcome" in which the outcomes of the treatment are not accurately determined. For this reason, some aspects must be clear in the article to minimize these errors. Firstly randomization, the blindness (whether double or triple), the description of the reasons why patients leave the trial in an Intention to Treat analysis, and finally the assumption of data evaluators who must be blind in evaluating the data [7].

Going into detail, the evaluation of the methodological quality of an RCT must be seen through the excellence of the experimental design and of the study hypothesis (i.e. whether it is a study of superiority, equivalence or non-inferiority, if the measures of outcome and these are clinically relevant, objective and measured or if they are combined or not combined. The calculation of the sample, the duration of the follow-up and finally what type of statistic was made (per protocol or an intention to treat) is of particular interest. Furthermore, for the methodological evaluation there are some important questions to consider. One of them is whether "the referring drug is adequate" while another is whether "the margin of superiority is clinically significant".

The Research Pharmacist should know some statistics if he wants to address these issues. It is well known that the Intention to Treat analysis

considers all subjects allocated in the initial conditions and even of the lost patients. This is an excellent analysis as it takes into account everything that actually happens; in fact at its base it says that once randomized the patients are all taken into consideration in the final analysis. The difference in Outcome between an analysis is known Intention to Treat and *per protocol* where in the latter a relative risk reduction could be observed which is not evident in the former one.

A careful reading of an article must always keep in mind where the benefit for the patient lies, i.e. it must be observed whether the results are clinically relevant. There are three things to observe:

1) the magnitude of the effect (deducible from the relative risk, absolute risk and the number of patients I have to treat to observe a new adverse event);
2) the precision of the estimate (across the confidence interval);
3) the outcomes considered (consider whether the outcomes are combined. The components of the combined endpoint must be comparable in terms of clinical relevance; otherwise, the results for each component of the endpoint must be reported).

Furthermore, the observation of the generalization of the results of the study, the consideration that the patients studied are those that I normally observe in my daily practice and the verification that the care setting in which the trial took place is comparable to the one where one operates are reasonable important.

In conclusion, a good methodological quality of a clinical study, the availability of recent and transparent research, remembering that non-inferiority studies are among the most "drugged", the adequateness of one or more studies taken as reference in the decision-making mechanisms can be proposed only by a multidisciplinary team where everyone uses their own expertise to come out with a balanced judgement focused on the patient's well-being.

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5. The STROBE Statement for Observational Studies

C. Iacono, C. Confalonieri, E. Sciorsci, A. Pasquale

Observational research, sometimes erroneously considered a "minor" research, has found new interest in recent years.

This change of pace can be attributed to the nature of the information that only observational research can provide.

Observational studies mainly provide information of an epidemiological and managerial nature, the implications of which are important both for health governance and for individual clinical centres.

Health governance uses observation research as an observatory of the changing reality of epidemiology and technology to verify the needs, satisfied or still to be satisfied.

Individual clinical centres also rely on observational research to govern the structure, analyze diagnostic-therapeutic pathways, immediate and long-term clinical results, and evaluate the use of resources in order to allocate them in an appropriate and dynamic way.

The greatest risk for researchers who approach observational research is to consider, in advance, easy to implement it and generally with an iso-resource approach. This approach leads to deficiencies in the study protocol which can be translated into various substantial amendments, into a meagre method of analysis, a poor quality of results and even worse in the difficulty of interpreting them.

The Strengthening the Reporting of Observational Studies in Epidemiology, created with the aim of developing recommendations on what should be included in an accurate and complete description of an observational study, stands as a tool to improve the reporting of observational studies. Thanks to a workshop held in September 2004, a group of researchers from some European countries elaborated a list of key points to consider, through the elaboration of reference texts, databases, bibliographic lists, personal archives, recommendations and studies empirical on how to write articles and methodological research. The meeting of this working group and the subsequent process of consultations and revisions resulted in a check-list composed of 22 items (*the STROBE document*) concerning the title, the summary, the introduction, the sections of the methods, the results and discussion of articles.

Eighteen items apply to all three study designs considered, and four are specific to cohort, case-control, or cross-sectional studies. A detailed article entitled *Explanation and Elaboration was published separately and is freely available on the PLoS Medicine, Annals of Internal Medicine and Epidemiology* websites where examples are described for each item in order to better understand the STROBE document.

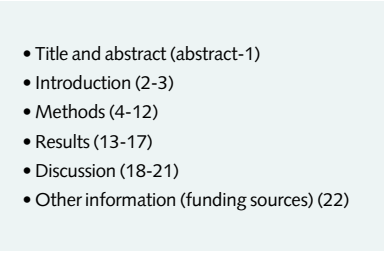

Fig. 1 – Distribution of items.

Appendix Table. **The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Checklist of Items That Should Be Addressed in Reports of Observational Studies**

Item	Item Number	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.
Introduction		
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported.
Objectives	3	State specific objectives, including any prespecified hypotheses.
Methods		
Study design	4	Present key elements of study design early in the paper.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.
Participants	6	(a) *Cohort study:* Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. *Case–control study:* Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. *Cross-sectional study:* Give the eligibility criteria, and the sources and methods of selection of participants. (b) *Cohort study:* For matched studies, give matching criteria and number of exposed and unexposed. *Case–control study:* For matched studies, give matching criteria and the number of controls per case.

Fig. 2 – STROBE *checklist section.*

The Strobe Statement provides the authors with an indispensable guide for improving the reporting of observational studies, favouring the evaluation of their strengths and limitations, including the generalization of the results: it consists of a checklist containing the essential elements in the description of the three main study designs in epidemiology: the cohort, case-control and cross-sectional studies. The aim is to provide a guide on how to correctly describe an observational study: the recommendations are not a rigid model for the design or conduct of studies and the checklist is not a tool for assessing the quality of the research itself.

Let us not forget that in 1985 D. Sackett laid the foundations of the critical approach with the book *ClinicalEpidemiology: a Basic Science for Clinical Medicine* with the aim of abandoning the same hierarchy of evidence for all clinical questions and to classify the study designs of quantitative primary research.

Recent regulatory developments, also on the subject of observational research, make it necessary to create a network of professionals active sponsors of research, a virtual venue for meeting and discussion. The Network dialogues, implements and shares its intentions with the Universities and the exponents of Scientific Societies in order to carry out a convergent path that can benefit the entire professional category. We believe the hospital pharmacist must know more and more about the architecture of clinical research, the anatomy of biomedical information and acquire methods and technical skills for bibliographic research by identifying the most appropriate study design for the different categories of questions as well as feeling the need of information, classify it and convert it into appropriate clinical-care questions, guaranteeing scientific credibility.

Research and continuous training become a daily work tool with a view to planning activities and a functional tool aimed at increasing the efficiency of the system in order to generate data that have a positive impact on the National and Regional Health Service as well as on the health of citizens.

From a national perspective, the analysis of data in many areas of health care and their revision, based on significant comparisons with other centres (*benchmarking*), must promote the comparison between hospitals, administrations and districts: when the data are connected, the assessment of access to care services in relation to demographic and social factors such as age, gender, socio-economic profile, place of residence, can be optimised. Many researchers have recently emphasized the importance of observational studies based on high quality clinical databases (HQCD).

Unlike randomized clinical trials, for example, observational studies concerning the results of medical intervention in clinical practice, since there is no randomization to treatment, involve a sample of an unselected population and the results reflect the true benefits but also the true complications of the treatment/intervention. In addition, observational studies may evaluate topics such as the comparison of a drug with the next available therapy or the use of a drug in the real world (*Effectiveness*) compared with its use in clinical trials (*Efficacy*); issues and differences, these, of crucial importance in the care of the real population (real word data) with respect to the limited time of the clinical study.

The decision-making process assumes efficacy evidence from clinical trials and applicability evidence from observational studies. This aspect is crucial

not only to identify the risk profile and the benefit for the individual patient, but also to characterize the frequency of long-term adverse effects, the consequences of the decision-making/therapeutic intervention at different clinical stages of the disease and the possibility to improve the effectiveness of interventions in clinical practice.

Strobe methodology finds application in the most varied fields of medical-health research.

In the field of paediatric urological surgery MK Farrugia and AJ Kirsch, with an article published in the *Journal of Paediatric Urology* in 2017, questioned the importance of evaluating the countless studies that, in the endoscopic treatment for paediatric bladder-urethral reflux, are published every year. The STROBE methodology, with its items, has proved to be the best way to classify and evaluate all the works, giving a weight to each of them in order of clinical evidence. The published study concludes by proposing a check list that can be used as a useful tool for authors and reviewers. On the importance of observational studies the Farruggia and Kirsch report, within the published study, a reference to an analysis conducted by the Cochrane Collaboration in 2014 where it is stated that the results of observational studies are completely overlapping with those obtained from randomized double - blind trials.

Another study published in BMJ in 2016 written by Evelina Tacconelli *et al.* explore recommendations for optimization of reports of epidemiological studies on antibiotic resistance and improvement of the quality of information transmitted for the purpose of optimal action of AntimicrobialStewardship. The study is divided into three steps. The first is a systemic review of the literature that analyzes the associations between antibiotic exposure and the acquisition of penicillin resistance to *Staphylococcusaureus* and/or *Acinetobacter multidrug resistancebaumannii*. The second evaluates articles that have been reviewed in light of the STROBE methodology items. The third step is the identification of potential items focused on the evaluation of antibiotic resistance. The analysis led to the identification of only 78 useful studies and in these only 5 items of the STROBE checklist with very low reliability values were identified. In conclusion, the analysis led to the definition that the data, brought to support the thesis of a relationship between antibiotic consumption and development of resistance, are poor and should be increased. The implementation of new items, proposed in the third intent, could make better studies available and help to increase the evidence that can serve as a basis for further progress.

Alice Mannocci *et al.* in an article published in 2014 in the *Journal of Public Health* are wondering about the impact of the reporting guidelines in public health journals in Europe. In the article the authors compare the applications of

three methodologies STROBE, CONSORT AND PRISMA. The study analyzes studies published in 7 journals dealing with public health over a 4-year period (2010-2013). The text analyzes the STROBE methodology, with its list of items, for observational studies, the CONSORT methodology, with its 25 items, widely used for the evaluation of randomized controlled clinical trials and finally the PRISMA methodology, developed to help the authors to improve the style of organization and presentation of data in systemic reviews and meta-analyses. The PRISMA Methodology uses a checklist of 27 items. The study analyzed 3,456 articles including 190 reviews/meta -analyses, 44 clinical trials, 2,117 observational studies, 2 mixed studies (reviews/observational) and 1,103 studies classified as other editorial products.

The analysis carried out showed that the largest application of the 3 methodologies mentioned above is found in the articles published in the *Italian Journal Public Health*. Furthermore, it is recorded that the works that follow the STROBE criteria are 5.1%, for the other journals it does not go beyond 0.6% of the journal published by Elsevier.

The application of the STROBE Methodology is an indication of the quality of the data that can be used by Company Facilities such as the Hospital Infections Committee, Clinical Trial Centre, Ethics Committee and HTA evaluation unit, working groups which rightfully include the pharmacist with his professionalism

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6. Epidemiological Studies and Studies of Real World Evidence

V. Russo, V. Caso, P. Abrate

Introduction

Epidemiology, from the Greek ἐπί: "above", Δῆμος: "people", Λόγος: "speech, study", is the study of the distribution and determinants of health-related situations or events in a specific population, and the application of this study to the control of health problems [1]. Epidemiological studies can be divided into observational and experimental. Observational studies are characterized by the absence of active intervention by the researcher, who limits himself to observing the phenomena, describing them (descriptive study) or analyzing any relationships between the observed phenomenon and some variables (analytical study) [2].

Descriptive epidemiological studies allow the study of the place and time distribution of a disease and to place the first hypotheses on one or more possible cause factors.

Analytical epidemiological studies serve to verify whether the supposedly cause factors are associated with the disease under study, if the association is proven in an evident and statistically significant way.

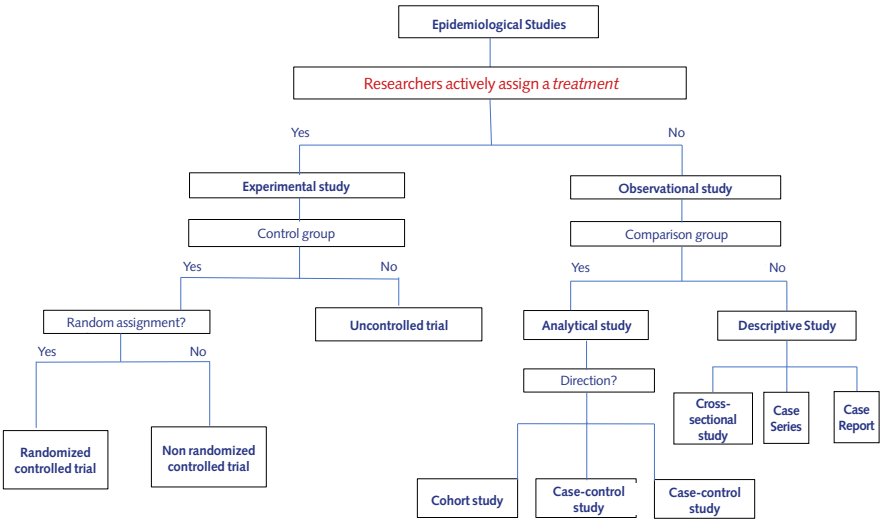


Fig. 1 – Classification of epidemiological studies.

Unlike observational studies, experimental studies are characterized by the active intervention of the investigator and allow us to verify whether the association is causal or not. The *randomized* controlled clinical trial (RCT) constitutes the reference standard for evaluating the effectiveness of health interventions [3]; however, the results relating to the population included in the study may not be generalized to patients treated in clinical practice; for this reason, scientific evidence generated in the real world (Real World Evidence - RWE) is assuming more and more value in the clinical and regulatory fields [4, 5]. In the pharmacological field, data generated in the real world produce evidence that complements and expands the data obtained from RCTs, providing valuable information on the safety and efficacy of a drug in a large and heterogeneous context of populations [6].

Real World Data and Real World Evidence

Real World Data (RWD) refers to all data relating to the patient's health status and/or the provision of health services that are collected and, outside the context of RCTs, during normal clinical practice [7]. The scientific evidence derived from the RWD analysis is defined as Real-World Evidence(RWE) [8]. RWDs can be collected prospectively or retrospectively: in the first case, the effects of a health intervention are evaluated by following the enrolled patients from the beginning of the study to its conclusion, to observe the results of the intervention itself; in the second case, events that occurred in a period prior to the study design are measured.

RWDs can be generated by:

- **Pragmatic** clinical trials i.e. randomized clinical trials which, with the aim of mimicking real-life conditions, use less stringent patient inclusion/exclusion criteria than conventional RCTs and consider outcomes whose clinical impact is as close as possible to that observed in the clinical practice [9, 10]. Table 1 summarizes the distinguishing features of randomized clinical trials versus randomized clinical trials.
- **Observational cohort studies,** which do not envisage the randomization of patients, as happens in RCTs, but their observation for long periods of time in order to evaluate the efficacy of health interventions or to answer etiology/risk questions [11]. They can provide alongside the cohort of subjects exposed to the treatment or risk factor, a parallel cohort not exposed (with parallel cohort). They are generally prospective, but can sometimes be retrospective.
- **Case-control studies** compare two groups of subjects: subjects exposed to the treatment or risk factor (cases) and controls with the same characteristics as the former, but from which they differ only in that they do not have the

Table 1 - Comparison between randomized clinical trial and pragmatic trial.

	Explanatory Trial	**Pragmatic Trial**
Targets	*Can the treatment work?* Theoretical efficacy Testing the hypothesis Ideal conditions	*The treatment works?* Practical effectiveness Compare therapeutic strategies normal clinical practice
Scope	Evaluate the cause and effect of the drug	Inform decision makers
Protocol	Strict protocol	Maximum generalization
Population	Selective Inclusion	Broaden Inclusion
Method	Data collection > normal clinical practice *Relevant research outcomes*	Data collection = normal clinical practice *Clinically relevant outcomes*

disease. The credibility and reliability of the study therefore depend on the correct selection of cases and controls. Therefore the case definition must be rigorously described in the study protocol and must consider the inclusion and exclusion criteria objectively. Case-control studies are used to evaluate the role of one or more risk factors in the etiopathogenesis of a disease, to evaluate the role of individual risk factors and their possible interaction [12].

- **Transversal study,** also called prevalence study, involves the analysis of data from a population at a specific time. The determination of the exposure to a particular risk factor – or the presence of any other condition of the subject – and the recording of the result take place simultaneously, that is at the same time. It is basically used to describe frequencies of diseases, or conditions, in relation to variables such as age and gender, place of occurrence or time. The transversal study can therefore be considered as a "snapshot" of the group of people examined and therefore the assessment of the presence of a phenomenon at the precise moment in which it was decided to carry out the survey. Unlike other types of observational studies, cross-sectional studies do not follow individuals over time, are inexpensive, and easy to conduct. They are useful for carrying out a preliminary assessment in planning a future more complex study and for assessing the health needs of a population [13].
- **Prospective registers:** The term register refers to a continuous and systematic survey activity over time. Prospective registries collect data from patients enrolled before the clinical event of interest occurred. The data collected serves one or more of the purposes of the registry. Data collection and storage are subjected to quality checks, so as to make the information collected in the register suitable and available for your purposes. Table 2 shows the possible purposes of a clinical registry.

It is important to remember that a prospective registry is not synonymous with an observational study. A study was created to answer a question, while a register is not identified by a specific cognitive objective but may have multiple objectives or its primary function may not be of a cognitive type. Table 3 describes the main differences between registries and observational studies.

- **Retrospective databases:** collect data from patients enrolled after the clinical event of interest or exposure occurred. The data sources are mainly medical records and outpatient reports. The lack of uniformity in the quality of the data collected can be a limitation. Retrospective databases have the advantage of being an effective way to rapidly obtain information on large numbers of patients, as well as having an inexpensive approach [14].

Table 2 – Research purposes of a clinical registry.

• Natural history of the disease
• Quality of health care
• Provision of health services
• Resource consumption
• Efficacy/safety ratio of interventions
• Cost-effectiveness ratio of interventions

Table 3 – Main differences between observational health registries and observational epidemiological studies.

Observational health records	Observational epidemiological studies
They can be multipurpose	They have one/few specific goals research/ evaluation
They don't have a set time	They have a deadline
They usually include collected data for other purposes (clinical, administrative)	They often include data collected ad hoc and sometimes "actions" (e.g. questionnaires, withdrawals)
They collect a lot of information which "might" prove useful	Data collection is aimed at the objectives of the study
They should fuel or facilitate observational studies	They provide a research protocol with a statistical plan

Advantages and Limitations of the RWE studies

The RWE studies reflect clinical experience in a wider and more diverse distribution of patients than RCTs and for a longer average follow-up time. They can provide insight into real-world treatment patterns, including dosing, compliance, adherence, off-label use, and the balance of a drug's efficacy and safety [15]. In this way they improve the validity of the data

obtained and their generalization with respect to RCTs [16]; they are also less expensive and faster to complete than RCTs [17]. RWE studies are now widely used as a post-marketing pharmacovigilance tool, providing an active surveillance system for the detection of any new safety signals [18]. Limitations of RWE studies include the quality of the data, which may be collected incompletely or inconsistently, thus reducing their clinical validity. The lack of randomization in most RWE studies contributes to the high external validity of the data, but reduces their internal validity, i.e., the extent to which any differences between the intervention and control groups can be attributed to the intervention itself, as opposed to other factors [17,19]. Table 4 shows the major differences between randomized clinical trials and Real World Evidence studies.

Table 4 – Main differences between Randomized Clinical Trials (RCT) and Real World Evidence (RWE).

	Randomized Clinical Trials (RCTs)	**Real World Evidence (RWE)**
Objective	Determine whether the hypothesis is valid under highly controlled circumstances	Determine whether the hypothesis is valid under usual circumstances
Patients	Default population	Diverse population
Inclusion criteria	Very strict	A little stiff
Treatment	Randomized, regimens defined	Not randomized (according to SmPC and medical judgement)
Grip	Generally high	Variable
Follow up	Limited	Possible long term
Scope	Regulatory agency approval	Drug evaluation in realworld

Regulatory Agencies

Regulatory Agencies, such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have fully recognized the value of RWD and RWE [20-21].

The European Medicines Agency (EMA), in February 2022, launched a coordination centre for health data called Data Analytics and Real World Interrogation Network (DARWIN EU). The role of the Coordination Centre is to develop and operate a network of real world health data sources across the European Union (EU) and to conduct scientific studies requested by Medicines Regulators and, at a later stage, requested by other parties interested. DARWIN EU will provide EMA and the National Competent

Authorities of EU Member States with access to valid and reliable RWDs. The evidence made available covers, for example, diseases, patient populations and the use, safety and efficacy of medicines, including vaccines, throughout their life cycle. They serve to support decision-making processes on medicines development and authorization and on pharmacovigilance, to the benefit of the various stakeholders: pharmaceutical industry, evaluation entities, patients and healthcare professionals [22,23]. The Food and Drug Administration has since 2008 activated Sentinel, an active surveillance system that uses existing electronic health data from multiple sources, for the purpose of creating a national electronic system to monitor the safety of approved medical products [24]. Today Sentinel is the world's largest database dedicated to drug safety, used to accelerate access and wider use of real-world data.

Conclusions

Evidence generated in the real world provides complementary information, which can complement and/or broaden evidence obtained from randomized clinical trial results. The integration of data from RWE study with those from RCTs is imperative to confirm drug safety in diverse populations and different clinical settings for longer follow-up times. Furthermore, if properly analysed, RWDs can act as a valid support for regulatory decisions and in particular for drug policies [25]. In this context, the study of the patterns of use of different combinations of drugs and of the relative associations with health or economic outcomes represents one of the potentialities of RWD. Despite the many advantages, only a few International Scientific Societies guidelines choose a RWD review process and use RWE to establish clinical practice recommendations [26].

The role of the pharmacist in the management of Real World Data (RWD) aimed at the development of clinical studies

Real World Data (RWD) is the term used to identify information collected outside of conventional clinical trials. RWDs available in clinical practice may relate to patient's personal data (age, sex), the drug used, the prescribed dosage and also the clinical results obtained. It is also possible to extract information that can be easily interpreted on the duration of treatments, enrolment over time, days of therapy lost, adhesion and toxicity.

The SSN pharmacist produces, manages, records and analyzes a considerable amount of data just in the performance of his ordinary activities.

The dispensing of medicines through direct distribution to hospital departments, the setting up of personalized therapies, the enhancement of drug treatment monitoring registers, the management of pharmacovigilance

reports are just a few examples of how much the pharmacist is immersed in data. It is also possible to find and integrate other data sources such as computerized and non computerized medical records, therapeutic diaries, even digital, if available.

Interaction in a multidisciplinary team with other professional figures can expand the set of available information, with particular regard to clinical outcomes.

Among clinical studies, those of drug utilisation have a significant impact on the interpretation of RWDs and represent a governance tool to ensure and monitor the appropriate use of medicines. Some basic outcomes can be obtained from the conduct of studies of this type, among which we can cite treatment adherence, persistence, switch, analysis of the prescribed dosage and toxicities.

To create and then analyze these indicators it is necessary to connect the various data sources through record linkage processes. In recent decades, the activity of integrating different sources has had a great development in many fields. A procedure for integrating data from different sources goes by the name of record linkage when it is implemented as an algorithmic technique whose purpose is to identify which pairs of records from two databases correspond to the same unit.

The reunification of units (whether they are individuals, households, businesses or other) which are present at the same time in two or more databases can be particularly simple if the units present in the two databases are associated with a single identification code, for example the tax code, assuming that this code is reported correctly on all occasions.

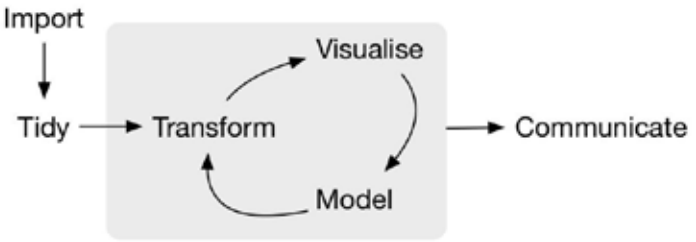
The tax code is the identification element most featured in the data sources that the pharmacist has at his disposal.

We have said that the data immediately available to the NHS pharmacist are many. Among these we can mention:

- patient identification code (Fiscal or tax Code);
- personal data (age, gender);
- medicinal product data (MA code, from which the other information on the medicinal product can be traced);
- disbursement date;
- quantity dispensed (from which it is possible to calculate the RDD – Received daily dose);
- standard prescribed quantity (expressed as DDD – Defined daily dose);
- actual prescribed quantity (expressed as PDD – Prescribed daily dose);
- interval between dispensing at the pharmacy, or Pharmacy Refill;
- expense.

If the availability of the data constitutes in itself an indispensable starting point for conducting drug utilisation studies, this is not sufficient to achieve the result. In fact, it is necessary to work on the data in a rigorous, logical and reproducible way.

The flowchart shown below represents the logical path that the pharmacist should follow when interfacing with raw data, as may be the direct dispensing of a medicine, prescriptions, data from SDOs or outpatient services and so on.



The path involves importing information into environments that allow it to be sorted and then transformed, visualized and modelled with the ultimate goal of effective communication.

All these steps involve direct work on the data. A job perhaps a little at the limit of the pharmacist's skills, because it involves the use of intermediate/advanced level information technology.

However, it seems essential for the profession of NHS pharmacist to acquire skills of this type, especially in this historical moment.

In addition to a greater ability to interpret, develop skills of data analysis can allow the pharmacist to confront, speaking the same language, with statisticians, data managers and computer scientists, as well as become more efficient in the daily work of data production, which is mentioned at the beginning, and therefore also in the interface with the clinical part, often not used to data analysis.

Through this approach it is therefore possible to obtain useful drug utilization indices from the data available to the NHS pharmacist. Let's look at some of them in more detail.

Grip

In 2003, the World Health Organization (WHO) defined adherence to treatment as "the extent to which a person's behaviour – in taking medications, following a diet and/or making lifestyle changes – corresponds to the recommendations agreed with the health personnel".

Introduction to Drug was published Utilization Research that has laid the foundations for drug utilization studies by introducing the indexes on which to build research in this area: the Consumed Daily Dose (CDD) and PDD. The CDD was later replaced by the RDD. These indices respectively describe the point of view of the clinician and the patient and represent the basis for one of the validated calculations of treatment adherence by integrating and, in some cases, replacing the DDD.

There are various methods of calculating this parameter and most of them are based on the pharmacy refill, i.e. the monitoring of pharmacy dispensing. The calculation of the RDD is given by the ratio between the dispensed dose and the difference in days between two successive dispensing. PDD, the prescribed dosage, must be closely monitored especially in cases where dosage adjustments are foreseen. In this case the most accurate method is given by the ratio between the RDD and the PDD since, above all in the case of drugs with personalized dosage (antitumor therapies for example), the DDD is difficult to standardize when not even valued by the WHO and, if PDD is not known, assessment of adherence may become unreliable or impractical.

The methods of calculating adherence most used when information on pharmacy refill is available are the MPR (Medication Possession Ratio) and the PDC (Proportion of Days Covered).

The MPR represents the number of days a patient has the medicine on hand in a given time period, divided by the number of days in the time period.

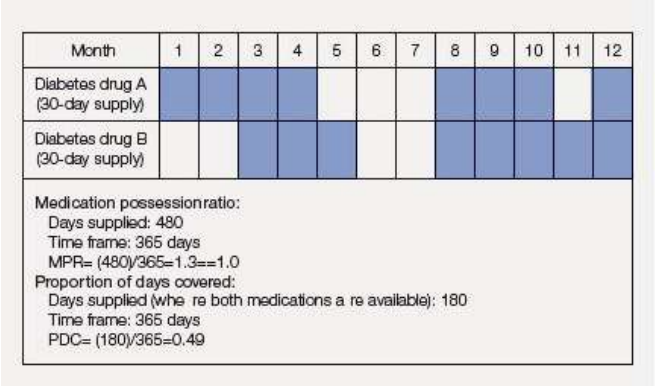
$$\text{MPR} = \left(\frac{\text{Sum of days' supply for all fills in period}}{\text{Number of days in period}} \right) \times 100\%$$

While the MMR does not accurately measure medication adherence to the extent that the patient is actually taking the medication as directed, it does assess whether the patient has access to the medication. This is an important part of the medication adherence process. Also, the MMR can be biased if the patient receives medications sooner than needed.

The PDC solves the problem of the possibility of having a distorted MPR by limiting the adherence ratio to 100%. The PDC is calculated as the ratio between the number of days in which the patient is covered by the drug and the number of days in which the patient is entitled to have the drug on hand.

$$\text{PDC} = \left(\frac{\text{Number of days in period "covered"}}{\text{Number of days in period}} \right) \times 100\%$$

The PDC report provides a more accurate representation of medication adherence because it eliminates the possibility of being unreasonably high.



Persistence

Treatment persistence represents the time a drug has been used and is calculated as the difference in days between the first and last dispensing. Persistence can be represented graphically and statistically by the Kaplan - Meier curve, assuming the end of treatment date as the patient discontinued therapy.

This curve expresses the "survival" of the treatment and is used in this case to correlate an event, the interruption of the studied therapy, with the time factor. The study event that establishes patient exit from treatment is any event that causes treatment discontinuation, such as progression, switch, hospitalization, intolerance, and/or adverse drug reaction.

In order to evaluate the persistence, it is necessary to define the parameters that identify the date of interruption of the treatment. In this regard, it is necessary to establish in advance the maximum admissible limit between two dispensations so that, once this limit has been exceeded, the end of the treatment can be identified.

This parameter cannot be standardized but is related to the type of drug, treatment and dosage.

In the analysis of persistence, the first and last dates are useful and, if the first date indicates the start of treatment, the last date is not indicative of the end of treatment because it identifies when the patient withdrew the last dose of drug but not when he stopped the therapy. In fact, despite having the entire cycle of therapy available, he could have used it only partially. Based on this premise, it is necessary to make a method assumptions in advance in

order to standardize the calculation methodology for all patients. In this way, the last interval is considered as if it were an ideal intake and the related dose completely and correctly taken.

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7. The Pharmacist's approach in carrying out an Observational Study, examples and explanations

B. Meini, A. Costantini, F. Santoleri, E. Pasut, M. Zito

With the effective entry into force of Regulation (EU) no. 536/2014 on clinical trials as of 31 January 2022, the way clinical trials of medicines are conducted in the European Union (EU) will undergo a major change, thanks to the harmonization of the evaluation and supervision processes for clinical trials in throughout the EU, through a Clinical Trials Information System (CTIS), with the main aim of making the EU competitive and attractive in terms of clinical research.

At national level, after a first legislative phase that laid the foundations for the reorganization of the Ethics Committees (Law 11 January 2018, no. 3, the so-called Lorenzin Law, articles 1 and 2), followed only by Legislative Decree 14 May 2019, no. 52, Italy arrives 31 January 2022 in delay with the consequent deeds.

At the same time, the field of medical devices and in vitro diagnostic devices (IVD) was also affected by regulatory renewal/upgrading, respectively with Regulation (EU) 2017/745 which entered into force on 26 May 2021 and Regulation (EU) 2017/746 (entry into force scheduled for 26 May 2022), in which the related aspects of clinical investigation are also set out.

However, the roles of the hospital pharmacist and of the national pharmaceutical services are confirmed within the framework of the legislation, both as a member of the Ethics Committees for clinical trials and as a competent figure delegated to manage the trial samples.

If at the IRCCS research is a *mission* and an integral part of the activity, while in the University Hospitals companies it is complementary, instead it is different in the Local Health Authorities where research is an added value to ordinary clinical activity, recognizing its clinical, organisational, economic and social impact in order to create value for the end user (patient), the payer (SSN(NHS)/SSR) and the multidisciplinary team (*reputation*).

It is now known that:

- the most qualified assistance is that which associates the **clinic** with **trials:** in other words, better care is taken where research is done;
- **research** and **treatment** must proceed together with attention to the quality of life of the sick and to sustainability on the part of the NHS;

- the complexity of the cases, the excellence in the treatments and the clinical research make it possible to carry out **continuous training in the field** for professionals, including the pharmacist, as foreseen and also recognized by the AGeNaS programs with regards to Non-Profit research.

Clinical trials today are represented by a complex mechanism which, in order to work, needs a multidisciplinary TEAM composed of various professional figures (Main Investigator, Pharmacist of Research, statistician, research nurse, laboratory technician, data manager). Consequently the success in conducting a trial is the result of the interaction between these different professionals. The absence of an adequate number of professionals dedicated to trials represents one of the main limiting factors for doing clinical research within the AASS.

In order for the above to be achieved, some general conditions are necessary:
coexistence with the institutional mission of the Healthcare Company (AS);
presence of adequate structures and corporate support tools;
regional policies, corporate guidelines and regulations;
absence of conflict of interests of the players;
knowledge and skills of individuals.

The hospital pharmacist and of the national pharmaceutical services has acquired knowledge and competence in the methods of Health Technology Assessment for years(HTA), Budget Impact Analysis (BIA), Cost Effectiveness Analysis, consultation of administrative databases (*Big Data)*. With the acquisition of other knowledge and skills (methodology of clinical trials and observational studies, basic principles of statistics and main dedicated computer software, knowledge of the pathology under study and clinical evaluation criteria; classification of toxicities, national and international legislation on the subject of studies on drugs and medical devices, principles of bioethics, knowledge of company processes (who does what), attention to detail, interpersonal skills; good knowledge of English and scientific writing), the pharmacist becomes an active protagonist (researcher) in the areas of Real Word Evidence and Outcomes Research.

The objectives that the Research Pharmacist must set himself when formulating a research hypothesis, according to the PICOS strategy (Population Intervention Comparison Outcomes Study Design), must be:

- review treatment profiles according to evidence of efficacy;
- support therapeutic innovation;
- respond to the real needs of sub-populations and individual patients;
- optimize the use of healthcare resources;
- promote rational organization action;
- guide access to new technologies.

With the period of the Sars-CoV2 pandemic, it emerged that the pharmacist has acquired awareness of the role of both a researcher and a specialized professional to support the design and planning of the execution of clinical and observational trials leading multidisciplinary teams.

Quality clinical research is correlated to a high standard of care at the pharmacy and the centre where it takes place. It is necessary to remember that in order for clinical research to be considered valid in its conclusions, it must be conducted by observing precise ethical-scientific rules and having followed the bureaucratic-administrative procedures defined by national and international control entities. Furthermore, professionalism, time, motivation and enthusiasm are required to be able to comply with these rules and carry out these processes.

Observational Studies

The main phases of the research are:

1. formulation of the research question on the basis of a circumscribed problem;
2. review of related literature;
3. formulation of the hypothesis;
4. selection of the appropriate study design;
5. elaboration of the study protocol, defining: study population, sampling, intervention (in the case of an experimental study) and comparison, method of measuring the variables, data collection and processing;
6. interpretation of results;
7. data communication.

Primary research includes observational and experimental studies, and is distinguished from secondary research which integrates the results of primary research through their evaluation, selection and synthesis. Secondary research includes systematic reviews, guidelines, HTA reports.

In his figure as a collaborator in the patient care process, the pharmacist can actively promote observational studies. These are characterized by the absence of active intervention: in fact, the researcher limits himself to the observation and collection of data.

Well-structured and rigorously conducted observational studies are of fundamental importance, for example to verify the efficacy of a treatment after its marketing and use in a "real" population, almost always different from that of the clinical study that led to its placing on the market. Or to verify its safety and any very rare adverse effects, not detectable in a limited sample population as occurs in the pivotal study.

Observational studies can be [1-2]:

- descriptive. The researcher describes only the event. For example case reports and case series used to describe rare adverse drug events;
- analytical. In addition to describing the event, the researcher also analyzes the data statistically. For example cohort studies, case-control studies, cross-sectional studies. Not all of these studies require a control group.

It is necessary to pay attention to the object of the research because not all treatments can be the subject of an observational study in Italy: the 2008 *Guidelines for observational studies on drugs* of the Italian Medicines Agency (AIFA) prescribe that observational studies can be conducted only for pharmacological therapies prescribed in normal clinical practice and in the indications for use of the Marketing Authorization (MA) of the study drug [3]. Observational studies of off-label treatments cannot therefore be authorized by the Ethics Committee.

Practical applications: drug utilization

Pharmacoutilisation is characterized by a set of analytical and descriptive methods for quantifying, understanding and evaluating the processes of prescribing, dispensing and consuming medicines as well as testing interventions to improve the quality of these processes [1]. Observational studies are an important tool for carrying out analyzes of drug utilization whose main objectives are the description of levels of adherence to and persistence of treatment. These analysis lay the foundations for performing efficacy analysis in Real Life and represent a bridge between pharmacists and clinicians.

In this regard, 4 practical examples are reported which describe what has been said previously with an approach that could be defined as pyramid-like (Fig. 1):

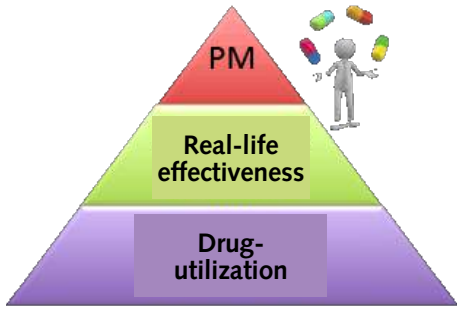


Fig. 1 – Pyramid approach: from drug use to Patient Management (PM).

1. **Drug Utilization Analysis:** Patient Adherence and Persistence with Imatinib, Nilotinib, Dasatinib in Clinical Practice [2];
2. Single-center **Real-Life efficacy analysis: Medication Adherence to Tyrosine Kinase Inhibitors: 2-Year Analysis of** Medication Adherence to Imatinib Treatment for Chronic Myeloid Leukemia and Correlation with the Depth of Molecular Response [3];
3. **Multicenter Real - Life efficacy analysis:** Adherence, persistence and efficacy of dasatinib and nilotinib in the treatment of patients resistant or intolerant to imatinib with chronic myeloid leukemia in chronic phase: an Italian multicenter study over two years in real life [4];
4. **Patient management projects:** Using a treatment diary to improve the medication adherence in patients with chronic myeloid leukemia [5].

In the first work [2] drug utilization analysis was conducted with the aim of describing adherence and one-year persistence in patients with chronic myeloid leukemia (CML) treated with imatinib, dasatinib and nilotinib. The cohort of patients analyzed was 102, most of whom were treated with Imatinib, 63. In this study, the analysis method of calculating adherence was described as the ratio between the Received Daily Dose (RDD) and the Prescribed Daily Dose (PDD). The RDD is the dose dispensed and, most likely, taken by the patient and is calculated as the ratio between the total dose dispensed and the interval in days between the two consecutive dispensing [6]. The PDD represents the dosage as indicated by the clinician and, especially for some pathologies such as onco-haematological ones, it can differ from the Defined Daily Dose (DDD) [7]. The use of the PDD minimizes the evaluation error in the calculation of the adherence when this differs from the DDD [8].

This first work in the field of haematology, conducted by pharmacists only, described adhesion levels of 0.83, 0.85 and 0.93 for imatinib, dasatinib and nilotinib, respectively, and an average of one-year persistence of 85% for all three drugs under study.

In the second work [3] thanks to the involvement of the haematological clinicians of the hospital of Pescara, the correlation between adhesion levels and the efficacy in Real Life as described by the transcript BCR- Abl has been studied [9] in patients with CML treated with imatinib at two years. In this, the correlation between adherence and therapeutic efficacy was demonstrated, describing that patients who had an adherence greater than 90% were also those who showed a better response to drug treatment described as complete remission of the disease. Conversely, patients with adherence levels below 0.8 were those who progressed and required switching to a second line of treatment.

In the third work [4] the second line of treatment was considered through a multicenter involving 6 hospital pharmacies and related haematology throughout Italy. In this study, in addition to treatment adherence, Progression-Free Survival was calculated(PFS) and Event-Free Survival (EFS). The two-year data analyzed on patients with chronic phase CML were found to be intolerant or resistant to imatinib and then treated with dasatinib and nilotinib, described levels of PFS equal to 93% and 76% EFS as the average of the drugs under study. No statistically significant difference was found between dasatinib and nilotinib which were found to have the same efficacy. The alarming figure, however, is that coming from EFS which, unlike PFS, describes treatment interruptions from all causes. Indeed, while PFS describes discontinuations due to disease progression only, EFS also describes discontinuations due to toxicity. This data is important since the patient, while not progressing, needs to change the line of therapy. This aspect reinforces the importance of reporting in the field of pharmacovigilance.

The fourth work [5] is an example of Patient Management. Patients referred to the Pescara hospital pharmacy were given a therapy diary in order to offer support to better follow their home therapy. The focus was on haematological patients in order to follow the in-depth study described so far. After a short introductory interview, the patient was given a therapy diary with the request to write down the time and dose taken daily and, on a scale from 1 to 5, report his general state of health. At each withdrawal of the drug following the first, the pharmacist was given back the filled-in part of the diary which was then subject to evaluation. We thus described the levels of adhesion as reported by the patient and, comparing the periods of taking the therapy without a therapy diary, evaluated whether the pharmacist's intervention through the therapy diary had improved adhesion to the treatment. Patients treated with imatinib, dasatinib and nilotinib who reported average adhesion values of 97.4% in the period of use of the diary versus 86.5% without diary were considered. The quality of life reported was an average of 3.46 on a range from 1 to 5. This study made it possible to demonstrate that the activity carried out by the pharmacist in direct distribution allowed, through the use of the therapy diary, an improvement in quality of care as an increase in adhesion to treatment which, as seen in previous works and ascertained by the international scientific panorama, is preparatory to therapeutic success.

At the conclusion of this brief argument on the realization of observational studies in the field of drug use, it can be deduced that the pharmacist has all the means at his disposal to perform analysis which offer important insights for reflection and improvement of clinical practice. It is necessary to get used

to measuring and monitoring one's activity which has important implications for public health.

Focus on Observational Studies on Biosimilars

Currently the biotechnological industry represents the backbone of the entire world pharmaceutical research; it is, in fact, a constantly growing sector. In recent years, the newest numerous patent expiries of biological/ biotechnological drugs on the world market have paved the way for the production of biosimilar drugs, thus providing the possibility of having additional therapeutic resources available for the treatment of many serious pathologies, with a considerable economic gain. Between 2013 and 2016, new biosimilar drugs were approved, Remsima and Inflectra (infliximab) which certainly play an important role in the possible replacement of Remicade, widely used in the dermatological, gastroenterological and rheumatologic fields. The Italian Medicines Agency (AIFA) defines the term "biosimilar" as a medicine, authorized by EMA through a centralized procedure, similar to the already authorized reference biological product and for which the patent coverage has expired. Biosimilar drugs are therefore similar in quality, efficacy and safety to reference biologicals but have a lower cost, which allows for the treatment of a greater number of patients and to widen access to high-cost therapies.

Infliximab is a tumor inhibitor Necrosisfactoralpha (TNF- α), a pleiotropic cytokine that has both pro-inflammatory and immuno regulatory functions. TNF - α is mainly produced by activated mononuclear phagocytes, but also by activated T cells, neutrophils, NK cells, and mast cells. The two forms of TNF- α (membrane mTNF and soluble sTNF), stimulate macrophages and other cells to secrete pro-inflammatory cytokines, such as interleukins (IL-1, IL-6 and IL-8), inducing lymphocyte activation T and the expression of adhesion molecules by endothelial cells. In the light of the studies carried out, TNF- α appears to be involved in the pathophysiology of autoimmune and chronic inflammatory diseases. The first anti-TNF- α to be introduced on the pharmacological market in 1998 is infliximab, a chimeric human-murine monoclonal antibody of the IgG1 type. Due to its pharmacological characteristics, it is used in various pathologies, alone or in combination with other drugs: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis, psoriasis, Crohn 's disease and ulcerative colitis.

The most common side effects encountered with infliximab administration are diverse including, neutropenia, leukopenia, dyslipidemia, depression, tachycardia, abdominal pain, nausea, impaired liver function, increased transaminases, arthralgia, myalgia.

Several studies, including PROSIT-BIO Cohort, have confirmed the overlapping of the biosimilar with respect to the originator (Fiorino et al, 2017), confirming that the efficacy and tolerability are comparable but that from an economic point of view the biosimilar is more advantageous.

Methods. To understand the trend of prescriptions and dispensations carried out, an analysis of drug use was conducted for the three-year period 2019-2021. The UOC of Pharmacy has launched a project involving the UOC of Gastroenterology. The medical records of the patients treated in the period under review and the dispensation carried out by the UOC Pharmacy were viewed and analysed, comparing the number of vials of Infliximab originator and Infliximabbiosimilar. From the number of packs dispensed it was possible to obtain the cost sustained by the Company and, to estimate, the savings achieved with the introduction of the biosimilar into clinical practice.

Results. From the analysis of the dispensation carried out, a growing trend was observed for the biosimilar, also confirmed by the data on the prescriptions of the last three years. In fact, in the three-year period 2019-2021, the number went from 56 to 215 packs (Fig. 1). Furthermore, the clinical data available and obtained from the analysis of medical records have shown good adherence to treatment with the biosimilar both in naïve patients and in patients who have made the therapeutic switch from originator to biosimilar.

Initiation of infliximab treatment biosimilar of patients was increasing and in line with national provisions: in 2019 patients treated with infliximabbiosimilar accounted for 25% while patients receiving infliximab originator accounted for 75%; in 2020, patients treated with the biosimilar represented 50% of the total; in 2021, 67% of patients were treated with infliximabbiosimilar while 33% used infliximab originator.

Analyzing the expenditure data, each bottle of Infliximab originator costs 456.50 Euros compared to 116.6 Euros for Infliximabbiosimilar. The savings obtained from the use of the biosimilar is evident (Fig. 2): considering that 327 were dispensed in 2021 and, of these, 215 refer to the biosimilar, the savings obtained amounted to 73,078.5 Euros.

Conclusions. To conclude, from the analysis of the data it is evident that the use of biosimilars is proving to be an excellent therapeutic resource, with an important reduction in costs necessary for the sustainability of the national health system and innovative therapies, in a context of rationalization of expenditure publish.

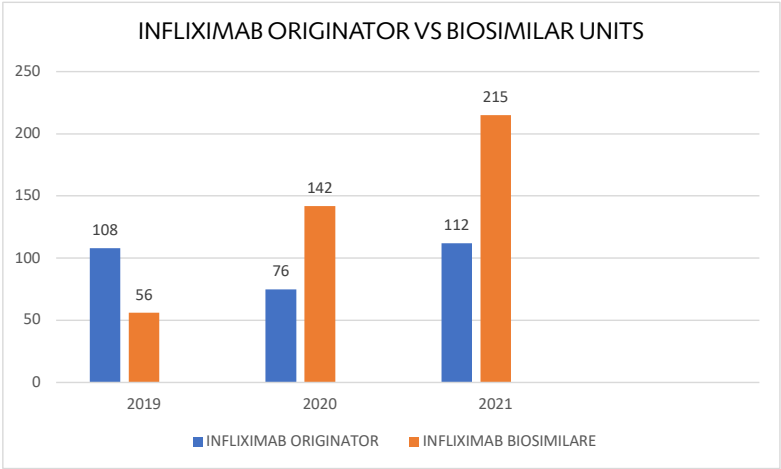
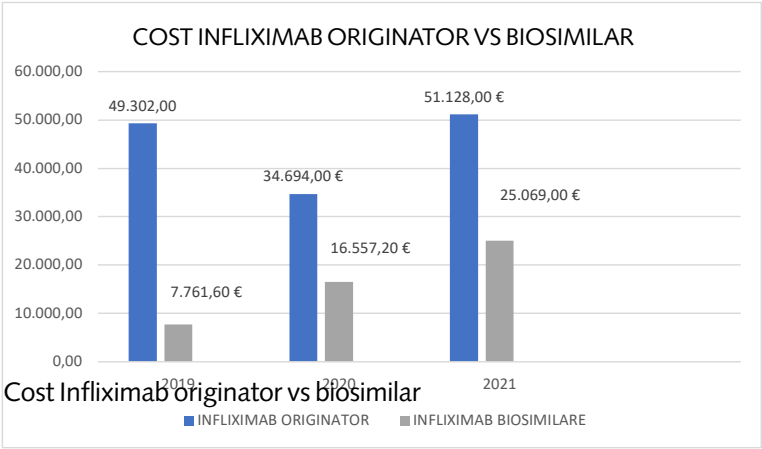


Fig. 1 – Packages dispensed in the three-year period 2019-2021.



Cost Infliximab originator vs biosimilar

Fig. 2 – Total price of packs dispensed in the three-year period 2019-2021.

Scarcity is a central fact of life. Since resources (land, money, fuel, time…) are scarce in relation to the uses we make of them, it is the task of rationality to allocate them.

H.A. Simon

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Module III: Non-Profit Research

Prefazione

Edited by the Scientific Tutors C. Polidori, G. Trifirò, P. Abrate, M.E. Faggiano, A. Bortolami, A. D'Arpino

Contrary to *Profit studies* in which the sponsor is a private company, for example a pharmaceutical company, in *Non-Profit studies* the sponsor is a public body or institution (ASL – Local Health Agency –, Research Institute, Onlus, collaborative group, one or more investigators…). Public institutions have all the technical and intellectual capacity to carry out a *Non-Profit study* through their professionals such as doctors and hospital pharmacists who can be active sponsors of these studies even if perhaps they have an organizational deficit that they certainly want to recover. The ability to plan, conduct and record data together with a guarantee of maximum transparency for the subjects involved in clinical trials make these protagonists real players and sponsors of good clinical practices well established by European regulations. Moreover, the participation of these professionals in particular in Ethics Committees strengthens their involvement. Surely the FO is constantly bombarded with real life data that must be made available to this *Non-Profit research* thus becoming a very important figure. Surely at the moment there are mainly two types of studies possible, the pharma-centric one and the PDTA-centric one but which must also be aimed at medical devices and all nutraceuticals and cosmetics. The results, then well presented following all the indications of the STROBE Statements will ensure that the conclusions/observations of the study can be made available to all those professionals who live in an environment common to the Italian researcher. Examples of *Non-Profit studies* are already present in Veneto and other regions that driven by considerations of expanding the therapeutic offer, always try to find resources through the study of therapeutic appropriateness as a last resort for acquiring new resources and health policy. The Italian Drug Agency must certainly play a key role in promoting and supporting *Non-Profit studies*.

1. Design, publication and ethics in Non Profit Research

A. Bortolami, G. Trifirò, E. Menditto, V. Russo, S. Crisafulli, Y. Ingrasciotta

Non-Profit research: definition and regulations

According to the Ministerial Decree (DM) of 17 December 2004, a Non-Profit trial is defined as a study financed and/or supported by public or research structures or bodies or institutions that have a Non-Profit purpose (sponsor), which are not owners of the patent of the trial drug or of the marketing authorization (MA) and which have no economic interests with the manufacturer of the trial drug [1]. Non-Profit clinical trials are aimed at improving clinical practice and recognized for this purpose by the competent Ethics Committee as a relevant trial.

The Ministerial Decree of 30 November 2021 [2], published in the *Official Gazette* (GU) of 22 February 2022, abolished the Ministerial Decree of 17 December 2004. Although without substantial changes in terms of definitions and requirements of No Profit trials, the new Ministerial Decree constitutes an important step forward for the collaboration between public and private, as it no longer provides that the ownership of the data relating to the trial, its execution and its results belong exclusively to the sponsor, but allows the transfer of data and results of a research Non-Profit both in the course of experimentation and once the trial is completed, for registration purposes: following this transfer, the specific provisions and facilitations envisaged for Non-Profit experimentation are no longer applicable.

The provisions of the Ministerial Decree of November 30, 2021 are not limited to clinical trials, but also apply to observational studies. According to the AIFA Resolution of 20 March 2008, for a study on a drug to be considered observational, the drug must be prescribed for the indications of use authorized in Italy during normal clinical practice [3]. Observational studies can also be either Non-Profit or Profit. For the qualification of a Non-Profit observational trial it is necessary to meet all the requirements foreseen for experimental studies.

The role of the Ethics Committee

According to the Decree of the Ministry of Health of 8 February 2013, "*Ethics Committees are independent bodies responsible for ensuring the protection of the rights, safety and well-being of people undergoing trials and for providing public guarantees of such protection. Where not*

already assigned to specific bodies, the Ethics Committees can also perform consultative functions in relation to ethical issues related to scientific and welfare activities, in order to protect and promote the values of the person. Furthermore, the Ethics Committees can propose training initiatives of health professionals on bioethics issues" [4]. The Ethics Committees must be made up of independent experts and include at least: three clinicians, a general practitioner, a paediatrician, a biostatistician, a pharmacologist, a regional health service pharmacist, the medical director or his permanent substitute (in relation to trials carried out at its headquarters) or the scientific director of the institution hosting the trial (in the case of Scientific Hospitalization and Treatment Institutes), a legal and insurance expert or a coroner, a bioethics expert, a representative of the health professions interested in the trial and a representative of the voluntary sector or patient protection associations. In relation to the topic of the study, the composition of the Ethics Committee may include the presence of clinical experts in the sector. For the assessment and decision regarding the admissibility of the trials, the Ethics Committees refer to legal documents and instruments shared at an international level as well as to all the regulations in force in this area at national and international level.

For the ethical aspects, the main references are the Declaration of Helsinki [5] and the Convention on Human Rights and Biomedicine [6]. These documents are aimed at protecting the dignity, rights and freedom of the human being with respect to the interests of research and underline the importance of informed consent. Regulation (EU) no. 536/2014 defines informed consent as "*the free and voluntary expression of a subject's willingness to participate in a specific clinical trial, after having been informed of all aspects of the clinical trial relevant to the subject's decision to participate or, in the case of minors and incapable subjects, the authorization or agreement of the respective legally designated representatives to include them in the clinical trial*" [7].

Non-Profit studies, the Ethics Committee has the responsibility of assessing whether or not the study is aimed at improving clinical practice, according to what is established by the Ministerial Decree of 17 December 2004. This assessment is fundamental, as the additional costs associated with the trials, supported by Non-Profit sponsors and deemed by the Ethics Committee aimed at improving clinical practice, can be covered by the appropriate Company Research Fund, established by the Ministerial Decree of 17 December 2004 [1]. In particular, the evaluation of the Ethics Committee must be aimed at verifying that the study satisfies all the requirements established by the Decree and that it is independent in the presence of third-

party lenders, on the basis of any agreements or deeds of donation that regulate the financing of the study.

Furthermore, according to the art. 6 of the Ministerial Decree of 30 November 2021 [2], the presentation of the observational studies and the related documentation must be entered by the sponsor in the AIFA Observational Studies Register, according to the forms published in the respective section of the institutional portal of the same Agency.

Observational studies, divided into prospective and retrospective, follow different approval procedures. The former require informed consent and can only be started after having received a favourable opinion from the competent Ethics Committee, valid for all the centres where the study will be carried out. In the case of retrospective observational studies, notification is sent to the Ethics Committee rather than seeking approval. On the basis of the specific institutional statute of the single Ethics Committees, these can proceed with a formal approval or with a simple acknowledgment.

Observational study design

The planning of an observational study requires the identification of the most suitable data source to answer the research question (for example administrative databases, spontaneous reporting systems, pathology/drug registers, general medicine databases, etc.), of the study population (e.g. children, adults, elderly, pregnant women, etc.), exposure (e.g. an individual drug or class of drugs), and the clinical outcome of interest. The research hypothesis, the type of observational study, the choice of sample size and the expected results must be clearly expressed in the protocol. It is then necessary to proceed with the planning of data analyzes and with the conduct of preliminary analyses. It is necessary that all these factors are accurately described in a study protocol, which will be submitted to the Ethics Committee. Substantial amendments to the study protocol must be notified to the Ethics Committee, based on the provisions for the specific types of study. The drafting of the study protocol is mandatory in the case of post-authorisation studies (Post-Authorisation Studies, PAS) imposed by the European Medicines Agency (EMA), which must be filed online on the EU PAS Register, a public register that aims to increase study transparency, reduce publication *bias*, promote information exchange and ensure adherence to the requirements set by the European legislation on pharmacovigilance. The study protocol also allows to facilitate the conduct of the study and understand its strengths and limitations.

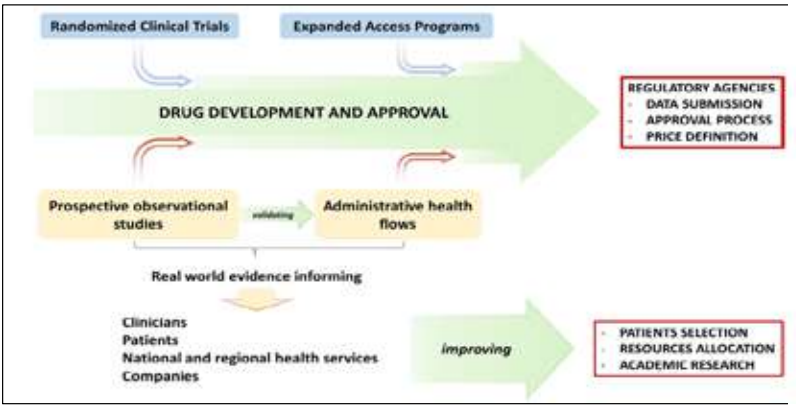
The importance of conducting Non-Profit studies is basically due to these factors:

- Improving clinical practice;
- Proposed and conducted directly by researchers;
- Multidisciplinarity of multiple professionals.

No Profit studies are essentially due to regulatory and financial difficulties, which are not always easily applicable, and the lack of studies that are not structured in a sufficient and innovative way.

Real World observational studies as randomized clinical trials often lack external validity. For example in oncology studies usually include selected patients who represent 2% to 4% of the overall cancer population and may under represent some patient categories, these problems could be solved by real world studies, Real World Data, where data collection from medical records reflects the experience of most cancer patients.

Real World Data (RWD) represent data relating to the health status of patients or the services provided and are usually collected in computer medical records and in various administrative databases of regional health facilities. They may concern hospitalizations, drug prescriptions and outpatient health services.



Real World Evidence is, as the term suggests, clinical evidence on the use, benefits and risks of a specific drug and more, and is based on Real World Data.

Whatever study is going to be conducted, clinical or observational trial, the goal is to generate evidence on the risk/benefit ratio of drugs, their efficacy and prescribing appropriateness. Even the EMA and FDA recommend and underline the importance of real-world retrospective and prospective studies and how much they represent a crucial tool in drug monitoring (Pasello G, CTR 2020).

In addition to the evaluation of drugs, Real World Data increasingly play a strategic role in evaluating health interventions with regard to the organizational aspects of health care and evaluating the Diagnostic Pathways of patients.

Real world data in the era of Immune Checkpoint Inhibitors (ICIs): Increasing evidence and future applications in lung cancer. Pasello G et al Cancer Treat Rev. 2020 Jul;87:102031. doi: 10.1016/j.ctrv.2020.102031. Epub 2020 May 16.PMID: 32446182

Real World observational study example

The added value of "Real World" observational clinical trials is to evaluate the appropriateness of care pathways as well as the safety and efficacy of drugs in patients usually excluded from randomized clinical trials.

In this sense, the MOST Study *"From Diagnostic-Therapeutic Pathways to Real-World Data: A Multicenter Prospective Study on Upfront Treatment for EGFR-Positive Non-Small Cell Lung Cancer". Pasello et al.* represents an example of a real world study in the oncology field that used the clinical records and administrative databases of hospital facilities.

The MOST study is a real-world data collection reporting multicenter adherence to defined diagnostic-therapeutic paths for patients with non-small cell lung cancer with epidermal growth factor receptor mutation in a region. This represents an essential element of evidence-based medicine, providing information about patients and situations that can be difficult to evaluate using only data from randomized controlled trials. This study may be of interest to various stakeholders (patients, clinicians, and decision makers), providing a meaningful picture of the value of a given therapy in clinical practice.

Introduction

The systemic treatment of non-small cell lung cancer (NSCLC) has undergone a remarkable evolution in the last 30 years. In particular, the launch of genomic sequencing programs has made it possible to further classify each histological subtype through the identification of molecular alterations underlying tumor growth and progression that could be potential targets for treatment. Most of the discoveries have been made in lung adenocarcinoma where epidermal growth factor receptor (EGFR) mutations are the target of tyrosine kinase inhibitors (TKIs) (gefitinib, erlotinib, afatinib) which, as a first-line treatment, induced progression-free survival (PFS) and improved response rate compared to platinum-based chemotherapy. The only head-to-head comparison between gefitinib and afatinib was the LUX-Lung7

phase II randomized clinical trial, which showed longer PFS and treatment failure time (TTF) in patients treated with afatinib compared with gefitinib. Indeed, no clear criteria are available for treatment selection among the three TKIs, although a different toxicity profile has been shown in recent meta-analyses. In addition, the results of the published study present some limitations regarding transferability to the real-world context because Caucasian patients and patients with impaired performance status were underrepresented.

Study	Treatment	N	RR(%)	PFS (months)	OS (months)	Cross-Over
IPASS *Mok et al, NEJM 2009*	Gefitinib Carbo/Paclitaxel	132 129	71.2 *P<0.001* 47.3	9.5 *P<0.001* 6.3	21.6 *P=0.99* 21.9	Permitted. 2° line TKIs: 64%
FIRST-Signal *Lee et al, JCO 2012*	Gefitinib Cis/Gem	22 6	84.6 *p<0.002* 37.5	8.4 *P=0.084* 6.7	30.6 *P=0.64* 26.5	Not permitted. 2° line TKIs: 75%
NEJSG002 *Maemondo et al, NEJM 2010*	Gefitinib Carbo/Paclitaxel	114 110	73.7 *P<0.001* 30.7	10.8 *P<0.001* 5.4	30.5 *P=0.31* 23.6	Permitted. 2° line TKIs: 95%
WJTOG 3405 *Mitsudomi et al, Lancet Onc 2010 (Updated 2012)*	Gefitinib Cis/Docetaxel	86 86	62.1 *P<0.001* 32.2	9.2 *P<0.001* 6.3	35.5 *P=0.44* 38.8	Not permitted. 2° line TKIs: 91%
OPTIMAL *Zhou et al, Lancet Oncol 2011*	Erlotinib Carbo/Gem	82 72	82.9 *P<0.001* 36.1	13.1 *P<0.001* 4.6	N/R N/R	Unknown
EURTAC *Rosell et al, Lancet Oncol 2012*	Erlotinib Cis or Carbo + Docetaxel or Gem	86 87	55 *P<0.001* 11	9.7 *P<0.001* 5.2	N/R N/R	Permitted. 2° line TKIs: 76%
LUX-Lung 3 and 6 *Sequist et al, JCO 2013* *Wu et al, Lancet Oncol 2014*	Afatinib Cis/Pem Cis/Gem	230 (LUX-L3) 242 (LUX-L6) 115 122	56 67 23 *P<0.001* 23 *P<0.0001*	11.1 11 6-9 *P<0.001* 5.6 *P<0.0001*	28.2 23.1 28.2 *P=0.39* 23.5 *P=0.61*	Permitted[1]. 2° line TKIs 75% 56%

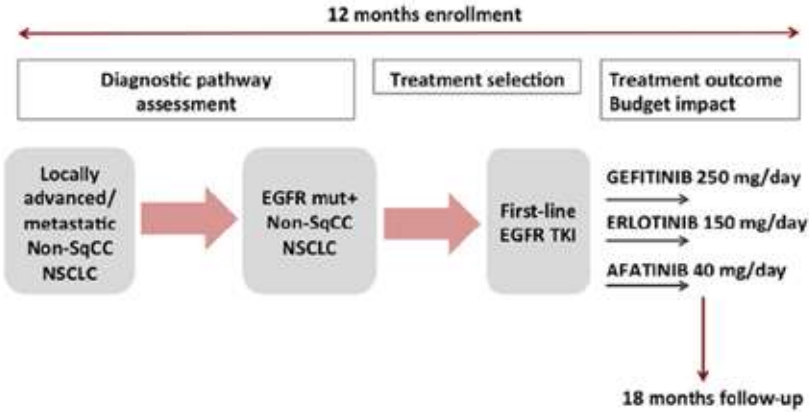
On the other hand, the molecular characterization of NSCLC is still suboptimal in many cancer centres both in terms of the proportion of patients with available molecular tests and the time to obtain molecular results before starting treatment.

The diagnostic-therapeutic paths in oncology have been encouraged by scientific societies and improved in all countries in recent years, in order to promote quality and value in cancer care, to provide evidence-based treatment protocols for patient presentations specific, to balance efficacy, safety, toxicity and cost.

Methods: the MOST study is a multicenter observational study conducted in 18 medical oncologies in the Veneto Region, aimed at monitoring the

diagnostic-therapeutic path of patients with nonsquamous lung cancer with EGFR mutation, considering first-line treatments with TKIs which consisted of one of three recommended drugs available in this setting at the time of the study: gefitinib; erlotinib and afatinib 40 mg.

In the figure below, a schematic representation of the study:



Objectives: The primary endpoint of the study was to evaluate the compliance of the participating centres with the diagnostic-therapeutic paths and with the therapeutic recommendations defined and expressed by the Veneto in particular:

a) proportion of nonsquamous NSCLC with EGFR mutation testing available at diagnosis;
b) time lag between the date of receipt of the diagnostic biopsy at the pathology unit and the histological report (including the EGFR mutation test);
c) number of EGFR mutation analyzes performed automatically by the pathologist (reflex testing) or on request by the physician; d) Proportion of EGFR mutant patients who received EGFR TKIs first-line and with each EGFR TKI.

The secondary endpoint of the study was to evaluate in a "real" practice the treatment outcome of the participating centres and the analysis of the budgetary impact of first-line EGFR TKIs.

The source of the data is the medical records and the data has been collected in an electronic form (*Case Report Form*).

Treatment outcome was reported in terms of median to treatment failure (mTTF). The impact of each drug on regional health system expenditure in

clinical practice was evaluated against the prediction based on the pivotal study.

Results: EGFR mutation testing was performed in 447 enrolled patients, within 12 working days (Fig. 1); 126 EGFR mutant cases were enrolled and received an EGFR TKI as first-line treatment in 98% of cases: 69 (55%) gefitinib, 33 (27%) erlotinib and 22 (18%) afatinib (Fig. 3).

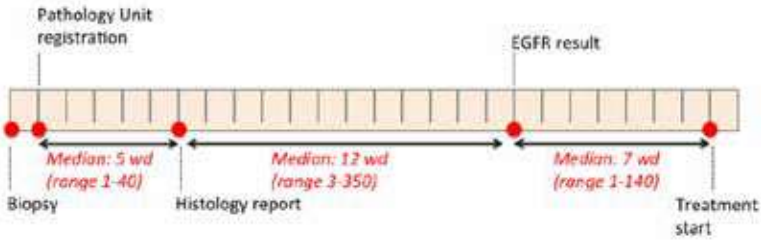


Fig. 1 – EGFR test outcome time.

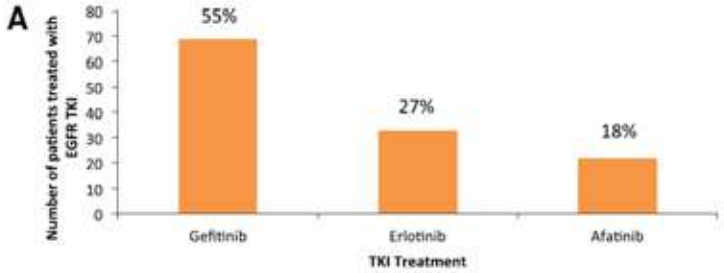


Fig. 2 – EGFR treatment distribution.

The mTTF was 15.3 months in patients who received an EGFR TKI, with no differences between the three study groups (Fig. 4). Budget impact analysis showed an estimated cost of €3,238,602.17 according to the median TTF of patients treated within the MOST study, while the estimated cost according to median progression-free survival from the pivotal studies phase III was €1,613,318.19 (Fig. 4).

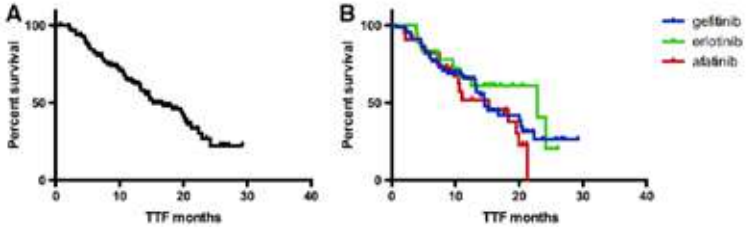


Fig. 3 – Median to treatment failure (mTTF).

Drug	Reimbursement method	MOST pts (n = 109)	% treatment interruption (MOST)	% treatment interruption (pivotal trials)	mTTF MOST, mo	mPFS pivotal trials, mo	Monthly price, €	Cost/patient based on mTTF (MOST, PBR excluded), €	Real BI based on mTTF (MOST,PBR excluded), €	Cost/patient based on mPFS (pivotal trials, PBR excluded), €	Theoretical BI based on mPFS (pivotal trials, PBR included), €	BI gap (real theoretical), €
Gefitinib	3 mo PBR	89	9	14	14.6	9.5	2,160	27,434.43	2,007,949.98	20,808.14	1,234,764.73	773,185.25
Erlotinib	50% CS (first two packs)	18	NA	NA	22.9	9.7	1,865	40,834.08	735,013.49	16,221.76	291,991.66	443,021.83
Afatinib	6 mo PBR	22	18	34	15.3	11	1,796	33,978.82	495,638.68	19,752.86	286,811.49	208,827.21
Total		109							3,238,602.17		1,813,557.88	1,425,044.29

Abbreviations: BI, budget impact; CS, cost sharing; mPFS, progression-free survival; mTTF, time to treatment failure; NA, not applicable; PBR, payment by result; pts, patients.

Fig. 4 – Budget Impact Analysis.

Conclusion: The importance of real-world clinical and administrative health data collection to improve scientific evidence on the safety and efficacy of medical treatments is also highlighted by this study.

Furthermore, this study, which determines the treatment failure time with EGFR TKI, allows to effectively calculate the expenditure of the regional health service for the three drugs while the price negotiation is defined on the basis of pivot phase III studies. Our budget impact analysis, based on the reimbursement criteria and the different duration of treatment between the MOST and the RCT studies, showed a gap of €1,625,283.98, thus suggesting the potential application of the world data real in the drug price negotiation process.

Stages for the development of a research project

Healthcare research

The integration between health care insurance, training activities aimed at improving the quality and effectiveness of health services and scientific research as the engine of health progress, have been a fundamental *trait d'union* since the establishment of the National Health Service (SSN). Specifically, in this chapter we will focus on the basics of **health research**, defined by the Ministry of Health: "*Health research is to be understood as an integral part of the activities of the National Health Service (SSN) as it*

is a fundamental element for guaranteeing citizens effective health care, efficient and of good quality, responding to the real needs of assistance and care of the country. The objective of health research is not scientific and technological progress as an end in itself, but the improvement of assistance, treatments and services, with the final aim of significantly increasing the health of citizens and therefore their expectations and quality of life".

Health research, therefore, is not limited exclusively to the study of pathologies and the development of new therapeutic approaches, but is also a useful governance tool for health policies. On the other hand, training and information activities aimed at health professionals are also part of health research.

- In this context, to promote innovation and the development of scientific research, as well as to improve health care, numerous **research announcements are published every year funded** both on national and European territory. Some of the most important are as follows:
- Horizon Europe - European Commission;
- Finalized research announcements - Ministry of Health;

Announcements of Independent Research - Italian Medicines Agency (AIFA). Participation in funded research notices requires the possession of particular requirements and correspondence to specific thematic areas to be followed. Therefore, the first step to take is to identify the most suitable program to finance your project idea. In the case, for example, of Finalized Research Announcements there are different types, among which you can choose:

- Ordinary targeted research projects (RF): they are the main type of project.
- Co-financed projects (CO): are research projects to which private funding is secured by companies with activities in Italy, in order to guarantee the development of ideas and/or whose patent is owned by the IP or by the NHS institution submitting the project.
- Ordinary projects presented by young researchers (GR): research projects presented by researchers under the age of 40.

Once the target has been identified, it is advisable to have a clear idea of what your project intends to achieve in order to be able to verify that the research idea is in line with the eligibility criteria of the notice. The next step consists in the "drafting of the idea" through the creation of **the research protocol** that describes in a clear and organized way all the aspects that will concern the future project.

In this chapter we will try to provide some suggestions on what are the main steps to follow for the presentation of a project proposal in the context of funded research.

Funded research

The health research programs in Italy are promoted, among others, by the Ministry of Health and differ in **current research** and **targeted research**, as regulated by articles 12 and 12 bis of Legislative Decree no. 502/1992, through the two types of research.

By **current research** means research oriented towards the development of knowledge in the biomedical and public health fields, is conducted through projects of national research organizations and public and private institutional subjects whose research activities have been recognized by the State as being aimed at public purposes. The major recipients of current research are public and private scientific hospitalization and treatment institutes-IRCCS.

Targeted **research**, on the other hand, is divided into projects and implements the objectives defined by the strategic guidelines of the national health plan. Public and private research bodies, universities and also public or private companies can contribute to the execution of the projects.

Then there is the **independent research on drugs**, a type of research that investigates areas for which there is no concrete commercial interest, but which nonetheless have a great impact in the health sector. In fact, AIFA was the first European body to have included the promotion of **independent research on drugs among its institutional missions,** not only for its interest in purely scientific aspects, but also for those of a regulatory nature.

In this regard, the independent research on drugs financed with the AIFA tender pays particular attention to some thematic areas of interest in a given period. For example, the AIFA 2017 notice promoted research with particular attention to the following thematic areas:

a. Rare diseases;
b. Paediatric diseases;
c. Gender medicine;
d. Safety and efficacy of drugs in elderly and ultra-elderly populations;
e. Antimicrobic resistance.

The AIFA 2018 Notice, on the other hand, focused on five different thematic areas:

a. Rare diseases;
b. Controlled comparative clinical trials;
c. Chimeric Antigen Receptor T-cell (CAR-T cells).

Therefore, in all these thematic areas, independent clinical research can contribute to developing new knowledge, indispensable both for optimizing current clinical practice and for better orienting decisions of a regulatory nature.

The phases of the development of a research project

The research project proposal is the document describing the purpose of the research, the objective(s) to be pursued, the applied methodology, the statistical tools that will be used and the organization of the various phases of the research. Therefore, you must ensure that you provide the reader with a clear description of your proposed project. When preparing a research project, it is appropriate to ask yourself some questions:

1. Is the purpose of the study clearly stated?
2. Are the objectives of the study in line with the purpose?
3. Has a study design been produced that makes the purpose of the research easily achievable?

Below is a diagram that describes the design process to be followed in the drafting of a research project proposal.

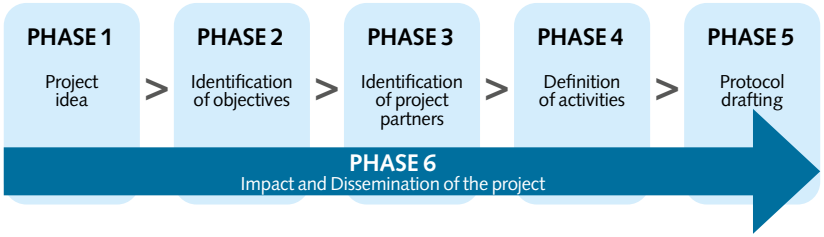


Fig. 5 - Description of the design process (adapted from EuroPAFormez "How to submit a project proposal under EU direct funding").

Phase 1: Idea of the project

The idea of the project was created with the aim of providing possible solutions to the problem described in the tender to which it intends to participate. The first step in the drafting of the research protocol corresponds to the specific definition of the project idea. It will therefore be necessary to verify whether your research idea respects two fundamental criteria:

- My research idea **fills the cognitive gaps** with respect to the subject under study present in the literature up to that moment;
- My research idea **brings novelty** to what has already been published on the subject.

Phase 2: Identification of research objectives

The objective or objectives of the project must certainly be in line with the questions established by the Notice in which one intends to participate. They must be clear, measurable/quantifiable and above all they must be concrete and achievable.

Phase 3: Identification of project partners

A crucial point is represented by the choice of the right partnership. In fact, the partnership is nothing more than a collaborative relationship between all those who will take part in the research project and who have common interests aimed at pursuing the objectives of the study. The establishment of a good partnership represents a particularly relevant aspect in the realization of the research project. In fact, when drafting the protocol, it is noteworthy to specify and verify any previous or existing collaborations with the project partners. Therefore, the partnership must be established already in the initial stages of the elaboration of the idea.

In this phase, a crucial step is represented by the choice of the Main Investigator (PI) (MI), also known as the scientific manager of the project. The Main Investigator must respond to specific characteristics such as:

- Must have **proven experience and skills** in the topic of interest;
- Must have **ability to carry out research independently;**
- Must have a **significant number of publications** as lead author in internationally accredited journals.

The MI (PI) is the only subject responsible for the implementation of the project towards the examining commission because:

- He is the one who receives the funding of the commission and ensures its distribution to each participant;
- manages financial operations;
- provides reports on the progress of the project.

The other project partners can be both natural persons and entities/ organisations with previous experience in the implementation of financed projects, and less experienced people who have proven experience in the project's sector of competence. The number of people who will take part in the project may vary according to the type of project, the duration, the bodies involved, the number and type of interventions to be carried out. Finally, it should be considered that the project partners establish a collaborative and coordination relationship with the MI (PI) already in the initial stages of drafting the proposal; therefore, once the project has been adjudicated, their contribution consists in the pursuit of one or more objectives of the study.

Phase 4: Definition of the activities

Another crucial aspect in drafting a research protocol is feasibility or applicability. In order to prove the feasibility of the project, it is necessary to indicate in detail, in the research protocol, the times required for the realization of each phase of the project. Generally, the project goal timeline is shown graphically through the use of a **GANTT chart.**

The GANTT chart is a calendar that marks the chronology and duration of the various project activities. It consists of a horizontal axis that represents the project's time frame, divided into one or more incremental phases (for example, days, weeks, months) and a vertical axis that represents the various activities that make up the project.

				Months	1				2				3			
				Quartiles	1	2	3	4	1	2	3	4	1	2	3	4
WBS	ACTIVITY NAME	DURATION (days)	START	END												
1	Phase	90	dd/mm/year	dd/mm/year												
1.1	Activity	60	dd/mm/year	dd/mm/year												
1.1.1	Objective	30	dd/mm/year	dd/mm/year												
1.1.2	Objective	90	dd/mm/year	dd/mm/year												
1.2	Activity	120	dd/mm/year	dd/mm/year												
1.2.1	Objective	120	dd/mm/year	dd/mm/year												
1.2.2	Objective	90	dd/mm/year	dd/mm/year												
2	Phase	90	dd/mm/year	dd/mm/year												
2.1	Activity	150	dd/mm/year	dd/mm/year												
2.1.1	Objective	210	dd/mm/year	dd/mm/year												
2.1.2	Objective	180	dd/mm/year	dd/mm/year												
2.2	Activity	150	dd/mm/year	dd/mm/year												
2.2.1	Objective	120	dd/mm/year	dd/mm/year												
2.2.2	Objective	30	dd/mm/year	dd/mm/year												

Fig. 6 – Example of GANTT diagram.

Phase 5: Drafting of the protocol

Title and keywords: The first step in drafting a scientific project is choosing the title. The title should be catchy, clear and concise that clearly identifies the goal of the work being performed. Furthermore, it is good that the title contains the keywords that are repeated the most in the project. The title is usually followed by an acronym which is referred to throughout the Project.

In addition, it is good practice to provide a list of keywords whose purpose is to facilitate the classification of the study in the field of interest of a given discipline. The keywords could refer, for example, to a pathology, to the study tools, to the investigation parameters.

Background: The next step corresponds to drafting the background of the study. A fundamental aspect in the drafting of the rationale is the clarity and cognitive skills with which the subject of experimentation is exposed. The background, therefore, must include a *ratio* explaining the reasons why the research deserves to be conducted in the light of what is already known. The rationale must be considered as the instrument through which one tries to convince the reviewer to finance his study. In drafting the background we should include a critical evaluation of current knowledge on the subject, highlighting knowledge gaps and deficiencies on what has already been published and the advantages that our trial can bring. Furthermore, the rationale should be written in a clear and punctual manner respecting the dimensions indicated in the Notice for Proposals.

Objective: The research project proposal may contain one or more objectives, their number should be kept low as too many objectives would be difficult to pursue and could indicate poor applicability of the project. First, we should define a **primary objective** that represents the main objective, i.e. the one that plays an important role in the study. The **secondary objective** may or may not be included in the study. The latter concerns more general, non-specific objectives (such as, for example, the creation of a database).

Study Design: When designing a research project, it is necessary to accurately define the methodology and study design (for example, whether it is a randomized controlled trial, a cross-sectional, case-control, retrospective, etc.). This phase is of fundamental importance since it explains how the project proposer really intend to pursue the objectives set and, therefore, it must be explained in detail.

Study setting: When drafting a protocol, a section must be dedicated to the study setting, i.e. the description of the place/organisation where the trial will be conducted. It is also important to check whether studies involving the same geographical area or the same population have been previously published in the literature, in order to be able to quickly identify any problems encountered with the same trial setting.

Study population: In this section, a detailed description of the population covered by our scientific investigation should be carried out, following some general rules (number, demographic characteristics, etc.) and adequately defining the criteria for inclusion and exclusion. When we talk about **inclusion criteria** we refer to those characteristics that perfectly describe the population of a study. These characteristics, necessary for a participant to be included or not in the study, can be based on factors such as age, gender, having or not having a certain pathology and so on.

The **exclusion criteria, on the** other hand, concern all those characteristics that make the participants ineligible for the study. The identification of the exclusion criteria is essential to ensure that only subjects with the required prerequisites are enrolled, thus reducing *bias* as much as possible. This will ensure greater success of the study and reduce the probability of statistical error during subsequent data analysis.

Data source: A brief description of the type of data used to conduct the study is given in the section dedicated to the data source. The data sources can be

varied and depend on the type of research to be conducted. Some examples are administrative databases, interviews, medical records.

Sample size and statistical analysis: Another very important aspect in the drafting of a research protocol is the definition of the sample size and the analysis of power. This calculation is used to estimate the number of participants needed to measure the primary outcome with an accepted power. In the section dedicated to statistical analysis, a brief description of the statistical methods used to achieve the objectives of the study is provided (for example, t-test, chi-squared). This description should detail how the statistical methods relate to the achievement of the study objectives.

Study Outcomes: In drafting a study protocol, researchers must define the **primary outcome** and possibly one or more **secondary outcomes**. Generally, the primary outcome refers to the most important and relevant findings of the study. Secondary outcomes may provide information of additional research interest.

Ethical considerations: A valid study protocol must consider the inclusion of a section dedicated to ethical considerations. In this section, the authorizations issued by the various Ethics Committees to conduct the study are not presented, rather it is a declaration of commitment to proceed with the experimentation in accordance with the principles of ethical conduct in human research, respecting personal data and respecting the laws and regulations of the country in which the research is conducted.

Bibliography: Finally, to support the project idea, it is necessary to include the most relevant bibliographic references used for drafting the research protocol, taking care to avoid quoting abstracts, unpublished observations, works sent to journals and in progress evaluation, secondary sources and unread sources.

Phase 6 - Impact and Dissemination

The impact represents any kind of benefit that the study can bring to the NHS. It need not necessarily be of a financial nature since the impact brought about by the innovation can be social, technical, commercial, environmental, and must therefore project beyond the duration of the project.

Dissemination, on the other hand, is nothing more than the dissemination of the results of a research project. It is a communication activity that encourages the use of the results by various stakeholders (other researchers, industries, decision makers).

When drafting a research protocol it is good practice to create a plan for the **dissemination and exploitation of the results.**The plan should contain the **measures to be implemented** both during and after the end of the project and furthermore, it should outline the strategy to be adopted for knowledge management and **data protection.**

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2. Choice of Scientific Sources and Bibliography in Non-Profit Research

D. Scala, E. Menditto, V. Russo

The sources' selection

In designing a new research project, the first step is to become acquainted with the state of the art related to the selected topic, that is, to analyze as many as possible studies published on the topic you intend to investigate in depth. This survey allows, on the one hand, to get to know the literature in the field and, on the other, to understand whether the founding idea of the research is original or not. If the research idea is original, the collection and selection of the material found through careful and rigorous bibliographic research will provide a solid base to refer to in order to support the results obtained, to compare them with the most important previous contributions and to suggest any insights on the topics covered. Thus, the selection of sources and a well-done bibliography are important parts of any research paper: the bibliography must always be accurate and written properly to let other researchers find the information you found, so that they be able to fully read it.

Ways and strategies to search for sources, in particular, the use of the most frequently consulted database "Pubmed" (https://pubmed.ncbi.nlm.nih.gov/), are fully described in Volume 2 of *The SIFO Manuals: Guidelines for Scientific Writing*.

In this publication, the authors focus on explaining the new features introduced in Pubmed in early 2020 and not described in the previous handbook. The new PubMed interface features are aimed at making Pubmed a modern tool, equipped with a fast, reliable and intuitive search method, capable of providing people with the world's leading sources of biomedical information (Fig. 1).

Some features and functions in the old system are available in the new one: the *Advanced Search* (advanced search), the *Search Details* (the visualization of strategies), the *Downloadable Search History* (search strategies and search results chronology), the *OutsideTool Iicons* (LinkOut to full text), *My NCBI* (a space where you can save search strategies and bibliographies), Links to MeSH terms.

To these, new features are added. You can now see snippets from the abstract where your search terms or terms mapped from your search terms appear. The new PubMed allows you to browse PubMed results from the

Fig. 1 – Pubmed interface version 2020.

abstract format. If you hover your cursor over the arrow of the previous or next result, an abstract of the previous or next result will appear. You can also find a navigation menu, to quickly get you to the part of the record of interest. New PubMed offers a citation saving feature that supports AMA, MLA, APA, and NLM citation style formats. Once you have found your desired articles, you have to select "Cite", located below the article abstract, select your desired format by clicking on "Format", which automatically formats to AMA. In addition, the new interface allows users to share citations to Facebook or Twitter and to copy a permalink to share from the results page. Once you have found your desired articles, you have to select "Share" below the article abstract, to share to social media, select either the Facebook or Twitter icon, to copy the permalink, either highlight and copy, or select the copy button. You may then paste in your desired location. You have, finally, your links to the full text, including up to 5 icons for your library subscriptions, to bring you and your patrons to your institution's online subscriptions. Note that you have the full PubMed experience on any size screen, including the ability to save and email citations, use the Clipboard, and send citations to My NCBI Collections on your mobile device.

The new PubMed system comes with improved mapping between British and American spelling, so you don't have to worry about including the variant forms in your search. In addition to the familiar automatic term mapping to MeSH, the new PubMed includes additional useful synonymy, including plural forms. Whereas the legacy PubMed used only the first 600 variations of a truncated stem, the new PubMed features unlimited truncation. The Best Match sorting algorithm will bring the most relevant results to the top of your search results.

Figure 2 shows the citation in the abstract format with the new features. In the side menu you can find Links to the full text, including the publisher icon

Fig. 2 – Citation in the Abstract format.

and the PubMed Central icon; quick ways to save the citation information: the Cite button, and your Favorites button, which saves the citation to My NCBI. The social media links provide you a link back to PubMed, so you can easily share information with your colleagues on Twitter or Facebook. The navigation menu within the record.

The Cite feature allows you to easily generate a properly-styled citation in AMA, MLA, APA or NLM citation format. You can also download the citation in .nbib format, which is a standard citation format used widely in reference management software (p.e. EndNote, Mendeley, RefWorks, ecc.) (Fig. 3).

Figure 4 shows the search results on a topic, for example, Medical Humanities Education.

Results are sorted by "Best Match" (default). A graphic of the distribution of articles by year of publication is shown. You can temporally limit the search by acting directly on the graphic. "Save", "Email", "Send to" features allow users to save to a file, email or export one or more selected citations. Abstract

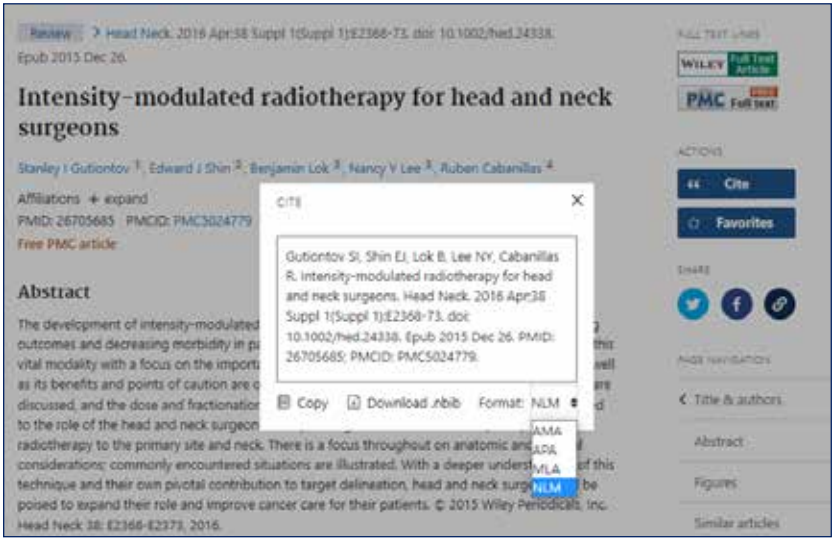

Fig. 3 – Cite button feature.

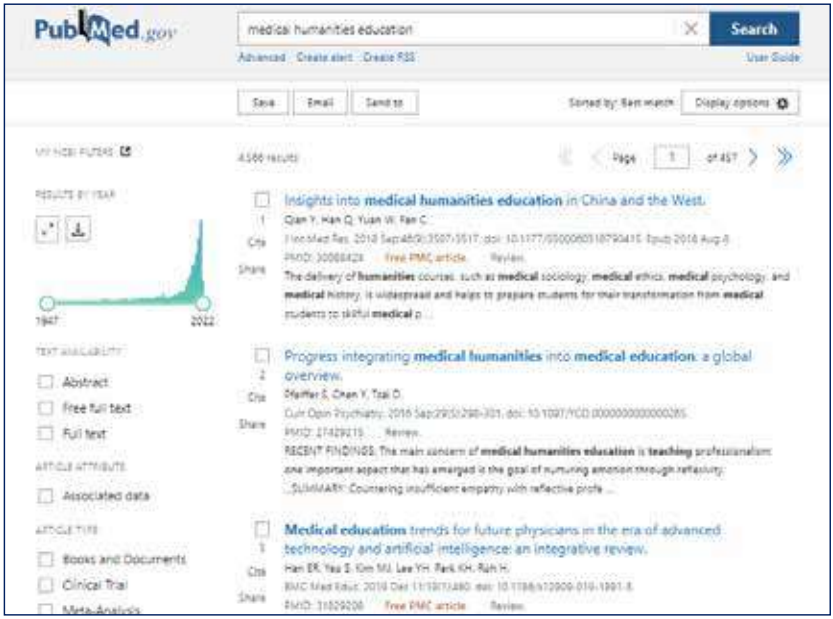

Fig. 4 – Search results display.

snippets are displayed. There is the choice to narrow the search by acting on the filters, access to the Advanced search function, to set an Alert by the feature "Create alert" and the "Cite" and "Share" buttons. You can scroll through the results from the abstract format by hovering the mouse over the tabs "Prev. Result" or "Next Result" and the abstract of the previous or next article will appear (Fig. 5).

"Send to" feature allows the user to temporary save citations. The Clipboard provides a place to collect up to 500 items from one or more searches. Items saved to the Clipboard are stored in your browser cookies and will expire after 8 hours of inactivity; you can save citations to "My Bibliography"; you can add up to 1000 citations to the "Collections" contained in your My NCBI profile, there is no limit to the number of collections you may store in My NCBI. In addition, collections can be made public to share with others. You can export citations as an .nbib file that can be used by many citation management program (Citation Manager) (Fig. 6).

Fig. 5 – Scrolling results form the abstract format.

Fig. 6 – Send to feature.

The Advanced Search function allows the user to search for terms in a specific field, such as author or journal. For some fields, an autocomplete feature will provide suggestions as you types (Fig. 7). The Advanced Search Builder includes also the Show Index feature, which provides an alphabetical display of terms appearing in selected PubMed search fields (Fig. 8), and finally it is possible to combine searches and build large, complex search strings.

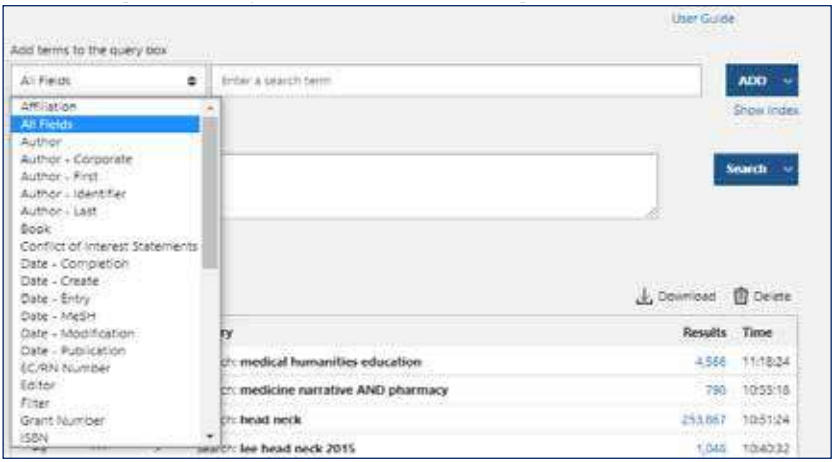

Fig. 7 – Advanced Search.

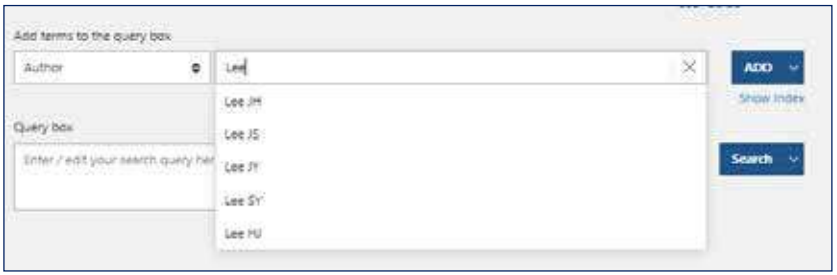

Fig. 8 – Advanced Search.

The History and Search Details function allows the user to view and to download the search history, and to generate a CSV file of current History items, to view (by clicking >) the details of the search, compare the results of multiple searches, and combine previously searches (Fig. 9).

You can expand the Search Details by clicking the ">" next to a query in History. When expanded, the details below a query in the History table show the search strategy used to run the search. Translations show individual term mappings using PubMed's search rules and syntax (Fig. 10).

Fig. 9 – History and Search Details.

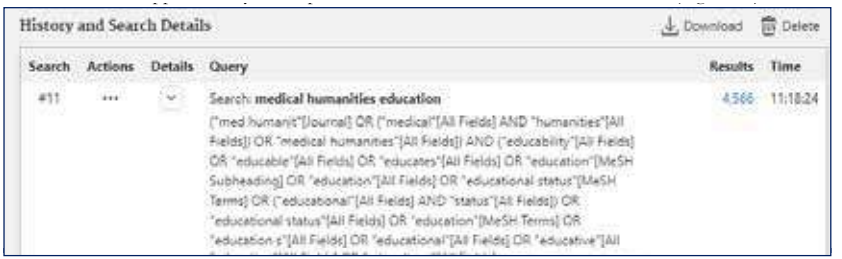

Fig. 10 – Search Details.

For more comprehensive information and assistance see Pubmed. User Guide is accessible from the main page. You can also explore Pubmed online tutorials and classes via the PubMed Online Training page.

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Writing a manuscript

The preparation of a manuscript is nothing more than the final moment of a broad and articulated process, which includes different operational levels in close interrelation with each other: from the collection of data to their analysis, from the drafting of the study protocol to the presentation of the manuscript to a publisher, each of these phases is, in fact, linked to the others.

The drafting phase of a manuscript constitutes the culmination of a certain study process which is necessary in order to be able to share the results achieved with the scientific community. From a methodological point of view, every article or book of a scientific nature must have the following purposes:

- Make a summary of the most relevant information obtained;
- Making a study accessible to the scientific community;
- Increase its impact (*Health Policy*).

Before starting the actual writing phase, since scientific knowledge is, by its nature, subject to continuous updating, it is necessary to collect and select the support material through a careful study of the reference literature. In this way, a systematic *corpus* of notions will be created from which to draw to support and validate one's arguments.

Once the documentation has been collected, it is necessary to define the study protocol. The study protocol allows, in fact, to clarify:

- what the research objective was;
- how the study was conducted;
- what results have been achieved;
- whether any changes have been made with respect to the initial protocol (and whether these have affected the final result);
- what implications research results may have for public opinion both in the academic field and in clinical practice.

Scientific data are the elements on which to base any form of biomedical writing, be it original articles, revisions, research reports or letters to the editors.

In the following pages, original articles (hereafter articles) will be examined in particular, since they are the most widespread form of writing in the biomedical literature.

The Choice of the Magazine

Writing an article requires first of all choosing the journal in which to publish it. A fundamental aspect lies in not submitting the article to different journals at the same time, as it is often one of the conditions for non-acceptance.

Journals can be divided into those with and those without peer review. There are different types of biomedical journals, the choice must therefore be based on the relevance of the contents of the study to those of the journal. To find out the *modus operandi* of the journal, before considering submitting a scientific article to the aforementioned, it is advisable to consult the homepage or, more commonly, the Instructions for authors page, namely the so-called guidelines for authors in which the rules and standards of writing set by the publisher are reported.

Before being published, a manuscript is read by one or more referees (group of experts on the subject also called reviewers), who evaluate its originality and quality. This review process is called "peer review" or peerreview. It is the editor of the journal chosen for publication who carries out a preliminary evaluation of the article and determines whether to send it to the referees to start the review process (Fig. 11). There are two types of peerreview:

- single-blind, in which the authors of the study do not know the referees who will judge it, who, thus, feel free to evaluate the paper without the fear of external influences;
- double-blind, where the authors do not know the reviewers and viceversa.

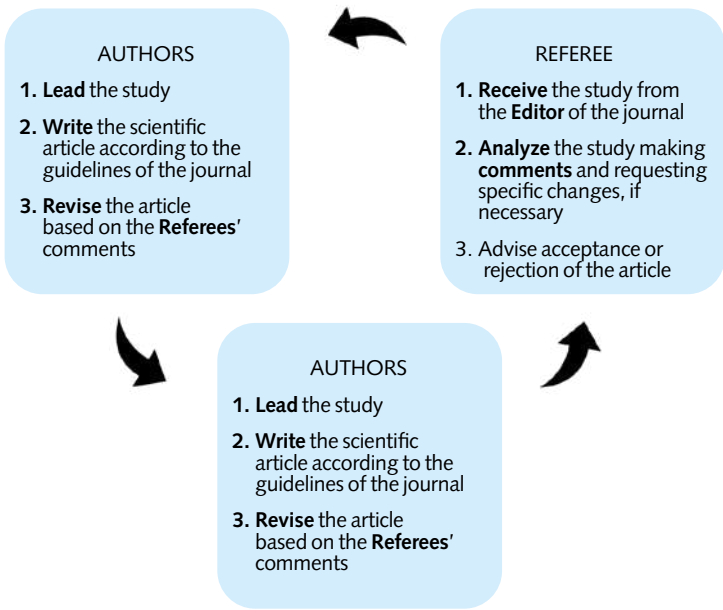

Fig. 11 – The process of publishing a scientific article.

The Guidelines

Another essential step in the composition of an article concerns the examination of the largest possible number of scientific works related to the subject. For this purpose, it may be useful to compare with the main existing guidelines, as reported by the EQUATOR Network Enhancing the Quality and Transparency Of healthResearch (Table 1).

Table 1. Guidelines for the correct drafting of the main types of studies.

Type of Study	Guidelines
Clinical practice guidelines	**AGREE** **RIGHT**
Preclinical studies conducted on animals	**ARRIVE**
Case reports	**CARE** → Studio-specific extensions available
Economic evaluations	**CHEERS**
Randomized controlled trials	**CONSORT**
Research studies on therapeutic adherence	**EMERGE**
Systematic and meta–analytical reviews	**PRISMA** → Studio-specific extensions available
study protocols	**SPIRIT** **PRISMA-P**
qualitative studies	**SPQR** **COREQ**
Quality improvement studies	**SQUIRE** → Studio-specific extensions available
Diagnostic/prognostic studies	**STARD** **TRIPOD**
Observational studies in epidemiology	**STROBE** → Studio-specific extensions available

These guidelines are drawn up by a panel of experts whose purpose is to provide a grid, which allows a specific type of study to be correctly described. For example, the *2010 CONSORT Statement* provides guidelines for reporting randomized clinical trials and includes a checklist of twenty-five table and a flowchart. The *EMERGE* Guidelines are, instead, required for the conduct of research studies on adherence to drug therapies, reporting a checklist of ten elements. Yet another example is the *STROBE* Guidelines which consist of a *checklist* of twenty-two elements, that should always be included in the description of observational studies in the epidemiological field. The STOBE Guidelines are available in four versions, the first being the most generic, while the other three are specific to the type of observational study (cohort, case-control and cross- sectional studies). Naturally, these guidelines are to be considered "recommendations" and not a rigid model to be reproduced when conducting a research.

The structure of the manuscript

From a structural point of view, an original scientific article must be composed of the following "sections": title, abstract, keywords, introduction, materials and methods, results, discussion, conclusions, and bibliography.

On the other hand, the article cannot be free from ethical aspects (Fig. 12), such as:

- **Authorship**, containing all the information of the co-authors of the article such as name, surname, affiliation and email address;
- **Contribution of the authors,** most often specified according to the guidelines of the International Committee of Medical Journal Editors (ICMJE);
- Conflicts of interest, necessary to fill in especially if the research has been economically financed by public or private external bodies;
- Ethical Approval, it is necessary to specify if the study required ethical approval. If so, it should be stated that the study was conducted in accordance with the Declaration of Helsinki, and approved by an Institutional Review Board (or Ethics Committee) indicating the Organization, the protocol code and the date of approval. In the event that the study does not require ethical approval, it is necessary to provide a detailed justification or alternatively declare "Not applicable";
- **Copyright** and **Privacy.**

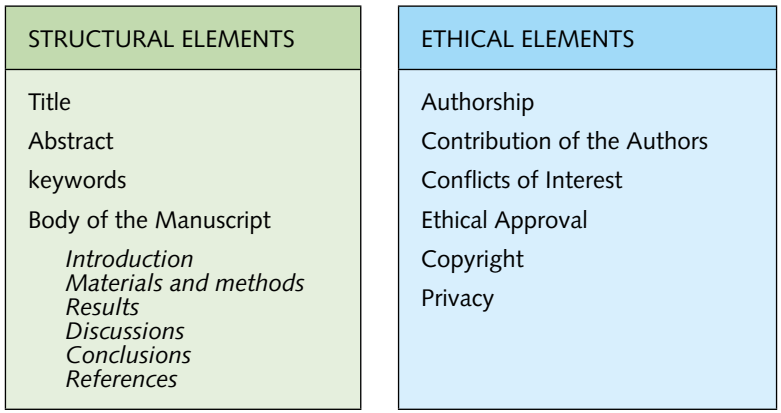

Fig. 12. – Structural and ethical elements for writing a scientific article.

A manuscript is made up of a series of parts, which will be analyzed in detail below.

Title

The title can be considered the "business card" of an article and, therefore, must meet some requirements:

- it must be consistent with the contents of the work and accurately indicate the topic of the study;
- it must contain some keywords able to summarize the contents present in the work and allow the reader to trace the article in the electronic databases.

The title of an article should be neither too long nor too short (in which case it could risk being devoid of relevant information). It must attract the reader's attention, but must not be ironic, pompous, or contain acronyms or abbreviations.

Abstract

After the title, the abstract is the first part of written text that appears to the reader, although it is in fact only a summary of the entire article, often elaborated after having finished writing it in order to extract the key concepts. The abstract must contain those concepts that characterize the article and, at the same time, capture the interest of the reviewer and the reader; the abstract must also comply with the editorial rules established by the journal (for example, it must be small, on average 250-300 words, not contain figures, images, bibliographic references, abbreviations or acronyms).

Generally, based on the journal chosen for submission of the article, the abstract can be requested in a structured or unstructured form. Most journals prefer a structured form which consists in reporting the key points of each section of the article such as: background, objective(s), methods, results and conclusions of the study.

Keyword

The key words, or more commonly known by the English term "keywords", must be chosen from among those that are most relevant and recurring, example, that are able to represent the study. Their main purpose is to allow the reader to get to know the key arguments of the article before reading it in its entirety so as to be able to identify the main topics covered *ab initio*.

A second purpose, no less important, is their use in compiling indexes and bibliographic directories. Therefore, it is preferable to obtain the keywords from the text of the manuscript and not from the title, thus increasing the possibility of dissemination of the article once published. Finally, also in this case it is the selected magazine to dictate the minimum or maximum number of keywords required (generally from a minimum of three words to a maximum of ten).

Introduction

In the introduction the research hypothesis and the objective of the study must be explained. In this regard, it is necessary to highlight the innovative elements present in the research compared to the reference scientific literature. And, to support this, recall the state of the art on the subject and the most significant bibliographic sources related to the subject addressed. At this phase it is very important not to anticipate data, results and conclusions.

Materials and methods

The "Materials and Methods" section is the main part of an article, as it contains everything that has been done in the research. In this section, first, the form of study conducted must be stated, i.e. whether it is a trial, an observational study, a cohort study, a case-control study or a prevalence study. It is then necessary to specify the number of subjects included in the study and their inclusion and exclusion criteria. In addition to this, the type of intervention must be indicated, specifying the outcome and the way in which it was measured, and the statistical analyzes carried out, explaining which tests and which statistical software were used. If the method used was derived from an already published work, it is necessary to insert the bibliographic references (the more bibliographic references inserted, the more "robust" the research carried out will be considered).

The ethical principles and consent of the subjects considered in the study must also be reported in the "Materials and Methods" section. In particular, if the study is a trial, the signed consent of the patients and the declarations of compliance with ethical principles must be reported. Furthermore, if the procedures followed the standards imposed by the international authorities or by the Declaration of Helsinki of 1975. If, however, it is an observational study for which retrospective data were used, it is necessary to specify whether the opinion of the Ethics Committee was requested or authorization from the health management.

In the section "Materials and Methods" absolutely no figures and tables should be inserted. The aspects relating to ethical issues can also be reported in a specific paragraph immediately after the method or at the end of the thesis under the denomination of "Ethicalstatements".

Results

In the "Results" section the results are illustrated in a logical sequence, respecting the order in which they were described in the "Materials and Methods" section. The results must be presented in a clear, concise manner, with emphasis on the most relevant aspects. In addition, all findings should

be described, not just those that are of greater significance. Some journals prefer to divide the "Results" section into several subsections to discuss the different results obtained separately.

Discussion

The "Discussion" section is probably, along with the abstract, the most read part of an article. In this section, the results of the research are analysed, with an emphasis on the various implications in clinical practice. These results must be compared with those of other studies, highlighting both the points of similarity and those of divergence. Within the "Discussion" it is very important to state the limits of the research. It must be considered that all studies may have intrinsic limitations and, as such, must be declared and argued. On the other hand, it is also necessary to give value to one's own research, specifying the strong points of the study and the results obtained. Ultimately, it would be interesting to state in this section what could be future developments obtained from the research that has been produced.

Conclusions

Each article should conclude with the key findings of the research performed, including suggestions for possible future studies.

Tables and Figures

The use of graphs and tables is strongly recommended to increase the understanding and synthesis of the results presentation. However, it is necessary not to abound in graphs or tables that are too full of data, which would be difficult to understand. It should also be considered that most journals impose a maximum number of graphs and tables (generally a maximum of five or six tables and figures). Clarity and simplicity are essential elements in the elaboration of a graph and a table. It is important that data is not presented twice, in tables and in text. Generally, the data are presented in tables and graphs, while the results are presented in the text.

Bibliography

The goal of the bibliography is to allow the reader to verify the arguments of the authors. It is important to carefully check the correspondence between the citation in the text and the bibliographic entry. Again, the form in which each reference is reported is specified by the journal and may differ slightly. Typically, a scientific article reference should include the following information, in different order based on journal preference: Author(s), Study Title, Journal, Year of Publication, Volume of Issue, Number of Pages, *Digital*

Object Identifier System or better known as doi (i.e. the unique identification code for each published article). Among the useful tools for managing bibliographic references, Mendeley is mentioned(https://www.mendeley.com), widely known for its level of diffusion and use.

Thanks
Acknowledgments are a useful tool used to provide a brief statement of the contribution of any participant or consultant who is not included in the list of authors of the manuscript, but who nonetheless contributed in some way to one or more phases of the study or implementation of the scientific article.

Bibliography editing software

Bibliographic management software allows you to collect, catalogue and organize different types of materials, take notes, automatically create bibliographies, format citations according to different bibliographic styles, share bibliographic material with other collaborators. In this regard, for example, Mendeley is one of the most popular software and is completely free. Mendeley is categorized as a so-called "reference manager" and helps the author to memorize, organize, comment, share and cite the references of his research. It consists of a web version and a synchronized desktop version. The web application is integrated by the desktop version, which allows you to interact with word processing programs (Word or similar), generate bibliographies, insert and update citations in a text document according to the citation style preferred or required by the journal chosen for submission.

Creating a personal account allows you not only to create your own virtual library, but also to participate in the typical "social community" activities such as participating in online groups, sharing bibliographies and searches, sending and receiving messages, customizing your profile.

How to download Mendeley?

Mendeley software, it is necessary to download it from the internet by connecting to the site https://www.mendeley.com/, and clicking on: "Create a free account". The next step is registering your profile, entering the requested information in the form. After completing the registration field, you can choose the suitable word version and download it. If the software is installed correctly, the program icon should appear on the desktop. At this point you can access it by entering your registration credentials so you can start creating your personal library.

Fig. 13 – Image of the downloadable version of Mendeley.

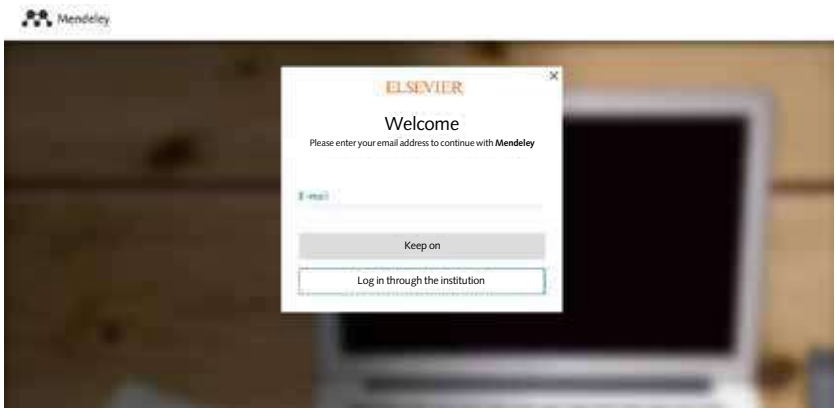

Fig. 14 – Mendeley recording window.

How to import bibliographic references?

The references can be imported directly from the web through the different platforms available. To proceed with the import of the references it is necessary:

- Connect to the platform you want to consult (PubMed);
- Perform a search and select the results whose references you want to save;
- Click on the "Save to Mendeley" button.

Fig. 15 – Example of bibliography import from PubMed.

During the import phase, a save window will appear in which it is possible to set a series of options, such as:

- import the pdf of the article;
- select a destination folder (previously created);
- add notes and tags.
- Another way to add new references and documents in.pdf is to import them directly from a folder on your pc. To import this way you need:
- click on the *Add new section*;
- *Add Files*, to import files;
- *Add Folder*, to import file folders;
- *Add Entry Manually*, to manually enter the references, i.e. type all the fields; author, title, etc.

Select the reference you want to import and then click "ok".

The imported references can be organized in folders and shared with workgroups through the "Groups" function.

Fig. 16 – Example of bibliography import from PC.

How to insert citations and bibliography while writing a work

Mendeley is a useful tool that allows you to enter a bibliography at the same time as writing an article. This operation can be performed as follows:

- open a word document in which you intend to insert the bibliographic references;
- click on the references section;
- click on the "Open Mendeley" item to select the bibliographic styles directly from the drop-down menu;
- click on "Insert citation", search by author, title or year or select a document from the library;
- select the article or book and click on "ok" to automatically quote that text in word.

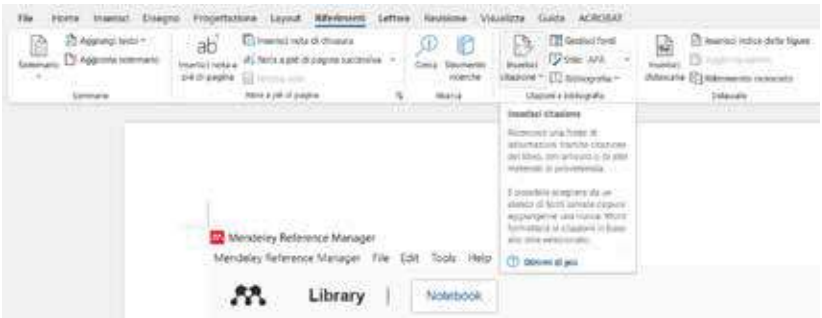

Fig. 17 – Example of inserting bibliography in the text.

Choosing the citation style to use

The style of the citation is another fundamental aspect to consider as it changes according to the magazine chosen. Mendeley allows you to choose different styles based on your magazine preference.

Citation style is the order in which the following information appears in the citation:

- Author(s);
- Title of study;
- Magazine;
- Year of Publication;
- Volume number;
- Number of pages:
- Digital Object Identifier System (doi).

There are different styles depending on the discipline to be addressed, so it is of fundamental importance to agree with your supervisor which citation

system to adopt. The general recommendation is to choose one and maintain it throughout the article. The most conventional and most used styles are *APA, Harvard, Chicago, MLA, Oscola, Vancouver.*

There are specific citation styles that derive from editorial choices of publishing houses. Mendeley, as a specific reference manager, understands all the standardized styles recognized by most journals, scientific associations or universities.

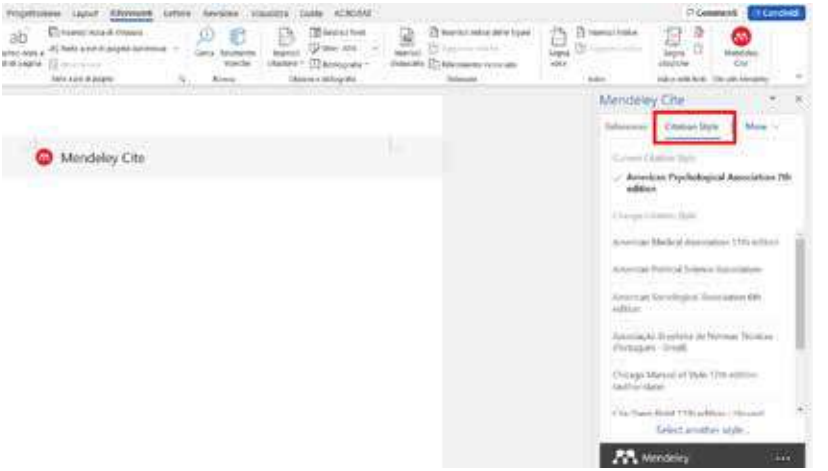

Figure 18 – Choice of citation style in Mendeley.

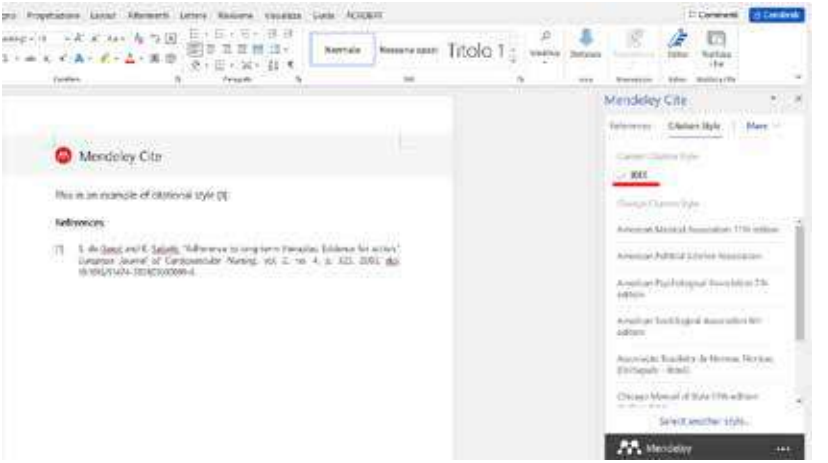

Fig.19 – Example of citation style.

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3. Pharmacovigilance and Device-Vigilance in Non-Profit Research

A. Marra, M. Ferri, M.R. Puzo, M.C. Galizia

What is Pharmacovigilance?

The science and activities related to the identification, evaluation, understanding and prevention of adverse reactions or other drug-related problems.

COMMISSION STAFF WORKING DOCUMENT Accompanying the document Commission Report Pharmacovigilance related activities of Member States and the European Medicines Agency concerning medicinal products for human use (2012 – 2014) **Brussels, 8.8.2016 SWD(2016)** 284 final

"Pharmacovigilance is planned monitoring of the safety of medicines so that anything that affects their safety profile can be swiftly detected, assessed, and understood and appropriate measures can be taken to manage the issue and assure public health."

Fig. 1 – Source: *World Health Organization.*

The main objectives of the pharmacovigilance activity are:

- identify new adverse reactions (ADRs) as quickly as possible;
- improve and broaden information on suspected or already known adverse reactions (SUSARs);
- evaluate the advantages of a drug over other drugs or other types of therapy;
- disclose such information to make therapeutic clinical practice more correct and appropriate.

The two faces of Pharmacovigilance

The Pharmacovigilance activity develops throughout the life of a drug, from the pre-registration phase, in the context of interventional studies to the post-marketing phase, including observational studies, with similar methods, in order to obtain the greatest possible number of safety information on the drug and with the aim of ensuring that the risk/benefit ratio of a drug is always favourable for the patient and the population.

Interventional clinical trials (RCTs)

Non-interventional clinical studies - post-marketing

Fig. 2 – The two faces of Pharmacovigilance.

Pharmacovigilance in clinical trials

Pharmacovigilance in clinical trials is defined as the collection and reporting of adverse events and adverse reactions to drugs used in clinical trials

In this context, the objectives of pharmacovigilance are:

1) collect information on the safety profile of the medicinal product being tested
2) ensure the safety of the participants in the trial, interrupting it promptly if the risk/benefit ratio is no longer favourable.

The EU Clinical Trials Directive (2001/20/EC) implemented in Italy with Legislative Decree 211/2003 describes the rules of good clinical practice in the execution of clinical trials of medicines for clinical use and, in particular, in the context of decree there are specific references in the field of pharmacovigilance. Obviously it does not apply to observational studies that fall within marketing uses in these stydies pharmacovigilance activity is regulated by Legislative Decree no. 219 of 2006.

1) European Directive 2001/20/EC

2) Legislative Decree no. 211 (June 24, 2003)

Implementation of directive 2001/20/EC relating to the application of good clinical practice in the execution of clinical trials of medicinal products for clinical use.

References to pharmacovigilance in SC:

art. 16 – Adverse Event Notification

art. 17 - Notification of serious adverse reactions

art. 18 – Indications relating to rapport

Does not apply to observational studies (Legislative Decree 219/2006)

These regulations do not apply to observational studies that are performed in the post-marketing phase.

A series of legislative acts then followed which regulated the activity of Pharmacovigilance in the field of clinical trials, such as for example the Ministerial Decree 17 December 2004 for Non-Profit trials.

Until the adoption of the European guidelines on clinical trials implemented by the Italian Medicine Agency (AIFA) in 2012

3) Guideline CT-3 (June 2011) of the EC implementing Directive 2001/20/EC

4) ICH E2F guideline (September 2010) Note for guidance on development safety update reports

5) AIFA Resolution of 20 September 2012 (Resolution no. 9/2012 – "Italian Official Gazette" of 29/9/2012)

Adoption of the CT-3 guidelines (June 2011) of the EC implementing Directive 2001/20/EC, of the ICH E2F guidelines (September 2011) and establishment of a national database relating to to monitor safety of medicinal products in clinical trials.

Subsequently, Ministerial Decree of 30 April 2015 was issued "*Operating procedures and technical solutions for an effective pharmacovigilance action adopted pursuant to paragraph 344 of article 1 of the law of 24 December 2012, no. 228 (Stability Law 2013)*" in which EU Regulation 1235/2010, in force since 2 July 2012 and Directive 84/2010/EU were implemented.

Similarly to the provisions for trials promoted by pharmaceutical companies, even in Non-Profit trials, the responsibility for the pharmacovigilance activity lies with the Sponsor.

The Ministerial Decree of December 17, 2004 (replaced by the Ministerial Decree of November 30, 2021), in fact provides that:

- in the case of multi-centre trials, a single sponsor must be identified, also responsible for pharmacovigilance activities;
- the marketing authorization holder must make the pharmacovigilance data (eg the IB) available to the sponsor.

The sponsor is required to carry out the following activities:

- monitor adverse events in in its own centre (in the case of a trial promoted by a health/hospital/IRCSS agency);
- recording all adverse events reported by other centres (in the case of multi-centre trials);
- ensure that all relevant information are reported to competent Authorities and to the Ethics Committees of the information required by law.

The Ministerial Decree 17 December 2004 was revoked by the Ministerial Decree 30 November 2021 (GU n. 42 of 2-19-2022): "*Measures aimed at facilitating and supporting the implementation of clinical trials of non-profit medicinal products and observational studies and to regulate the transfer of data and results of non-profit trials for registration purposes, pursuant to art. 1, paragraph 1, letter c), of the legislative decree 14 May 2019, no. 52*", which reads in Art. 5 "Communication for the safety management of Trials" in paragraph 2: "Pharmaceutical companies licensed in the investigational medicinal product and the sponsors of Non-Profit trials have a mutual obligation to provide each other with safety data for subsequent pharmacovigilance and safety of clinical trials and for the decisions within its competence".

All **Adverse Events** (AEs) for which, in the opinion of the investigator or the sponsor of the clinical trial, there is a reasonable suspect that a causal relationship may exist with an Investigational medicinal product (IMP) are to be considered **ADRs.**

After an AE the following actions must be performed:

- The Investigator must record and evaluate the AE and send a report to the sponsor.
- The sponsor must evaluate and enter the AE in EudraVigilance (EVCTM).

1. Investigator registration and assessment

The investigator is responsible for assessing the severity of the AE and the causal relationship between the IMP and/or concomitant therapy and the AE.

The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor should be provided with the report.

In this case, the approach will be conservative and if at least one of the investigators and sponsors considers the event related to the IMP, it must be considered related for regulatory purposes.

In the case that an event is considered to be related to the IMP, it is no longer referred to as an "adverse event" but as an "adverse reaction".

Assessment of the causal link

Investigator's evaluation	Sponsor's evaluation	Causality for regulatory purposes
Unrelated	Unrelated	Unrelated
Related	Related	Related
Unrelated	Related	Related
Related	Unrelated	Related

2. Send report to the sponsor

The investigator immediately notifies the trial sponsor of any serious adverse events (SAEs), except those identified as not requiring immediate reporting.

Detailed written reports follow this notification (Legislative Decree no. 211/2003, art. 16).

3. Evaluation of the sponsor

The trial sponsor must provide for detailed registration of all AEs notified by the investigator (Legislative Decree no. 211/2003, art. 16. par. 4).

It is the responsibility of the sponsor:

- assessment of *Seriousness*;
- causality assessment;
- assessment of predictability (*Expectedness*).

The sponsor must ensure that all the following AE that have occurred on national territory are notified to the competent Authority and to the Coordinating Ethics Committee which has expressed the single opinion:

- have a reasonable possibility of being causally related to the investigational medicinal product;
- are serious;
- are unexpected.

That is, the so-called **SUSARs** (Suspected Unexpected Serious Adverse Reactions) any suspected serious and unexpected adverse reaction related to the IMP (study or comparison drug), which occurs in the study (Legislative Decree no. 211/2003, art. 16).

SERIOUS ADVERSE EVENT	SERIOUS ADVERSE REACTION
- results in death - requires hospitalisation or prolongation of existing hospitalisation - results in persistent or significant disability or incapacity - is a congenital anomaly or birth defect	

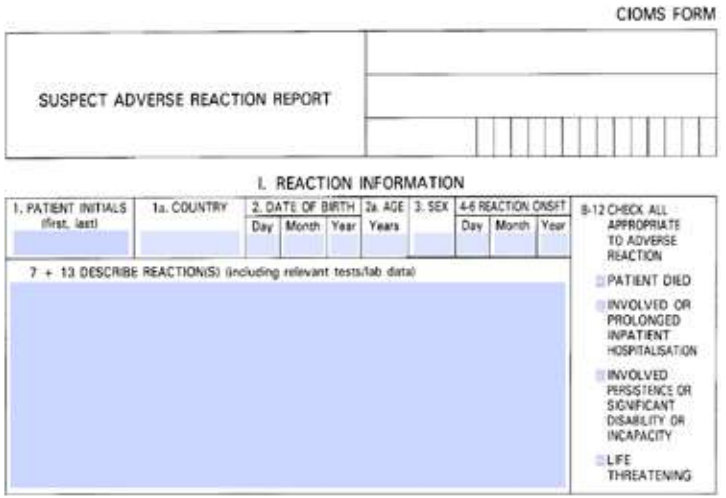
UNEXPECTED ADVERSE REACTION

nature and/or
severity (seriousness) and/or
intensity and/or
outcome

... unforeseeable based on the information available on the medicinal product at that instance

"SERIOUS" AND "UNEXPECTED" ADVERSE REACTION (SUSAR)

Reporting of SUSARs must take place through a specific form, the **CIOMS FORM**



CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
										PATIENT DIED
										INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
										INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY
										LIFE THREATENING

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

The minimum information that must be entered in the CIOM FORM is as follows:

- EudraCT number;
- study protocol code;
- patient initials;
- author of the report;

- description of the adverse reaction;
- suspected investigational drug (including name – active substance code)
- causal link.

IMP AND NIMP

Some clinical protocols provide for the use of medicines that are not IMPs and that are not defined in Legislative Decree 211/2003, but are defined in the Ministry Decree on Clinical Trial Application: **NIMP** (Non Investigational Medicinal Products)

ReTNIMPs(Regardless Trial NIMPs) namely NIMPs that would still have been administered to patients, even if the latter had not been included in the trial

PeIMPs(Products equivalent to the IMP) namely NIMPs equivalent from a regulatory point of view to IMPs * which are administered to patients only in account of their participation in the trial (costs borne by the sponsor)

In the event that SUSARs occur for NIMP, the reporting must take place as follows:

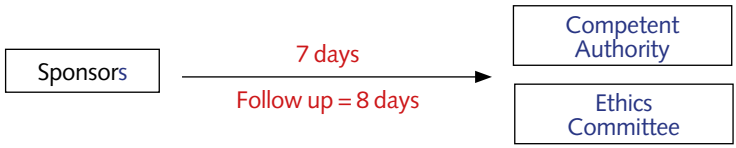
IMP	NIMP	
	ReTNIMP	*PeIMP*
SUSAR reported by the **sponsor**	SUSAR reported by by the **investigator,** in quality of healthcare professional (pursuant to Title IX of Legislative Decree 219/2006)	SUSAR reported by the **sponsor**

The sponsor enters the aforementioned SUSARs directly into EVCTM (Eudra Vigilance Clinical Trial Module).

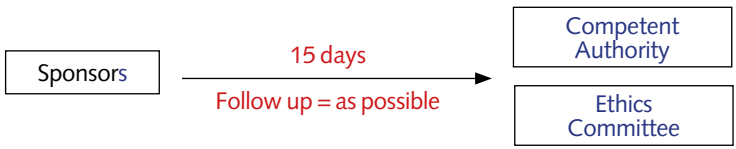
Since 31 January 2014, **registration with Eudra Vigilance** has become mandatory for the reporting of SUSARs and therefore, starting from 1 February 2014, the sponsors, or the Contract Research Organization (CRO) delegated by them, are required to send SUSARs exclusively to **Eudra Vigilance Clinical Trial Module (EVCTM).**

In conclusion, the Investigator shall notify the Sponsor any SUSARs concerning IMPs and Pe-IMPs, whereas SUSARs related to ReTNIMPs must be sent to the Local Pharmacovigilance Manager of the hospital/local health trust. The former will be entered in the Eudravigilance database, the latter will follow the path of post-marketing reports of suspected adverse reactions and will be entered in the National Pharmacovigilance Network.

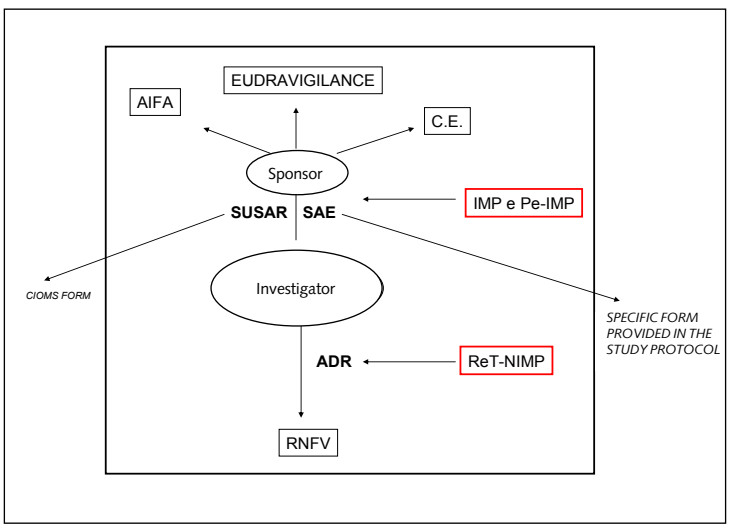
SUSARs that are fatal or life-threatening



All other SUSARs



Interventional studies



The Development Safety Update Report (DSUR)

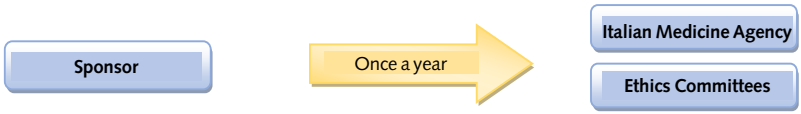
During the clinical development of an investigational drug, periodic review of safety information is critical to the ongoing assessment of risk to study participants.

For this purpose, a risk analysis document is drawn up: DSUR.

DSUR is a document intended to provide a common standard for periodic reporting on medicinal products under development (including medicinal products already on the market undergoing further study).

DSUR also informs regulatory bodies and other interested parties (such as Ethics Committees) on a regular basis about the results of these analyses and the evolution of the safety profile of an investigational drug, informing them of proposed or forthcoming measures taken to address security issues.

The sponsor shall provide the Member States in whose territory it takes place and the Ethics Committee a list of all the suspected unexpected serious adverse reactions observed during the entire period and a report on the safety of the persons undergoing clinical trials.



DSUR has a well-defined structure

Content of DSUR

1. Introduction
2. Worldwide Marketing Approval Status
3. Actions Taken in the Reporting Period for Safety Reasons
4. Changes to Reference Safety Information
5. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period
6. Estimated Cumulative Exposure
   a. Cumulative Subject Exposure in the Development Programme
   b. Patient Exposure from Marketing Experience
7. Data in Line Listings and Summary Tabulations
   a. Reference Information
   b. Line Listings of Serious Adverse Reactions during the Reporting Period
   c. Cumulative Summary Tabulations of Serious Adverse Events
8. Significant Findings from Clinical Trials during the Reporting Period
   a. Completed Clinical Trials
   b. Ongoing Clinical Trials
   c. Long-term Follow-up
   d. Other Therapeutic Use of Investigational Drug
   e. New Safety Data Related to Combination Therapies
9. Safety Findings from Non-interventional Studies
10. Other Clinical Trial/Study Safety Information
11. Safety Findings from Marketing Experience
12. Non-clinical Data
13. Literature
14. Other DSURs
15. Lack of Efficacy

It is a review and an annual overall assessment of the security information collected during the periodic reporting period, which:

- Examines whether the information obtained by the sponsor during the reporting period is in line with previously safety knowledge;
- Describes new safety-related issues that could impact clinical trial participants;
- Summarizes current knowledge and management of identified and potential risks;
- Provides an update on the status of the clinical research and development programme, as well as the results of the trial;
- It reassures regulatory entities that sponsors are adequately monitoring and evaluating the evolution of the safety profile of the medicinal product.

Below is the line-listing of adverse events which must be:

Line Listings of Serious Adverse Reactions during the Repòorting Period

Non-interventional studies (or "Observational" or "Registers" or "FV Projects" or "Compassionate Use" or "Special Use")

The **AIFA Resolution dated 20 March 2008,** "*Guidelines for the classification and conduct of observational studies on drugs*", provides that adverse reactions occurring in the context of these studies are reported in the same way as is required by the regulations in force for spontaneous reports (post-marketing), as confirmed in the Ministerial Decree of 30 April 2015. For this purpose, the new National Pharmacovigilance Network (RNF) and the updated AIFA operating procedure can be used (section 5.2 referring to "Reports from Studies"), which entered into force on 20 June. The new web form compliant with the R3 international standard (at the link: https://servizionline.aifa.gov.it/schedasegnalazioni/#/). Previously, until 9 June 2022, ADRs could be reported through Vigifarmaco reporting site.

With reference to the form of the Healthcare Professional only, the box of interest for the studies is number 13, as in the following figure:

INFORMATION ON REPORTING AND ON THE REPORTER
13. INDICATE WHETHER THE SPONTANEOUS REACTION WAS OBSERVED IN THE CONTEXT OF:
Spontaneous reporting ❑
Study reporting ❑
Specify the type of study:
from special uses (compassionate use, law 648/1996, nominal therapeutic use) ❑ **non-interventional** ❑
specify the name of the study:

Update: AIFA Operating Procedure for Local Pharmacovigilance Managers (RLFV)

The new version of the operating procedure for the activities of the Local Pharmacovigilance Managers (RLFV) is made available on the AIFA website at the link https://www.aifa.gov.it/-/educazione-procedura-operativa-aifa-per-i-responsabili-locali-di-farmacovigilanza-rlfv. The procedure is updated to the latest regulatory changes introduced on the RNF and on the management of reports of suspected adverse reactions – Revision 02 of 10 December 2021.

New National Pharmacovigilance Network (RNF)

With the launch of the new National Pharmacovigilance Network (RNF) (https://www.aifa.gov.it/rete-nazionale-di-farmacovigilanza), on **20 June 2022** will come into force **the new reporting forms of suspected adverse reactions** to drugs and vaccines, one for healthcare professionals and one for patient/citizens.

For online reports, **a new platform will be available on the AIFA portal that replaces the Vigifarmaco system, no longer operational from 9 June 2022** (link https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse). European pharmacovigilance legislation requires all healthcare professionals and citizens to report any suspected adverse reactions (serious and non-serious, known and unknown). **A suspected adverse reaction can be reported either by completing** the report form and sending it to **the Pharmacovigilance Manager** of the healthcare professional organization by e-mail or fax, or to **the Marketing Authorization Holder (MA)** of the suspected medicinal product that caused the adverse reaction **or directly online on the AIFA website**. The updated forms are available on AIFA website

available the **updated forms according to the new international standard format ISO Individual Case Safety Report (ICSR) ICH E2B(R3), established by art. 26(2)(a) of the Implementing Regulation (EU) no. 520/2012.**

From **30 June 2022,** this format will be mandatory in all EU countries for sending and receiving suspected adverse reaction reports to and from *Eudra Vigilance,* the European database of suspected adverse reactions to medicines authorized or under investigation in the European Economic Area (EEA), to which the RNF is directly connected.

Reporting forms have been graphically enhanced for greater usability and understanding by users. Furthermore, **additional fields required by the new standard have been introduced for the acquisition of a greater number of information relating to adverse reactions, suspected drugs and laboratory and/or instrumental tests which will allow an increasingly accurate evaluation of the safety profile of medicines.**

The data collected within the reporting forms will be processed in compliance with the data protection rules established by Regulation (EU) N 679/2016.

The new forms replace those currently in use and, in order to facilitate their compilation, **each form is published together with a relative compilation guide.**

Focus on the Device-Vigilance in DMs

By clinical investigations with medical devices we mean clinical studies, including feasibility studies, of devices not yet CE are marked, or CE marked but substantially modified or CE marked but used for a different intended use than that covered by the marking.

These investigations can be aimed at CE marking and marketing (so-called *Pre-Market Investigations*) or they can also be conducted for research and study reasons (so-called *Pre-Market Non-Profit Surveys*).

In addition to the latter, clinical investigations not planned for commercial purposes and for CE marking are also considered Non-Profit and can be promoted by Universities, Hospitals, Research Institutes, Scientific Societies, and Institutions other than manufacturers.

As specified in the document of the Ministry of Health "Clinical investigations with medical devices", published in 2015, Non-Profit Investigations are not explicitly governed by European Directives. "*However, in Italy, as in most Member States, even in cases where a commercial objective is not identified, such investigations are assessed on the basis of the same principles used for commercial investigations*". Therefore, "*the Ministry of Health applies, for the protection of patients' health and for*

obvious reasons of logic and analogy, the same procedures envisaged for clinical investigations aimed at CE marking".

On 26 May 2021, Regulation (EU) no. 745/2017 of the European Parliament and of the Council, of 5 April 2017, relating to medical devices, which amends Directive 2001/83/EC, Regulation (EC) no. 178/2002 and Regulation (EC) no. 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.

This regulation, is quoted literally, "*on the basis a high level of protection of the health of patients and users, sets high standards of quality and safety for medical devices, ensuring in particular, that the data obtained from clinical investigations are reliable solid and that the safety of the subjects participating in such investigations is protected*".

Within the Regulation (EU) no. 745/2017, Chapter VI - "Clinical Evaluation and Clinical Investigations" with articles from 61 to 82 and Annex Xv "Clinical Investigations", regulate clinical investigations with medical devices in a uniform way in the Member States.

Articles of the regulation referring to clinical investigations with Medical Devices

CHAPTER VI - Clinical evaluation and investigation
Articles:
61 – Clinical Evaluation
62 – General requirements relating to clinical investigations conducted to demonstrate the conformity of devices
63 – Informed Consent
64 – Clinical investigations on incapacitated subjects
65 – Clinical investigations on minors
66 – Clinical investigations on pregnant or breastfeeding women
67 – Additional national measures
68 – Clinical investigations in emergency situations
69 – Compensation for damages
70 – Application for clinical investigation
71 – Assessment by the Member States
72 – Conduct of a clinical investigation
73 – IT system for clinical investigations
74 – Clinical investigations relating to CE certified devices
75 – Substantial changes to clinical investigations
76 – Corrective measures to be taken by Member States and **exchange of information between Member States**
77 – Notification by the sponsor at the end of a clinical investigation or in the event of a temporary interruption or early termination
78 – Procedure for the coordinated evaluation of clinical investigations
79 – Review of the coordinated evaluation procedure
80 – **Recording and reporting of adverse events that occur during clinical investigations**
81 – Implementing acts
82 – Requirements relating to other clinical investigations
Annex XV - Clinical investigations

According to the provisions of the Ministry of Health, Non-Profit clinical investigations, like commercial clinical investigations, must respond to the "General requirements relating to clinical investigations conducted to demonstrate the conformity of devices" (Article 62 of Regulation (EU) No. 745/2017) and therefore, as provided for in paragraph 1 of said article, they must be "*planned, authorised, conducted, recorded and transcribed in accordance with the provisions of this article and of articles from 63 to 80, of the acts adopted pursuant to the art. 81 and Annex XV if they are carried out as part of the clinical evaluation for conformity assessment for one or more of the following purposes:*

a) establish and verify that under normal conditions of use the devices are designed, manufactured and packaged in such a way as to be able to carry out one or more of the specific purposes listed in art. 2, point 1, and provide the expected performance specified by the manufacturer;

b) establish and verify the clinical benefits of a medical device specified by the manufacturer;

c) establish and verify the clinical safety of the medical device and any unwanted side effects under normal conditions of use of the device and evaluate whether they represent an acceptable risk compared to the benefits achieved by the device".

From the operational point of view, as stated by the Ministry of Health in the circular of 25 May 2021, also for the Non-Profit clinical investigations, "*as of 26 May 2021, the obligations and provisions of the Regulation referring to the European database EUDAMED are not applicable, since this is not already operational, as provided for in Articles 70 to 82 for clinical investigations*". Therefore, in the meantime, Directives 90/385/EEC and 93/42/EEC continue to apply to comply with the obligations set out in the same articles for the exchange of information.

When Non-Profit clinical investigations concern medical devices bearing the CE marking, in order to FURTHER evaluate the devices in the context of their intended use, "*the additional provisions envisaged by art. 74, par. 1, which requires prior notification, with an advance of 30 days from the beginning of the clinical investigation and the articles also apply 62, 75, 76, 77, 80 and the provisions of Annex XV*".

If, on the other hand, for a medical device that already bears the CE marking, a Non-Profit clinical investigation must be conducted to assess conformity outside the scope of its intended use, art. 62 of the Regulation and the provisions relating to devices not bearing the CE marking.

In the case of substantial changes to the protocol, during Non-Profit clinical investigations, the provisions of art. 75 of the Regulation, in order to

evaluate the substantial changes to a clinical investigation, and it also defines the timing for the submission of notifications.

The exchange of information, also in this case, follows the dictates of art. 103 and the provisions set out in Annex XV.

The notification to the Ministry of Health must be accompanied by the positive opinion already expressed by an Ethics Committee which is valid at national level, as the pronouncement of the Ethics Committee is mandatory and potentially interdictive.

Until the entry into force of the EUDAMED database, notification of the outcome by the Ministry of Health will continue to be sent with Pec certified email.

As for the Ethics Committees, those that can express a valid opinion for the purpose of validating the application to initiate a clinical investigation by the Ministry of Health must be one of the Ethics Committees established according to the Decree of 8 February 2013 and therefore recognized at national level.

In the case of **multi-centre trials**, the opinion is defined: **Single Opinion** and is delivered by the Commission to which the coordinating investigator for Italy belongs.

In the case of **monocentric trials**, the opinion is defined as: **Opinion** and is expressed by the Commission to which the principal investigator belongs.

The provisions applicable to the Ethical Committees of the Ministry of Health and of Public Health also apply in the context of the Non-Profit clinical investigations which are listed below apply:

«*The opinion of the Ethics Committee which can express the valid opinion at national level, due to its* **consultative nature***, its* **compulsoriness** *and its* **potential prohibitive effects***, must be formulated* **before the adoption of the ministerial decision on the** *authorization of the clinical investigation or on the rejection of an application or on the refusal of a substantial modification.*

For authorization applications and notifications of substantial changes not accompanied by the opinion of the Ethics Committee which can express the valid opinion at national level, the **Ministry of Health requires the acquisition of the same** *within the deadlines set for the adoption of the ministerial decision (45 days extendable to 65).*

In the case of silence or interlocutory pronouncement of the Ethics Committee which can express a valid opinion at national level and called by a sponsor to express its opinion on the clinical investigation, **the Ministry of Health requests the formal pronouncement on the ethical review of the investigation***, also informing the national coordination centre of the Ethics Committees, so that the latter is aware of the impediment that precludes the adoption of the ministerial decision.*

In cases of a conditional opinion expressed by the Ethics Committee which can express a valid opinion at national level, **the conditional clause will be considered as an interlocutory pronouncement** *if it is not resolved upon expiry of the binding time limits for the adoption of the ministerial measures envisaged by the regulation*".

During clinical investigations, including Non-Profit ones, the provisions of art. 80 of the European Regulation "**Recording and reporting of adverse events that occur during clinical investigations**":

"*1. The sponsor fully records all of the following aspects:*

(a) any adverse event of a type identified in the clinical investigation plan as a critical factor in assessing the results of that investigation;

b) any serious adverse event; 5 May 2017 L 117/69 Official Journal of the European Union IT

c) any defect of a device which could have caused a serious adverse event in the absence of appropriate measures or intervention or if the circumstances had been less favourable;

d) any new conclusion relating to any event referred to in letters a) to c)".

4. The Non-Profit Clinical Trial in Italy: methodology and planning according to the to the Scientific Society FADOI

D. Manfellotto, S. Frasson, G. Gussoni

FADOI (Federation of Associations of Hospital Internist) is a Scientific Society founded in the early 1990s with the aim of consolidating the role of Internal Medicine within the Italian hospital and healthcare organization. Through the Foundation of the same name, a legal entity that plays the role of CME Provider and sponsor of Non-Profit clinical research, FADOI works for the development of medical-scientific knowledge and aims to contribute – directly or in collaboration with universities, health public and/or private, other research institutions and other Foundations and Associations – to the development of clinical research, training and updating activities and health education initiatives of the population in the field of diseases of interest to Internal Medicine.

Internal Medicine is an eclectic medical specialization with a strong multidisciplinary vocation, which has difficult diagnoses as its main field of activity, and the management of complex patients, often elderly, pluripathological and extensively pre-treated. For such a complex discipline, the commitment to clinical research is not just an interest, but a real necessity to drive continuous improvement in assistance and treatment.

The FADOI Foundation operates through two corporate organizational structures, the Department for Clinical Research and the Department for Training and Updates, linked together by the activity of the "FADOI Study Centre", a professional structure with dedicated personnel who take care of the planning and the implementation of research and educational projects promoted by FADOI at national and international level. In the specifics of clinical research, the organization of "Centro Studi FADOI" (FADOI Trials Centre) is able to autonomously carry out most of the activities connected with clinical studies (from the generation of of research demands to the drafting of the protocol, from obtaining the necessary ethical and administrative authorizations to the development of electronic data collection forms, from the Project Management activity which guarantees the oversight of all operations related to the development of the project up to the statistical analysis and internal and external reporting of the results obtained). In its 15 years of activity, "Centro Studi FADOI" has carried out over 50 Non-Profit

clinical studies, observational and interventional, national and international, with publications in peer review journals and an Impact Factor complexive of more than 200.

Through the organization described above which integrates clinical and professional skills and harmonizes the main missions and dimensions of the Scientific Society (research, training, promotion of the discipline of Internal Medicine) FADOI has tried over the years to build a virtuous process for which research is linked hand-in-hand with training and assistance: from the assistance emerge the unmet clinical needs that provide stimulus, impetus and direction to research, and for its part research proposes knowledge and strategies to be used in the healthcare field. In this perspective, and keeping faith with the attitude of Internal Medicine towards multidisciplinary and multiprofessional dynamics, FADOI some years ago promoted the establishment of a scientific association (ANIMO) which brings together nurses working in Internal Medicine departments, and with which most of the research projects and training events promoted by FADOI are carried out.

The combination of clinical research (understood as a planned, systematic and structured collection of data) and education has in fact been used by FADOI in a series of projects, which have been refined over time from a methodological point of view, and in which a real-life observation of clinical behaviour and outcomes was conducted before & after an educational intervention dedicated to the Centres participating in these studies. Through these pragmatic researches it has been possible to demonstrate that a structured and targeted educational intervention is able to positively influence the appropriateness of the management of diseases (both acute and chronic) and to improve outcomes.

The promotion and implementation of research projects creates a direct advantage for patients who, through the evidence produced and their participation in studies, can access innovative treatments, accurate diagnostic investigations, as well as more assiduous monitoring; but the health professionals themselves can benefit from significant advantages in terms of acquiring a methodological rigor that research requires, as well as motivation, professional growth and cultural exchanges. In this context, the participation in studies of small, peripheral clinics with less experience in clinical research can also represent an added value. Especially in pragmatic studies, which aim at strategic objectives for clinical practice, such as definition of the duration or intensity of a standard treatment, evaluation of a maintenance therapy, reduction of side effects, overall management strategies of a disease etc., the possibility of counting on the contribution of real-world data produced on a large scale can only increase the validity and representativeness of the results.

Thus a model of "*diffuse research*" is created which could be accompanied by a significant improvement in knowledge, as well as in the assistance efficiency of the National Health Service (NHS/SSN). FADOI relies on a network of over 200 centres in Italy, mapped and stratified according to specific clinical interests (for example cardiovascular, respiratory, endocrine-metabolic diseases, etc.) and expertise in participating in research projects: the extent of this allocation of Centres and their versatility thus allows FADOI to have an adequate basis for the selection of hospitals to be involved in the projects.

FADOI's commitment to clinical research has so far been carried out almost exclusively in the context of so-called "Non-Profit" clinical research, also defined as "independent" or "non-commercial", although perhaps a more correct denomination would be "research by Non-Profit Sponsors". This type of research should be considered not as an alternative but as complementary to industrial research, and for it we could identify a series of missions, which by way of example but not exhaustive could include:

- integrate scientific knowledge on new therapies, with a focus on strategies as well as on single treatments;
- study populations (and pathologies) neglected by commercial research;
- compare new therapies with already established ones;
- pursue objectives (e.g. safety of treatments/diagnostic pathways) and develop research models (e.g. observational/pragmatic) that tend to be poorly practiced by industrial sponsors, and possibly adhering to real-life;
- promote the integration between research and training;
- focus its attention on the unmet clinical needs;
- enhance the role of patients as "disease experts", to better meet to their needs and optimize project planning.

Non-Profit studies in our country was characterized by the Ministerial Decree of 17 December 2004, "*General prescriptions and conditions relating to the execution of clinical trials of medicinal products, with particular reference to those aimed at improving clinical practice, as an integral part of health care*", which defined the terms of classification of this type of study and envisaged some benefits for them: the exemption from paying the fee of the Ethics Committees; the costs for medicines used within the scope of the Marketing Authorization remain the responsibility of the NHS; the insurance for the study should be included in the scope of the insurance coverage envisaged for the general clinical or research activity of the hospital.

There was also the constraint according to which a research classified as Non-Profit could not be aimed or used for the industrial development of the drug and nevertheless for profit. The latter concept is theoretically

understandable, in fact restrictive and limiting, both scientifically and ethically, because in fact it compromised the possibility that a positive result generated by a Non-Profit research could have a registration declination and therefore a recognized place in clinical practice.

The Ministerial Decree of 17 December 2004 directly and indirectly generated, in the first years of its application, a significant increase in Non-Profit research in Italy, but this impetus was soon exhausted, and over the last 10 years the number of Non-Profit clinical trials on drugs has practically halved.

The reasons behind this involution are different:

- *limited real impact of some of the benefits provided for by the 2004 Ministerial Decree*, which have proved to be rarely applicable (*ad hoc* funds available only in a few structures), or weakened by subsequent regulatory interventions and practice (as regards the insurance coverage of studies), or insufficient to cover the range of Non-Profit pharmacological trials actually authorized (most of which did not concern areas covered by the marketing authorization and for which the supply of the drug at the expense of the NHS was therefore not envisaged);
- *doing research requires increasingly specific, advanced and up-to-date skills and training.* Sufficient to say that, with the entry into force on 31 January 2022 of Regulation (EU) no. 536/2014 on clinical trials, the authorization for an interventional drug study must be requested through a single European portal. While on the one hand this system will probably be able to streamline processes in large international industrial trials, for other realities, at least in the short-medium term, it could become a limiting passage since it requires skills and specific training of which the individual researcher or groups of unstructured researchers hardly have;
- *doing quality research requires resources both in terms of dedicated personnel and funding.* Unfortunately, in the field of Non-Profit research, there is often the difficulty of moving from the planning phase to the implementation phase of the study, in most cases due to lack of resources. With the same dimensions and complexity of the experimental design, the Non-Profit studies have management costs on average much lower than the industrial ones (just think of the often significant fees that the latter guarantee to the participating Centres), but in order to be able to promote a research there are in any case expenses, such as for example: the preparation of a data collection form (preferably electronic); a central and/or on-site monitoring system of the collected data; the activities of Project Management and Data Management, pharmacovigilance and Quality Assurance. To these can be added the costs relating to the materials necessary for carrying out the study, or to any extra-routine exams which must be reimbursed to the NHS.

One aspect that should never be overlooked is that concerning the level of quality with which clinical trials must be conducted. It is necessary to underline that the Regulation (EU) no. 536/2014 does not distinguish between commercial and non-commercial research as regards the quality standards that studies must guarantee, and it should also be remembered that, however trivial it may appear, quality costs money. The paths through which funding for a Non-Profit clinical research can be found can be schematically represented by:

National and international public funding → In Italy, the three main strands of funding, each with its own objectives, fields of application and access possibilities for the different types of sponsors, are represented by the Notification for targeted research of the Ministry of Health, the PRIN Notices of the Ministry of University and Research, and by the Notification for independent research of the Italian Medicines Agency. Among the main critical issues related to these tenders, in addition to the globally undersized funding compared to the needs and potential of our country's research system, there are the complexity and rigidity of the application procedures, the low and uncertain frequency with which are proposed, and the very long times that elapse between the presentation of the application and the actual financing. In a world where scientific knowledge evolves at breakneck speed and with increasingly global competition, the possibility of obsolescence of the search demand and the solution that the study proposed for these tenders intends to face becomes a real risk. In the current historical phase, the possibility of accessing funding under the National Recovery and Resilience Plan following the CoViD-19 pandemic deserves a separate discussion. Unfortunately, for the majority of potential researchers, the mechanisms for contributing to this funding are poorly known, and this risks concentrating the future availability of these resources, in the hands of few, as often happens in Italy. At the international level, however, a significant potential opportunity is represented by the framework programmes of the European Community, which aims to increase Europe's competitiveness in the field of scientific and technological innovation. In the most recent editions of these programmes, Italy's participation has unfortunately presented a negative balance between the amount of the contribution that our country has offered for the establishment of the community fund, and that of the funding received. The causes of this failure are probably to be described as a limited attitude and habit of our research system to a network logic (prejudicial condition in this type of notifications) and to a scarce support offered by national institutions to Italian researchers in the phase of application of the research proposals.

Unconditional grants from a private lender → The "private lenders" category may include credit institutions, insurance companies, Foundations that operate within the scope of their own philanthropic initiatives, but for the vast majority of cases, as documented by a research conducted by Cergas -Bocconi in 2019 [1], the Non-Profit clinical research is financially supported by drug companies operating in the therapeutic areas addressed by the project being financed. If a Pharmaceutical Company is interested in the research project, there is the possibility for it to grant an unconditional grant (therefore leaving the ownership of the data to the Non-Profit sponsor, and without intervening in the definition of the trial or in the analysis and reporting of the results), which can almost always cover only a part (generally 50%) of the necessary expenses. If from a formal point of view this is understandable in a logic of independence of the project, the objective difficulty remains in carrying out a study with undersized resources. Secondly, given the ever-increasing presence on the market of multinational pharmaceutical companies with properties and headquarters outside Italy, it is increasingly difficult for the Italian branches of these companies to directly grant or promote the granting by the headquarters of a loan to Italian researchers or research groups.

Self-financing → Some research centres are able to independently finance their own clinical research project, making use of funds obtained from their involvement in sponsored trials and which provide a fee for the centre. This can represent a virtuous solution, but feasible in fact only for the large reference centres or for those Institutes (the so called IRCCS, which have the mission to combine research and patients' care). For its part, FADOI too, as a Scientific Society, has on some occasions adopted a method of subsidizing projects proposed by its members, selected with peer reviews mechanisms and financed thanks to economic resources acquired by the Society through training activities and membership fees.

The D.M. December 17, 2004 for Non-Profit studies was recently repealed following the entry into force of the Decree of the Ministry of Health of 30 November 2021 "*Measures aimed at facilitating and supporting the implementation of clinical studies of non-profit medicines and observational studies and to regulate the transfer of data and results of non-profit trials for registration purposes, pursuant to art. 1, paragraph 1, letter c), of the legislative decree 14 May 2019, no. 52*". Among the innovations introduced by this Decree, the most relevant is the possibility of transferring data and results of Non-Profit trials, by the Non-Profit sponsor to a commercial

entity, and for registration purposes. This legislative intervention had been repeatedly requested by FADOI in proposal documents which had gathered a broad consensus among Scientific Associations, Research Institutes, Patients' Associations and the Ethics Committees themselves [2], and had been announced for the first time with Law no. 3/2018. The Decree of 30 November 2021 defines the ways in which the transfer of data and results can take place, thus opening up a perspective whose effective extent will have to be verified in the coming years.

A novelty introduced instead by the Regulation (EU) no. 536/2014 is the possibility of co-sponsorship of a clinical study, including that between public and private entities, and between Profit and Non-Profit realities. Also in this case, the next few years will tell if and how much this option can in fact favour the execution of projects proposed by researchers or academic entities, which can no longer be defined as Non-Profit if carried out in partnership with a Profit co-sponsor (but the most important thing is that they can be carried out). The driver of the effective implementation of this form of collaboration, on a regulated and transparent basis, will in all probability once again be the interest of private companies (with their investment capacity) in promoting and supporting it.

From what was formerly stated, it is clear that FADOI is interested in Non-Profit research, which in addition to expressing itself in the implementation of numerous projects, over the years has also resulted in an intense awareness raising activity of the institutions for the promotion of clinical research in general and of the Non-Profit one in particular [2-5]. Around this activity, FADOI has gathered the sharing and collaboration of many important realities in the world of health and research in our country (including, among the most authoritative, the Italian Society of Hospital Pharmacy and Pharmaceutical Services - SIFO). The "recipe" for a virtuous system could include a series of interventions that would facilitate the clinical research system in Italy (not only Non-Profit) and among these:

- Funding for Non-Profit research as a fixed portion of the SSN (NHS) fund (at least 1%);
- Reinvestment of clinical research profits in other clinical research projects;
- Promotion of clinical research included among the criteria evaluation of the work of the General Directors of the Hospitals;
- Opinion of a single Ethics Committee valid on a national basis, and applicable for all types of study (including observational);
- Greater uniformity for the documentation to be submitted for requests for authorization for studies (consents, forms required by the various Ethics Committees, contracts, etc.);

- Adoption as a "rule" of some measures inserted "in derogation" during the acute phases of the pandemic CoViD-19 (namely the possibility of supplying the trial products directly to the patient's home, under the coordination of the Hospital Pharmacist and the Investigator; allow the use of facilities, for example Analysis Laboratories, closer to the patient's home; allow remote monitoring, etc.);
- Strengthening of digital infrastructures in research centres;
- Recognition and dissemination of professional research support figures
- Creation of a National Research Agency.

Clinical research can and must represent a strategic asset for Italy, for the value it can express in health, social, economic and employment terms. When it was most needed, the dramatic events of the pandemic have underlined these values, and the discipline of Internal Medicine, which has supported most of the care burden of hospitalized Covid patients, has directly and heavily experienced it. Specifically, in the case of Non-Profit research, and in particular that part of it aimed at improving clinical practice as an integral part of health care, an additional value for our country is associated with the possibility that research offers useful solutions for the efficiency and sustainability of the SSN/NHS. Building a research system that is accessible to all health professionals who want to find answers to everyday problems should thus represent one of the objectives of the SSN/NHS and the bodies that govern it.

The dimension of academic clinical research, due to the complexities that research increasingly imposes, must be based even more on the logic of networking, collaboration and inter-disciplinarily.

FADOI, like other scientific realities with whom it shares this vocation, intends to meet the challenges that modern clinical research poses, consolidating a professional model of planning and carrying out studies, capable of managing projects with quality and continuity and therefore offering answers to the scientific community, its associates and especially to the patients and to the citizens.

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5. Congress Lablife of Clinical Trials: resource and stimulus for the Non-Profit Clinical Research of the Hospital and Territorial Pharmacist, examples and explanations

D. Zenoni, D. Zanon, C. Confalonieri

This year marks 6 years since the first demonstration of our LIFE (interactive laboratory for expert pharmacists) laboratory. We remember the first edition with emotion, between hopes, perplexities and the desire to give something practical and applied, but at the opening of the congress it was immediately understood that we had hit the target.

Over time, our commitment to this initiative has brought appreciation and new incentives to do better and better.

Curiosity is the most powerful engine that pushes us every day a little beyond our limits, beyond our expectations and sometimes even beyond our potential. And this is the reason why you must never stop being pry in order to grow both humanly and professionally.

Today, despite having an academic preparation and a specialization, curiosity, passion and new skills are necessary to be recognized professionally. We can elect whether to let go and continue with everyday life or take up the challenge for a new and modern professionalism. It's a bit like having ready capital to invest in a more profitable way for one's professional development and, at the same time, knowing that with this one can contribute to the improvement of many people's lives and our habitat.

Over time we have tried to listen to the voices of our colleagues to create a laboratory full of request, provocations, exhortations to always do better and together.

Today the LIFE Laboratory is a network made up of hundreds of colleagues who, out of vocation and passion for their profession, want to share and grow together, trying in turn to sow seeds on school desks to make new and young colleagues grow.

Reading books, attending courses such as the LIFE Laboratory, being curious, are all paths that help us understand what excites us and where we want to go.

Among the various areas that we have developed and deepened over time, the Clinical Experimentation area certainly had great appreciation.

Recent developments, also on the topic of observational research, make it necessary to create a network of professionals active sponsors of research, a virtual venue for meeting and discussion.

The LIFE Laboratory represents the vector for sharing ideas and experiences between professionals and postgraduates; The Network dialogues, implements and shares its intentions with the Universities and the exponents of Scientific Societies in order to carry out a convergent path that can benefit the entire professional category.

This was the message that the SIFO Clinical Experimentation Area: drugs and medical devices (ASC) wanted to share with the students with the aim of describing the architecture of clinical research, the anatomy of biomedical information and acquiring methods and technical skills for bibliographic research by identifying the need for information, classifying it and converting it into appropriate clinical-assistance questions, guaranteeing scientific credibility as well as entering into the merits of the management of the experimental sample.

To date, the ASC wants to represent an important contact point to guarantee the member concrete answers to doubts or problems relating to clinical trials both from a regulatory point of view by exploiting the skills of hospital pharmacists who are members/contact persons of EC Technical-Scientific Secretariats and management relating to the experimental drug being able to compare themselves with hospital pharmacists of the Clinical Trial Centers, all aimed at guaranteeing the shareholder himself comparison and possible solutions to any problems.

During the training days, Regulation (EU) no. 536/2014, applicable from 31 January 2022, date of the go-live of the Clinical Trial Information System (CTIS), the single EU portal which binds its applicability as established by art. 99 paragraph 3. At the same time there will also be the reorganization and reorganization of the Ethics Committees envisaged by art. 2 of the Law of 11 January 2018. The focal point of the reorganization is the reduction to a maximum number of 40 Territorial Ethics Committees in addition to the 3 National Ethics Committees. This certainly represents the most difficult skein to unravel since the appointment of the members of the Territorial Ethics Committees involves the State-Regions Commission and the Regions.

There were numerous questions and interesting discussions with professionals and postgraduates:

- Will this number (40 EC) be sufficient to evaluate all clinical trials?
- Will it be sustainable from a financial point of view?
- Will the reorganization of activities and sessions take place in relation to the timing dictated by the European portal?

- Provision is being made for the activation of two separate paths for procedures according to Directive 2001/20 and procedures according to Regulation (EU) no. 536/2014?
- Will the Observatory dialogue with the CTIS?

These are just some of the questions that arose from the training days proposed with an information based part and a second practical part guaranteeing on the one hand the full involvement of the trainees and on the other the description of the active role of the Pharmacist as an essential part in the Research system:

- Management of the trial product and related registers;
- Inspections by the Competent Authority for investigational drugs/devices;
- Preparation of a *Pharmacy Manual;*
- Legislation on medical devices - Clinical investigations
- as a real **Researcher** and therefore scientific manager of Projects then evaluated by an Ethics Committee.
- Clinical research architecture: from observational studies to interventional studies;
- *Equator Network* to search for the guideline suitable for the study design;
- Strobes*Statement* and Strobe*Explanation* with the description of the single items.

Research and continuous training become a daily work tool in a perspective of planning activities and a functional tool aimed at increasing the efficiency of the system in order to generate data that have a positive impact on the National and Regional Health Service as well as on the health of citizens.

To conclude, we can say that the experience lived with the LIFE laboratory has been explosive in us and in those who have had the opportunity to participate and allowed us to consider that nothing is worth so much to give serenity, professionalism, love for one's work as not making an effort beyond one's abilities, this is the real message we wanted to pass on. Remembering that LIFE is life, research attentive to the needs of patients, even the most brittle, children, cancer patients, the elderly, patients suffering from rare pathologies.

Patients where responses are often rare and therapies are also rare.

An integral part of this laboratory was the protection of these categories, bringing galenics (paediatric, oncological, nutritional) to very high levels, giving space to those who have never had it, to the protection of the operator, in short, a "home" that takes care of everyone.

Our greatest fear is not that we are inadequate.
Our greatest fear is to be authoritative beyond all measure.
It is our light, not our darkness that scares us the most.
Acting like a little man doesn't help the world, there's nothing enlightening about withdrawing into yourself so that people around you will feel insecure.
We were born to bring forth the glory that is within us, it's not just in some of us, it's in all of us.
If we let our light shine unconsciously we give other people permission to do the same.
As we free ourselves from our fear, our presence automatically liberates others.

(from the film "Coach Carter" by Thomas Carter)

6. The contribution and training of Expert Patients in Clinical Trials: the point of view of the Patient Academy

S. Grigolo, L. Pazzagli

Informed patient or expert patient?

The term *informed* immediately refers to *informed consent* and to the *information* that the patient receives in the health field regarding clinical acts, procedures or participation in trials, as an element of the right and protection of the person in receiving medical treatment.

In this sense, the **informed patient** is the subject who receives the adequate information which puts him in a position to express a judgment and/or consent.

Referring to the etymology of the word information, from the Latin *informatio*, the term means "*instruction, education*", but can also refer to "notion, idea".

This double meaning is well suited to that idea of "feeling informed" that is generated in patients through the search for news on a medical act or a specific health condition, thanks also to the great availability of information provided on the internet and in the media and of simple access.

The process of publication and dissemination of scientific research results intended for scientific journals can be decoded or simplified for various purposes and interests on other media, while the patient who uses the information may not be a healthcare professional or an expert, able to know discern the authoritativeness of the sources and the truthfulness of the news in relation to the scientific evidence.

All of this can generate confusion and false expectations in patients with respect to evidence-based scientific communication.

It is therefore necessary to resort to training that makes patients knowledgeable in research and consciously educated, so that research and the scientific community can have expert patients at their disposal.

Starting from the experience of his own illness or that of a family member, the patient who follows the EUPATI academic course of advanced training on the development of innovative drugs and therapies thus becomes an expert patient.

The figure of the **expert patient** is the new subject who fully participates in the research process and no longer the subject participating in a clinical study as an indispensable co-protagonist, even if adequately informed by the investigators.

Once trained, the EUPATI Expert Patient will be able to put the skills acquired to good use at the service of the entire scientific and civil community, contributing to the quality of the research.

The expert patient

In 1999 in the White Book of the British Government *Saving Lives: Our Healthier Nation and the expression "Expert Patient"* was introduced in the National Health Plan of 2000, recalling the central role that the patient can have in the treatment paths and in the management of his illness. Thus began an ambitious training and change program necessary to face the great challenges of the 21st century, such as aging and chronic desease (Department of Health. The expert patient: a new approach to chronic disease management for the twenty-first century. London: Department of Health, 2001 cited in Expert Patient Working Group 2017, "Expert patient" Why? Who? How? Towards a shared definition, https://www.slideshare.net/gravitazero/expert-patient-why-who-how-towards-a-shared-definition/, accessed 12 April 2022).

The term *Expert Patient* was created in 1985 by Prof. David Tuckett of the University of Cambridge according to which medical treatments would be more effective if doctors recognized patients as experts on their own pathologies (Expert Patient Working Group 2017, "Expert Patient" Why? Who? How? Towards a shared definition, https://www.slideshare.net/gravitazero/paziente-esperto-perch-chi-come-verso-una-definizione-condivisa/, accessed on 12 April 2022).

From the initial definition of expert patient focused on improving the management of his own pathology "*People have improved health and reduced inability if they take the lead themselves in managing their chronic disease – with good support from the health service"* (Policy paperSavingLives: OurHealthierNation, 1999 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/265576/4386.pdf) has moved on to a definition that considers an expert patient who has experience of his disease (*Illness*) and expertise of the pathology (*Disease*) from which he is interested by making them available to the scientific community, patients, others who can take advantage or benefit from them (Recchia, Barbon Galluppi, Mazzariol, Taranto, 2016).

In Italy

Competence profile

Extract from Patient expert 3.0 - Patient (caregiver) expert in... "Patient expert in..." Working Group 2018-2019 New Trends n.2 - 2019; 5-17: DOI: 10.32032/TENDENZE201911.PDF, http://www.passonieditore.it/doi/tendenze/2019/tendenze201911.pdf/.

From the Round Table "Expert Patient - Towards a proposal for a shared definition" held on 22 September 2016 which involved the main *stakeholders*

including patient associations, representatives of institutions for the citizen, academics, pharmaceutical companies, the competence profile was drawn also subsequently referred to by the expert patient working group in... 2018-2019 reported in Table 1.

Table 1 – Competence Profile of the Expert Patient in... Working Group 2016.

Skills

1. Manage Effectively one's own condition or help another person manage their condition

A. Actively interact with your doctor by reporting any effect of the treatments that may be relevant for their adjustment;
B. Follow the prescriptions precisely (compliance);
C. Accurately detect the effects of therapies with reference to the main daily functions;
D. Keep in touch with other patients to discuss the effects of therapies

2. Inform other patients and/or their families about how to effectively manage a desease

A. Keeping yourself informed about the pathologies and therapies of the patients with whom you work;
B. Use social media and maintain relations with the media to disseminate information on pathology, therapy, strategies for coping with the pathology, healthy lifestyles, structuring of social and health services and give support to patients and/or their families, without ever replacing the doctor's advice;
C. Conduct individual interviews with patients and/or their families to share information on pathology, therapy, strategies for coping with the pathology, healthy lifestyles, structuring of social and health services and provide support to patients and/or their families, without ever replacing the doctor's advice;
D. Hold meetings with small groups of patients and/or their families to share information on pathology, therapy, strategies for coping with the pathology, healthy lifestyles, structuring of social and health services and give support to patients and/or their families, without never take the place of the doctor's advice;
E. Participate in public events as a testimonial and expert.

3. Contribute to the improvement of medical and care services for patients

A. Gather the opinions of other patients on medical and care services;
B. Develop ideas or projects to improve medical and care services;
C. Share your ideas or improvement projects with other patients;
D. Promote ideas or improvement projects agreed with other patients to the Medical Authorities and/or social and health services;
E. Participate in the testing of health and social-health care models.

4. Contribute to the activities of patient associations

A. Participate in the definition of the objectives and strategies of an association and their evaluation;
B. Collaborate with other patients and experts in the development and/or dissemination of information and informative material and advertising materials relating to the association;
C. Carry out activities for patients and the general public on behalf of an association;
D. Carry out activities on behalf of an association towards public authorities, health and care service managers, pharmaceutical companies, other beneficiaries.

5. Collaborate in the implementation of clinical trials on drugs, technical and medical devices and pharmacovigilance

A. Keep informed on the state of research and therapies on the pathologies of interest;
B. Collaborat e with researchers and healthcare personnel in defining the objectives and methods for carrying out the trials;
C. Participate in Ethics Committees and Regulatory Commissions in the field of clinical trials;
D. Share information about the characteristics of trials with other patients;
E. Contribute to the collection of information on the effects of medicines, techniques or health tools.

This recall allows us to introduce the flexibility of the skills acquired by patients since there is not a single *certified expert patient* but many experienced patients each of whom is certified in one or more skills.

In Europe

The European Patients' Academy on Innovation Therapies (EUPATI) was launched as a project of Innovative MedicinesInitiative (IMI) in February 2012 with the aim of fostering a general reflection on the knowledge and understanding of the drug development process in patients and the wider public, and their own involvement within (https://eupati.eu/about-us/history/).

Thanks to the acquisition of specific skills, patients expert in therapeutic innovation have the ability to work effectively with competent authorities, healthcare professionals and industry to influence the drug development process for the benefit of patients. The main objectives of the project are:

- Develop and disseminate accessible, well-structured, comprehensive, scientifically reliable and patient-friendly educational materials on drug research and development processes.
- To increase the capacity of patient experts and well-informed patient organizations to be effective advocates and advisors in drug research and development.
- Enable patients to provide advice and insights to industry, academic sector, institutions and Ethics Committees.

From February 2017 to August 2020, EUPATI was hosted by the European Patient Forum as an educational programme. A second IMI-funded project – Ensuring the Future of EUPATI (EFOEUPATI, 2018-2020) focused on the sustainability of EUPATI by ensuring the continuation of patient education in the medium to long term. On 11 August 2020, EUPATI was established as an independent Non-Profit foundation in the Netherlands.

Patients can be involved in the drug research and development process. The following diagram – created by Geissler, Ryll, Leto and Uhlenhopp – identifies some existing areas where patients are involved in the process. It distinguishes between the level of expertise in an area of disease required and the different areas where involvement may take place.

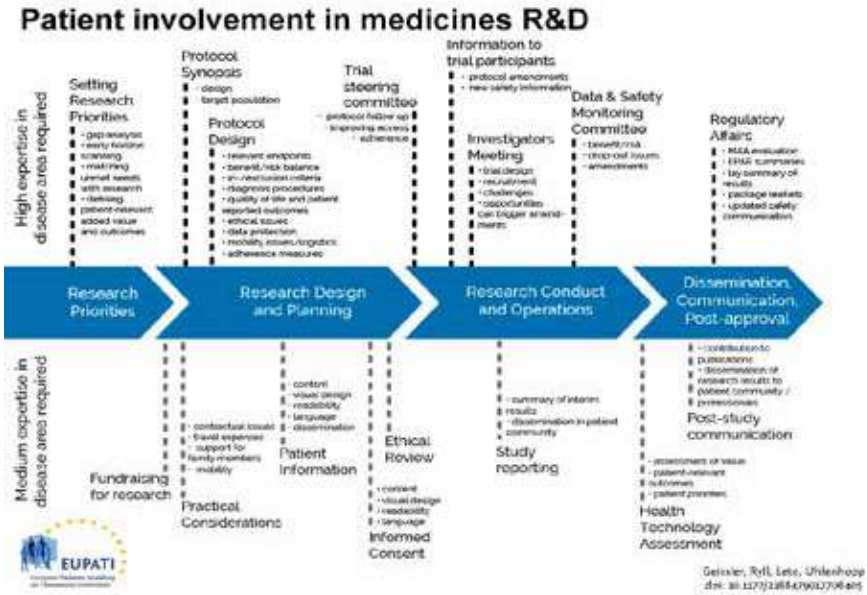

Table 2.

Values and principles

EUPATI builds on the strength of having a diverse group of stakeholders from different stages and perspectives of the medicines development process. The experience and insights of EUPATI consortium partners, network members and external consultants were supported by qualitative and quantitative research, as well as a systematic literature review conducted by EUPATI prior to content production.

The EUPATI Code of Conduct outlines the working culture within EUPATI, while the EUPATI Ethical Framework outlines the basic ethical rules.

They apply to all EUPATI Collaborating Partners and all those involved in carrying out work for EUPATI (https://eupati.eu/about-us/values-principles/).

In Italy

EUPATI Italy

The EUPATI Expert Patient is the person trained and informed in Research and Development of Innovative Therapies on the model of EUPATI Europe. With these skills, the EUPATI Patient Expert is able to initiate a direct and equal dialogue with institutions and decision-making entities operating in the healthcare world (researchers, academics, pharmaceutical companies, medical companies and institutions).

EUPATI Expert Patient Academy (AdPEE) takes its name from the European project EUPATI (*European Patients' Academy on Therapeuticinnovation*). In Italy, it offers certified, objective and exhaustive training in the field of Research and Development (R&D) and in particular on the methodologies applied today to ensure the safety of clinical trials and the safety and efficacy of drugs. The course is sponsored by AIFA, Farmindustria and the Istituto Superiore di Sanità (High Health Institute) (**#vogliamopazientiesperti - @EUPATI_IT - www.accademiadeipazienti.org**).

The EUPATI guidelines

In 2018, the EUPATI guidelines on patient involvement in R&D processes were published.

In a *multi-stakeholder partnership system* based on collaboration and cooperation, EUPATI interacts with patient organisations, universities, institutions and pharmaceutical companies in a logic of innovation based on networking and the valorisation and respect of mutual identities.
(Spindler P and Lima BS 2018. Editorial: The European Patients Academy on Therapeutic Innovation Guidelines on Patient Involvement in Research and Development. Front. Med. 5:310. doi: 10.3389/fmed.2018.00310)

Involve EUPATI patient experts in the HTA process

EUPATi patient experts acquire specific skills to be key stakeholders in HTA. The added value of their involvement can be summarized in the following points:

- Patients' rights: As ultimate beneficiaries, patients should be consulted on decisions related to their care;
- Patient and community values: Health care services should be aligned with the values needed by patients;
- Patients contribute evidence: the patient's perspective is unique in living with the disease, with the impact of treatment and services adding evidence to the HTA process;
- Improving HTA methods: Patient information can help identify *outcomes* for inclusion in scientific discussions and reported in HTA reports.

(Hunter A, Facey K, Thomas V, Haerry D, Warner K, Klingmann I, May M and See W (2018) EUPATI Guidance for Patient Involvement in Medicines Research and Development: Health Technology Assessment. Front. Med. 5:231. doi: 10.3389/fmed.2018.00231)

Involve patients in the ethical review of clinical trials

Patients can be involved in the ethical review of clinical trials at different points ranging from the initial phase to the final phase of the trial. At all stages, EUPATI patient experts can bring their perspective on ethical aspects and in particular:

- Verification of preclinical data and/or evidence indicated in the background;
- Research questions e.g. for specific indications, patient population etc.;
- Definition of trial objectives to ensure relevance to patients;
- Criteria for inclusion and exclusion of participants;
- and relevant endpoints;
- The adequacy of measurements and assessments e.g. quality of life questionnaires and patient outcome reports;
- Standard or "comparator" e.g. placebo or a standard active intervention, and acceptability to patients;
- The level of acceptable risk: patients can have their own position on the level of risk they are accepted and prepared for;
- Adequacy of the load required of the participants;
- Participation in the procedures for the preparation, administration and evaluation of the outcome of an experimental drug "closer" to the patients;
- Patient-friendly informed consent.

(Klingmann I, Heckenberg A, Warner K, Haerry D, Hunter A, May M and See W (2018) EUPATI and Patients in Medicines Research and Development: Guidance for Patient Involvement in Ethical Review of Clinical Trials. Front. Med. 5: 251. doi: 10.3389/fmed.2018.00251)

Involve patients in regulatory processes

Transparency and trust are essential values of the care relationship that are also built through active engagement processes (participation, consultation and information processes). Specifically, the following objectives are pursued:

- Support Regulatory Authorities in accessing real-life disease experiences and information on current drug use;
- Involve patients and their representatives to be listened to, consulted and involved in the development of policies and plans;

- Strengthen patient organizations' knowledge of the purposes of regulatory authorities in the context of drug information development, evaluation, permitting, monitoring and forecasting;
- Optimize communication tools to facilitate and encourage the establishment of information for patient organizations to support their role in the safety and rational use of medicines;
- Facilitate patient participation in risk/benefit assessments to identify patient values and preferences in current medication use.

(Haerry D, Landgraf C, Warner K, Hunter A, Klingmann I, May M and See W (2018) EUPATI and Patients in Medicines Research and Development: Guidance for Patient Involvement in Regulatory Processes. Front. Med. 5:230. doi: 10.3389/fmed.2018.00230)

Engage EUPATI patient experts in research with pharmaceutical companies

At an international level there are already successful experiences involving companies and patients such as Patient-CenteredOutcomesResearch (PCORI), FDA patient-focused drug development, Clinical Trial TransformationInitiative (CTTI) and the PatientFocused Medicine Development (PFMD), as well as EUPATI and other IMI-funded projects.

The directions that the company-patient interaction should propose are:

- Reference to existing codes of conduct which, although they can be improved, report the main assumptions applicable to company-patient interaction
- Patient Engagement to achieve the best benefit for all, including identifying and understanding hidden needs, research priorities, optimizing clinical trials and outcome measures and endpoints;
- Engage patients and patient organizations proactively and longitudinally, especially in the early stages of drug discovery, development and post-approval;
- Use of adequate language in order to make the interaction clear and transparent;

Professionalism, ethics and objectivity of patient behaviour in interactions.

(Warner K, See W, Haerry D, Klingmann I, Hunter A and May M (2018) EUPATI Guidance for Patient Involvement in Medicines Research and Development (R&D); Guidance for Pharmaceutical Industry-Led Medicines R&D. Front. Med. 5: 270. doi: 10.3389/fmed.2018.00270)

Involvement of patients in research: areas of intervention

Citizens and patients can therefore contribute to research not only as subjects participating in clinical studies, but also perform other roles at various levels,

throughout the research process and even afterwards, especially if informed and trained as expert patients.

In this sense, all research players can collaborate easier to obtain better results for the benefit of the entire population.

Table 2 (on p. 622) summarizes the areas of intervention divided into two macro-activities related to basic and advanced skills (EUPATI level).

Early clinical development

Patients or their representatives (*patientadvocate*) can be involved in early clinical development by forging partnerships and working relationships with regulators, Ethics Committees, investigators and industry.

Specifically, patients can provide a valuable contribution for evaluations on:

- *Study design,* studies must take into account patient needs which means that research priorities and the research outcomes being measured must be relevant and provide value to users of the drug;
- *Study Documents and Informed Consent Study documents and informed consent forms* (and the process) must be clearly understandable to all trial participants;
- *Study logistics* should be convenient for trial participants and take into account their needs, especially those arising from their indication/disease (e.g., travel to the trial site, time allotted).

Participation in clinical trials

Full awareness of ongoing studies by the patient community facilitates recruitment, the permanence in the trial until it is completed, and collection of more information.

Patient associations have an important role in this as well as allowing the dissemination of research results, which must be widely available.

Patient representatives may perform the following roles:

- *Lobbying for the development* of clinical trial for the condition that they/ their organizations represent funding a clinical trial;
- *Development Clinical research protocol*;
- *Formation of a research team* for a clinical study;
- Collaboration in the research;
- *Leading groups or discussion sessions* for research (*Community Advisory-Boards)*;
- *Collaboration in the drafting of a scientific article on the research results* related to the clinical trial;
- *Review and evaluation of* patient information to be used in a clinical trial;

- *Advice:* provide advice or be an advisory member, within committees of national or European Regulatory Authorities, Ethics Committees, Clinical Research Planning Committees;
- *Research participant as the* subject involved in testing the effects of a new treatment;
- *Information support:*
  - Provide information to patients on the possibilities of participating in a clinical study
  - Provide information on the pathology, demographics and/or other information on the characteristics of the members represented

Participation in Ethics Committees

The goal of a diversified EC composition is to ensure that the Committees can conduct multidisciplinary collective evaluations, drawing on the strengths of their members with diverse backgrounds and a thorough and independent ethical evaluation of research projects.

While the specific requirements differ greatly across Europe, a typical composition of a EC includes:

- at least five members who together have the qualifications and experience to ensure an adequate examination of the ethical, scientific, medical and financial aspects of a clinical trial;
- at least one ordinary person from a different educational (social sciences, law, etc.) and social background, while ensuring gender balance.
- In many countries, it is further required that there be three non-scientific members:
- a member with legal training;
- an ethicist;
- a member representing the community.

The members of the EC must be nominated for a term established by the recognized Authority according to a defined procedure. The EC may choose to invite external non-member experts to advise on particular (often scientific) aspects of a project.

The diffusion of the specific culture, the training of patients and the presence of the figure of the expert patient in the Ethics Committees are strengths for the development of quality clinical research in favour of the entire scientific and civil community.

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Conclusions and Acknowledgments

edited by the Scientific Responsible P. Polidori, A. Marinozzi, R. Langella

At the conclusion of this intense and fruitful journey into the world of Clinical Trials, in which all the Professional, Regulatory and Practical aspects of the two figures at the center of this Manual have been highlighted and exalted, the Pharmacist of Research and the Research Pharmacist, we would like **thank all the SIFO personnel** involved, the **Sponsors** that supported us, believed in us. Further, we would like to thank the **241 Professionals (of which 155 Authors and 86 Co-Authors)** that directly and indirectly gave their time and contribution to "forge" a unique, transversal and highly specialized and professionalizing editorial project in the world of Clinical Research in the planning and in particular in to the Multidisciplinary Scientific Board.

The driving force that generated this virtuous training-editorial path, which will also be available to the EAHP society as an English language version, consists of three determining elements-factors:

- **Scientific knowledge and Working needs should aim to improve one's own professional figure and both qualitatively and scientifically:** "*conditio sine qua non*" of our SIFO, also linked to an historical scientific memory, where we wanted to remember and commemorate the manual itself by recalling three illustrious colleagues, that unfortunately passed away prematurely and were also the source and inspiration of the training course and, in some cases, also participated to the events::
  - ***Stefano Federici*:** Director of the Hospital Pharmacy of the AO Melegnano, that thanks to his extreme preparation and passion for the profession was the Founder and Head of the Master course in Pharmacy and Oncological Pharmacology with the University of Milan and the Master course in Management of Pharmaceutical Departments with the University of Camerino; two training areas, which over the years have given a scientific and training imprint to hundreds of fellow pharmacists, vital lymph in doing and promoting research;
  - ***Stefano Bianchi*:** Director of Pharmacy of the Pharmaceutical Assistance of the Territorial Health Authority (USL) of Ferrara, always engaged with SIFO events, in training courses and scientific research in the field of indicators and aspects of Clinical Pharmacy with the University of Ferrara and Camerino, with a particular focus on Appropriateness, Adherence and Therapeutic Persistence; he was involved in the Ex Bologna 2020 edition (no longer carried out due to COVID-19, 630 P.

Polidori, A. Marinozzi, R. Langella subsequently postponed in 2021 via webinar), as moderator of the Session Research Pharmacist.
  - ***Francesco Paganelli*:** Pharmacist Manager Head of the U.Ma.CA Laboratory of the Hospital Pharmacy of the IOV Veneto Oncological Institute – IRCCS (Istituto Oncologico Venento), Padua, always involved in the management, logistics and setting up of Clinical Trials with paths and certifications of quality shared and implemented in the many SIFO initiatives and not only these ones; he was involved in the Ex Bologna 2020 edition (no longer carried out due to COVID-19, later postponed to 2021 via webinar), in the logistics and certification part of Clinical Trials, as an example of excellence and reference.
- **an overall vision and system perspective:** the Manual aims to be the expression of a multi-disciplinary reality in which all the subjects and professionals involved individually expressed their "*art in health professionalism*", but work and study collaborating together with quality, excellence and professionalism for a common good which is the health, welfare and protection of the patient and of the National Health System System in which he works.
- **a scientific contamination:** throughout the High Specialization process that has been carried out, the desire and the need to put all the science and knowledge communicated and transmitted on paper arose and grew overtime, giving a tangible tool of reference always available at hands' reach, useful and indispensable support to build that possibility and willingness to execute, promote and manage Clinical Research with quality, preparation and training.

In the wake of all these elements this scientific work, unique in its kinds, would like to be a reference tool for the SIFO society and both for the Hospital and/or Territorial Pharmacist, hopefully before a long series of manuscripts, which over time they will be updated and implemented with all the regulatory and scientific "Know-how" necessary so that the flame of doing would be always kept strongly burning to promote and managing Clinical Research and for the exaltation and quality of our Profession.

A heartfelt thanks to Prof. Carlo Polidori and Dr. Jessica Silicani for the adaptation of some texts translated into English.

"*Special thanks from Piera and Roberto is addressed to Andrea, that with his passion, dedication, perseverance and wisdom has been able to master, follow and manage, in an impeccable way, the complex direction of all the highly specialized multidisciplinary training and editorial planning in Clinical Trial knoledge. Heartfelt thanks!*"

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	*Gestione informatizzata del farmaco sperimentale: l'esperienza della SC Farmacia dell'IRCCS IRST di Meldola a garanzia di tracciabilità e sicurezza* (Computerized management of the experimental drug: the experience of the SC Pharmacy of the IRCCS IRST of Meldola to guarantee traceability and safety), C. Masini, L. Gasperoni
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	*La logistica del Campione sperimentale nell'Azienda Ospedaliera (AO) S. Croce e Carle Cuneo* (The logistics of the Experimental sample in the S. Croce and Carle Hospital (AO) Cuneo), E. Grande, C. Fruttero
	*La Gestione della Sperimentazione Clinica nell'A.O.U. Città della Salute e della Scienza di Torino* (The Management of Clinical Trials in the AOU City of Health and Science of Turin), E. Buffa, F. Cattel
	*S.C. Farmacia e U.Ma.C.A. dell'IRCCS Istituto Tumori "Giovanni Paolo II" di Bari* (SC Pharmacy and U.Ma.CA. of the IRCCS Cancer Institute "John Paul II" of Bari), P. Nardulli, M. Laforgia
	*L'ARNAS Garibaldi di Catania (Presidio "Garibaldi-Nesima" e Presidio "Garibaldi-Centro") e la Sperimentazione Clinica* (ARNAS Garibaldi of Catania ("Garibaldi - Nesima " Presidium and "Garibaldi-Center" Presidium) and the Clinical Trials), G.E. Fassari

	*La logistica della Sperimentazione Clinica nell'Istituto Oncologico del Mediterraneo* (The Logistics of Clinical Trials in the Mediterranean Oncological Institute), M.P. Vitale
	*L'Azienda Policlinico Paolo Giaccone Palermo e la Sperimentazione Clinica* (The Paolo Giaccone General Hospital Palermo and the Clinical Trials), A. Pasquale, C. La Seta
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