AGGIORNAMENTI DI STATISTICA E RICERCA CLINICA

Milano, 21 febbraio 2019

09.45-10.45

Disegni sperimentali adattativi (platform trial) e come leggere i dati di uno studio clinico

B. M. Cesana

DISEGNO DI UNA SPERIMENTAZIONE CLINICA

- STUDIO NON COMPARATIVO
- **BASALE → "INTERVENTO" → FINE**
- TR. "S": X_{1S} - $X_{2S} = \Delta_S + \Delta_Y$

STUDIO COMPARATIVO

BASALE → "INTERVENTO" → FINE

TR. "S": X_{1S} - $X_{2S} = \Delta_S + \Delta_Y$

TR. "C": X_{1C} - $X_{2C} = \Delta_C + \Delta_Y$

ENTITÀ DELLA RELAZIONE CAUSALE DELL'EFFETTO DI "S" RISPETTO A "C":

$$(\Delta_S + \Delta_Y) - [\Delta_C + \Delta_Y] = \Delta_S - \Delta_C$$

Bruno M. Cesana

Schumi and Wittes *Trials* 2011, **12**:106
http://www.trialsjournal.com/content/12/1/106

TRIALS

REVIEW Open Access

Through the looking glass: understanding non-inferiority

Jennifer Schumi* and Janet T Wittes

DEFINITIONS

Abstract

Non-inferiority trials test whether a new product is not unacceptably worse than a product already in use. This

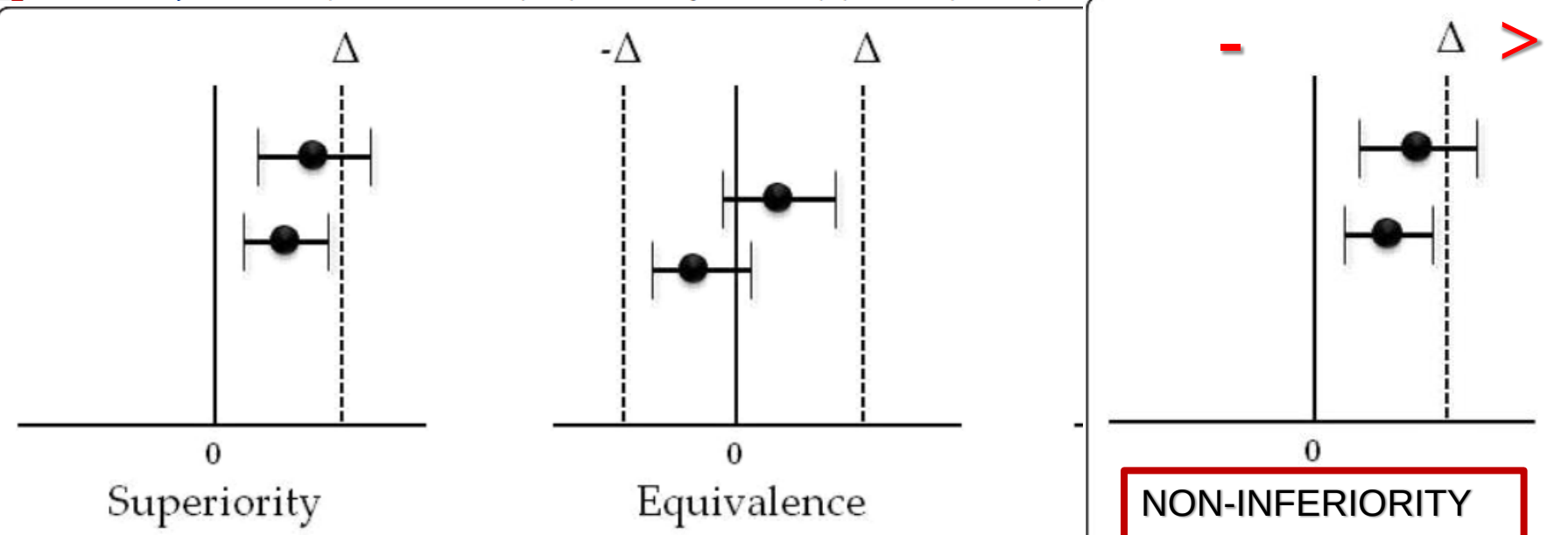


Figure 1 The role of Δ in superiority, equivalence and non-inferiority trials.

La Domanda CENTRALE della SCC
Le ipotesi STATISTICHE dello studio

6.1 DETERMINATION OF SAMPLE SIZE

The primary endpoint of PFS was used to determine the sample size for the study. Estimates of the number of events required to demonstrate efficacy with regard to PFS are based on the following assumptions:

- two-sided log-rank test at the 0.05 level of significance
- 80% power to detect a hazard ratio (HR) for GDC-0199+R versus R of 0.66, corresponding to an approximate median improvement of 2.3 months to 3.5 months (34% reduction in risk of a PFS event)
- exponential distribution of PFS
- an annual dropout rate of 5%
- one interim analysis for efficacy, 12 months after the last patient enrolled

Under these assumptions, 186 PFS events are required to achieve 80% power for the primary analysis of PFS in all patients. Assuming an enrollment of 20 months, it is planned to enroll 379 patients across the arms, randomized 1:1.

An efficacy interim analysis is planned approximately 12 months after the last patient is enrolled (see Section 9.10). Efficacy will be evaluated at a p value of 0.001 (corresponding to a hazard ratio of approximately 0.59). The minimum detectable difference at the final analysis corresponds approximately to a hazard ratio of 0.75. It is expected that, after a 9-month ramp-up, 24 patients per month will be recruited. Total enrollment is expected to take approximately 20 months.

Dimostrare (power = 0.80) che la nuova terapia riduca l'HR del 34% (una differenza tra le mediane di OS da 7.0 a 9.1 mesi. Studio SEQUENZIALE (una interim analysis).

4.5 Sample size

The primary endpoint will be the proportion with treatment failure. Thus, assuming a response rate of 90% at 48 weeks for different treatment arms, 115 subjects will be required per treatment arm to establish non-inferiority of DRV/r versus triple regimen, and of LPV/r versus triple regimen, with a maximum allowable difference of 12%, with one-sided significance level of p=0.025 and 80% power.

To account for a maximum of 10% major protocol violations that would be excluded from the on-protocol analysis, 125 subjects will be recruited in each treatment arm (375 subjects in total).

The non-inferiority margin is justified by the very expected virological failure rate in the reference group at 1 year (not leaving much room for superiority), and by the fact that besides virological efficacy, the novel treatment might have advantages in terms of toxicity and tolerability.

+Δ

Dimostrare (power = 0.80) una massima differenza accettabile minore del 12% da una risposta del 90% dello standard. NON-INFERIORITÀ

8.3 Sample Size Calculation

For a 1-sided log-rank test at an overall $\alpha = 0.025$ level of significance, 461 OS events (deaths) provide 90% power to reject the null hypothesis of equal survival distributions under the following conditions: exponentially distributed survival times with medians of 6 versus 7.0 months in the experimental group (docetaxel plus bevacizumab) and control group (docetaxel plus placebo), respectively (corresponding to a hazard ratio of 0.857); 1:1 treatment group allocation; and interim analyses for efficacy and superiority at 33% and 56% of the total OS events using the Lan-DeMets spending function boundaries with O'Brien-Fleming shape. Assuming uniform patient accrual over 24 months; a total study duration of 33 months; and a 10% dropout rate, the total sample size for this study will be 582 patients. This sample size was derived using SAS Proc SEQDESIGN.

Dimostrare (power = 0.80) una differenza tra le mediane di OS da 7.0 a 9.1 mesi. Studio SEQUENZIALE (una interim analysis per "futility" e superiorità).

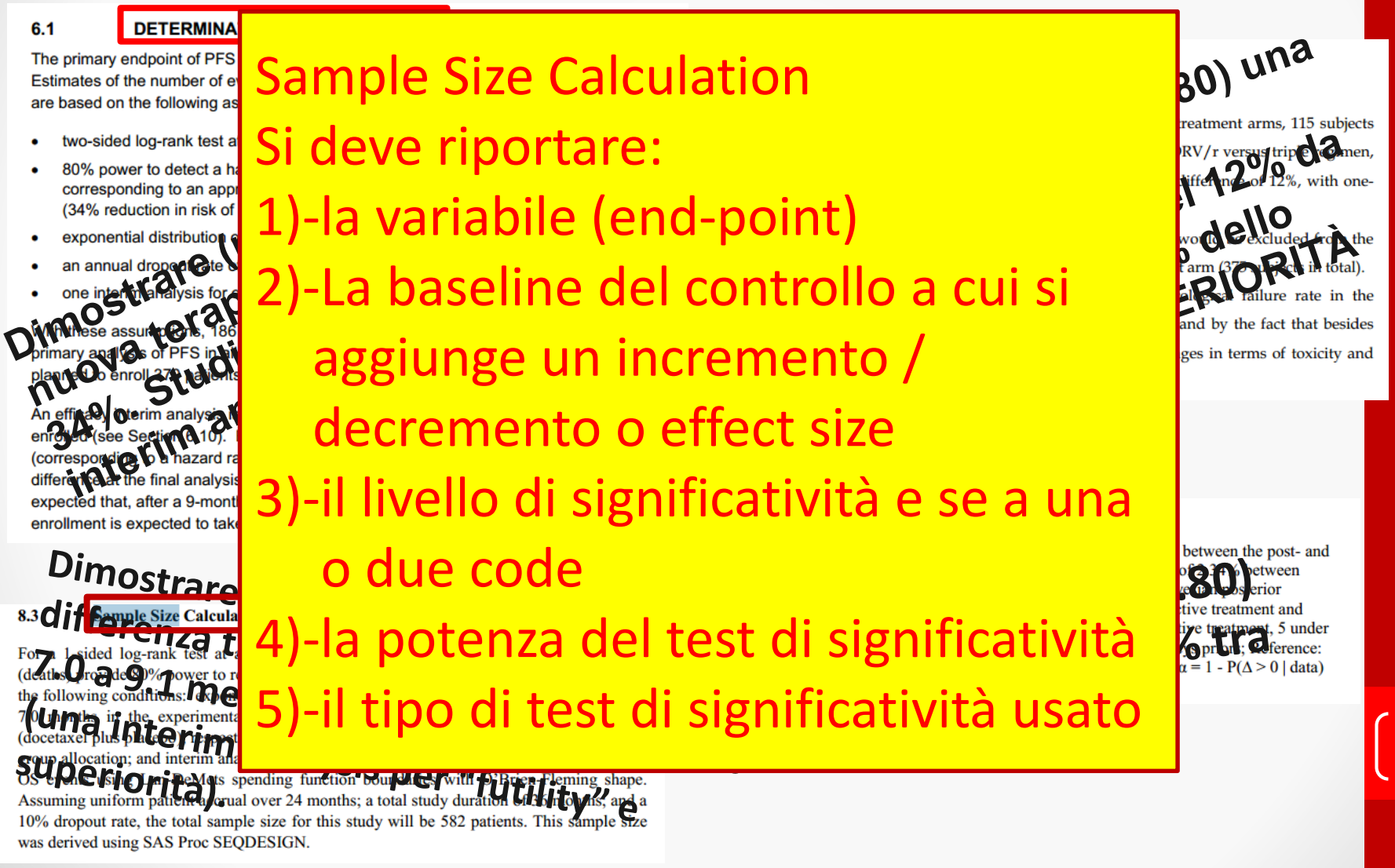
8.6 Determination of sample size

Assuming a standard deviation of 2.5% for the change in LVEF (CMR) between the post- and the pre-treatment measurements (see Bellenger et al.), a true difference of 2.5% between active treatment and placebo (Δ) will lead with a power of 80% to a Bayesian posterior probability $P(\Delta > 0 \mid data)$ of at least 80% that the difference between active treatment and placebo is positive (given the data) when 15 patients (10 under active treatment, 5 under placebo) will be evaluable for the analysis (using non-informative priors; reference: Calculations done with EQuery Advisor 2.0 based on the relationship $\alpha = 1 - P(\Delta > 0 \mid data)$ when non-informative priors are used).

Dimostrare (power = 0.80) una differenza di 2.34% tra due trattamenti.

Bruno M. Cesana

La Domanda CENTRALE della SCC
Le ipotesi STATISTICHE dello studio



Sample Size Calculation

Si deve riportare:

1)-la variabile (end-point)

2)-La baseline del controllo a cui si aggiunge un incremento / decremento o effect size

3)-il livello di significatività e se a una o due code

4)-la potenza del test di significatività

5)-il tipo di test di significatività usato

Bruno M. Cesana

Comitato Etico: COMPETENZE /

Supplemento ordinario alla "Gazzetta Ufficiale,, n. 53 del 3 marzo 2008 - Serie generale

Spediz. abb. post. 45% - art. 2, comma 20/b
Legge 23-12-1996, n. 662 - Filiale di Roma

GAZZETTA UFFICIALE

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PARTE PRIMA **Roma - Lunedì, 3 marzo 2008** SI PUBBLICA TUTTI I GIORNI NON FESTIVI

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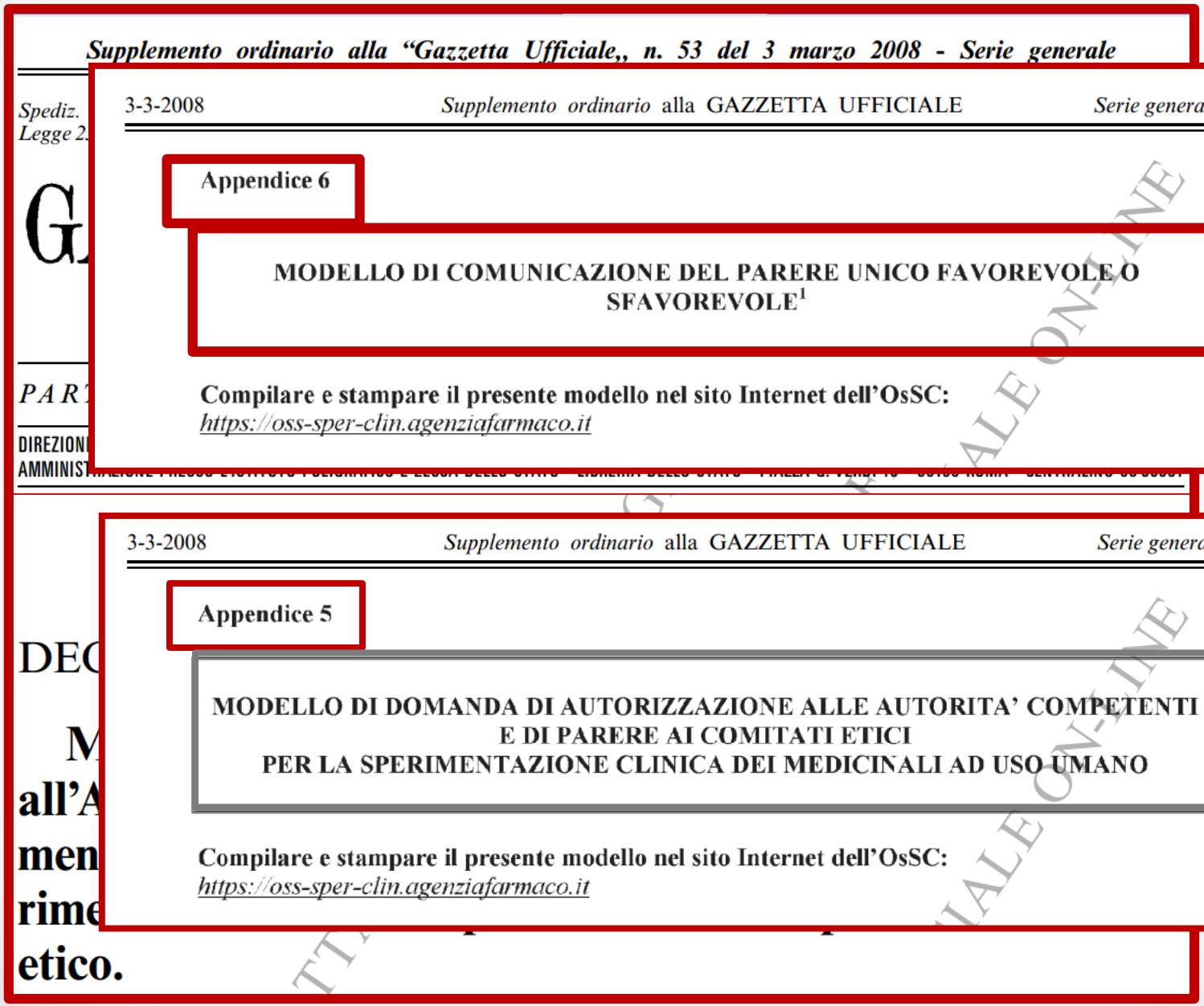
MINISTERO DELLA SALUTE

DECRETO 21 dicembre 2007.

Modalità di inoltro della richiesta di autorizzazione all'Autorità competente, per la comunicazione di emendamenti sostanziali e la dichiarazione di conclusione della sperimentazione clinica e per la richiesta di parere al comitato etico.

Comitato Etico: COMPETENZE /



Supplemento ordinario alla "Gazzetta Ufficiale,, n. 53 del 3 marzo 2008 - Serie generale

3-3-2008 *Supplemento ordinario* alla GAZZETTA UFFICIALE *Serie generale* - n. **53**

Appendice 6

MODELLO DI COMUNICAZIONE DEL PARERE UNICO FAVOREVOLE O SFAVOREVOLE[1]

Compilare e stampare il presente modello nel sito Internet dell'OsSC:
https://oss-sper-clin.agenziafarmaco.it

3-3-2008 *Supplemento ordinario* alla GAZZETTA UFFICIALE *Serie generale* - n. **53**

Appendice 5

MODELLO DI DOMANDA DI AUTORIZZAZIONE ALLE AUTORITA' COMPETENTI E DI PARERE AI COMITATI ETICI PER LA SPERIMENTAZIONE CLINICA DEI MEDICINALI AD USO UMANO

Compilare e stampare il presente modello nel sito Internet dell'OsSC:
https://oss-sper-clin.agenziafarmaco.it

Comitato Etico: COMPETENZE

Appendice 6

Modulo da utilizzare per la gestione transitoria a seguito della sospensione dei sistemi informativi dell'OsSC a partire dal 1.1.2013

MODULO DI COMUNICAZIONE AL RICHIEDENTE, AGLI ALTRI COMITATI ETICI E AD AIFA DELLA DECISIONE DEL COMITATO ETICO RELATIVA AL PARERE UNICO

Il parere finale (favorevole o non favorevole) deve essere trasmesso entro trenta giorni dalla data di ricevimento della domanda nella forma prescritta (entro sessanta giorni in caso di sperimentazione monocentrica)

Da completare a cura del comitato etico che ha rilasciato il parere unico:

A. IDENTIFICAZIONE DELLA SPERIMENTAZIONE

Comitato Etico: COMPETENZE

E. ELEMENTI VALUTATI
(selezionare NA nei casi in cui l'informazione non sia applicabile)

E.1 Dati di qualità del medicinale sperimentale

Le informazioni e i dati necessari a supportare la qualità dell'IMP sono adeguati ❑

Il promotore ha documentato che i prodotti in sperimentazione saranno preparati, gestiti e conservati nel rispetto delle Norme di Buona Fabbricazione (GMP) applicabili ❑

E.1.1 Eventuali elementi critici riscontrati *(testo libero):*

E.2 Dati di farmacologia non clinica e tossicologia

Esistono presupposti solidi e rilevanti che giustificano l'avvio dello studio ❑

E.2.1 Eventuali elementi critici riscontrati *(testo libero):*

E.3 Dati clinici

Esistono presupposti solidi e rilevanti che giustificano l'avvio dello studio (non applicabile per studi di fase I e II) ❑ ❑ **NA**

Lo studio consentirà di acquisire maggiori informazioni sull'IMP, di migliorare le procedure profilattiche, diagnostiche e terapeutiche o la comprensione dell'eziologia e della patogenesi delle malattie ❑

E.3.1 Eventuali elementi critici riscontrati *(testo libero)*

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E.4 Protocollo

Gli obiettivi sono coerenti con il razionale scientifico		❑
Il disegno dello studio è pertinente e rilevante		❑
Sono stati esaminati i seguenti aspetti:		
Mancanza del gruppo di controllo	❑	❑ NA
Disegno in aperto	❑	❑ NA
Assenza di randomizzazione	❑	❑ NA
Uso del placebo quale gruppo di controllo	❑	❑ NA
Disegno di equivalenza o di non inferiorità	❑	❑ NA

Comitato Etico: COMPETENZE

E.4 Protocollo

Gli obiettivi so

Il disegno dell

Sono stati esa

Mancanza del

Disegno in ape

Assenza di ran

Uso del place

Disegno di ec

ASPETTI CLINICI

Lo schema di trattamento con l'IMP risulta adeguato (via di somministrazione, dosaggio e posologia, durata della terapia)		❑
Il trattamento di controllo e lo schema di trattamento sono giustificati	❑	❑ NA
I criteri di inclusione/esclusione sono appropriati, chiari e ben definiti		❑
Gli esami, le visite e le procedure previste (specie se invasive) sono idonei a verificare gli effetti del trattamento		❑
La misura di esito primaria è clinicamente rilevante o correlabile a una misura clinicamente rilevante	❑	❑ NA
I metodi per rilevare la misura di esito primaria risultano adeguati	❑	❑ NA
Il calendario previsto per la rilevazione dei parametri di efficacia è appropriato	❑	❑ NA
I parametri selezionati per la valutazione della sicurezza sono congrui		❑
Il *follow-up* ha una durata sufficiente in relazione all'obiettivo dello studio		❑

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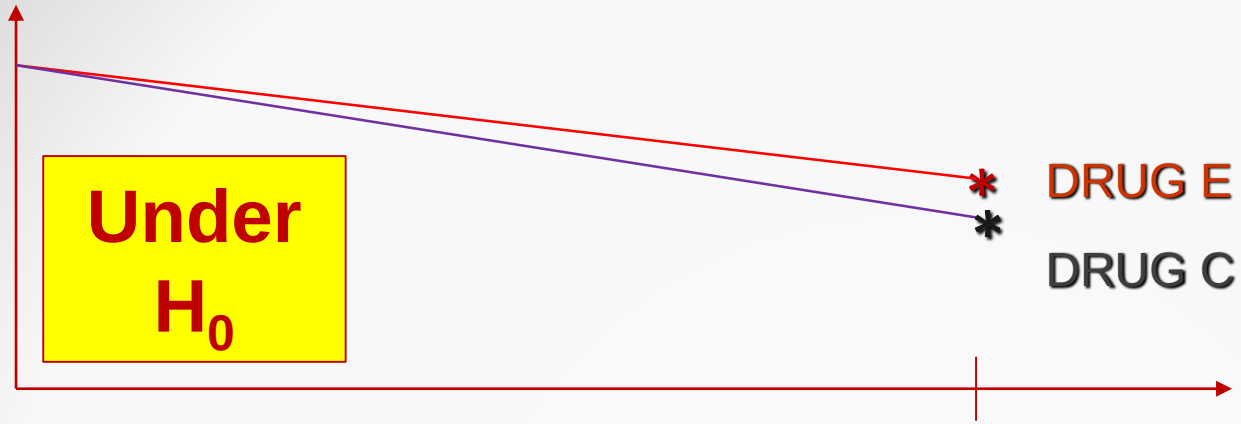
ASPETTI STATISTICI

La dimensione campionaria è stata calcolata in funzione della misura di esito primaria dichiarata	❑	❑ NA
Il calcolo della dimensione campionaria è corretto in relazione alla potenza prevista per lo studio	❑	❑ NA
Il piano statistico di analisi dei dati è coerente rispetto agli obiettivi		❑
La differenza attesa tra i trattamenti confrontati è significativa	❑	❑ NA
In caso di studio di equivalenza o di non inferiorità, la differenza considerata non rilevante è sufficientemente ristretta ed accettabile	❑	❑ NA
Il protocollo è conforme alle linee guida EMA in materia	❑	❑ NA
Se sì al punto precedente, specificarne i riferimenti *(testo*		
E.4.1 Eventuali elementi critici riscontrati *(testo libero):*		

Il *follow-up* ha una durata sufficiente in relazione all'obiettivo dello studio ❑



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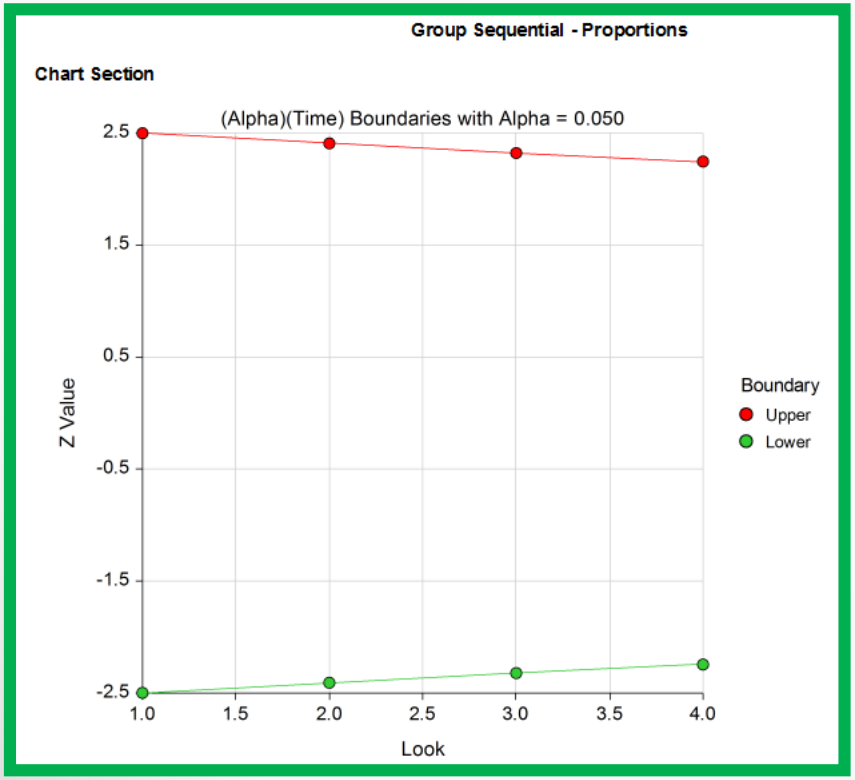

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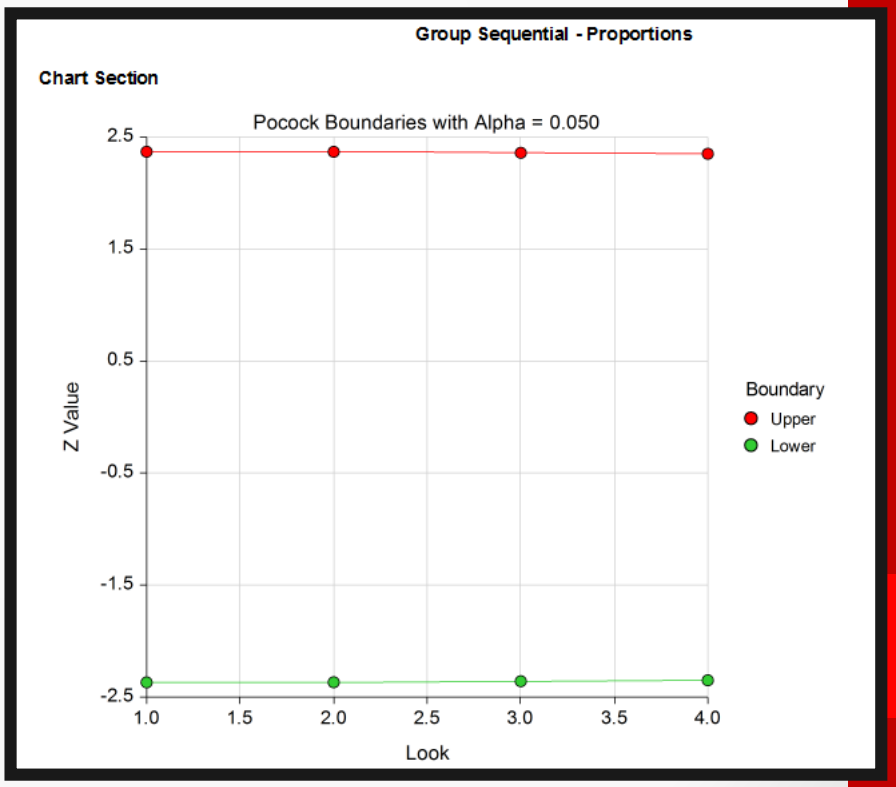

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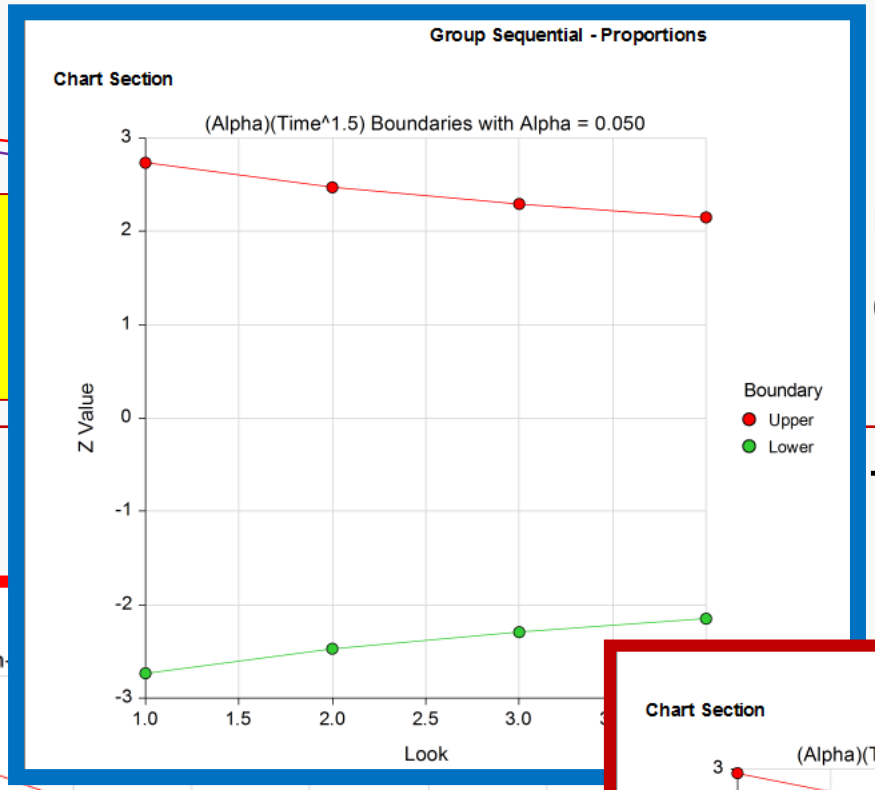

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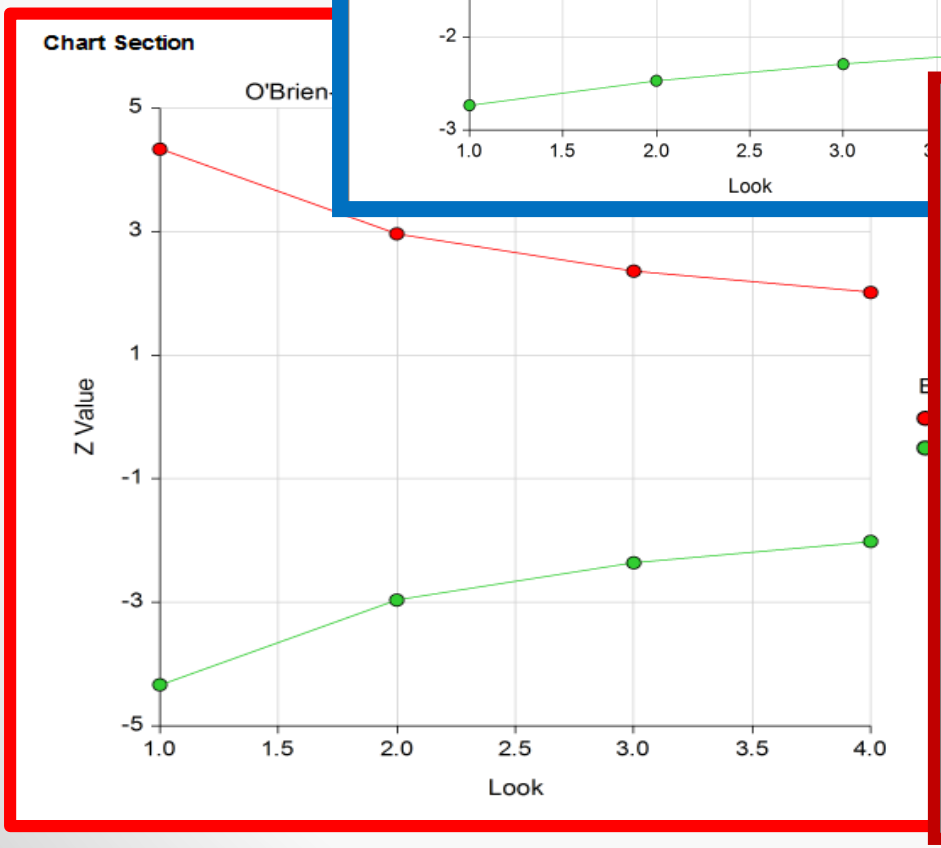

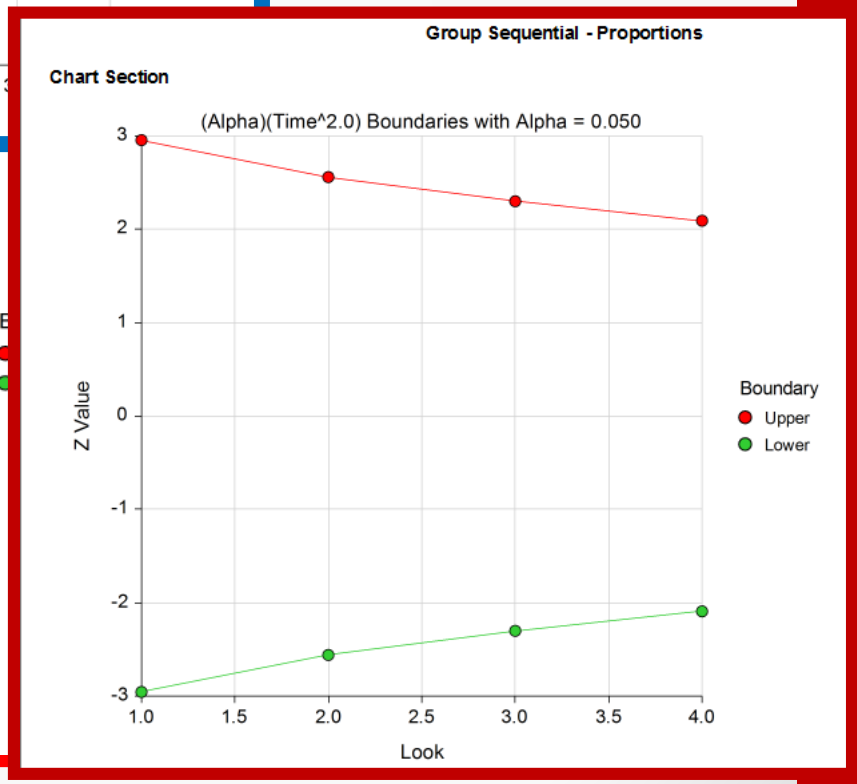

Bruno M. Lesana


Innovation
Stagnation
Challenge and Opportunity on the Critical Path to New Medical Technologies
FDA
U.S. Department of Health and Human Services
Food and Drug Administration
March 2004

INNOVATION OR STAGNATION?

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Executive Summary

This white paper provides the Food and Drug Administration's (FDA's) analysis of the *pipeline problem* — the recent slowdown, instead of the expected acceleration, in innovative medical therapies reaching patients.

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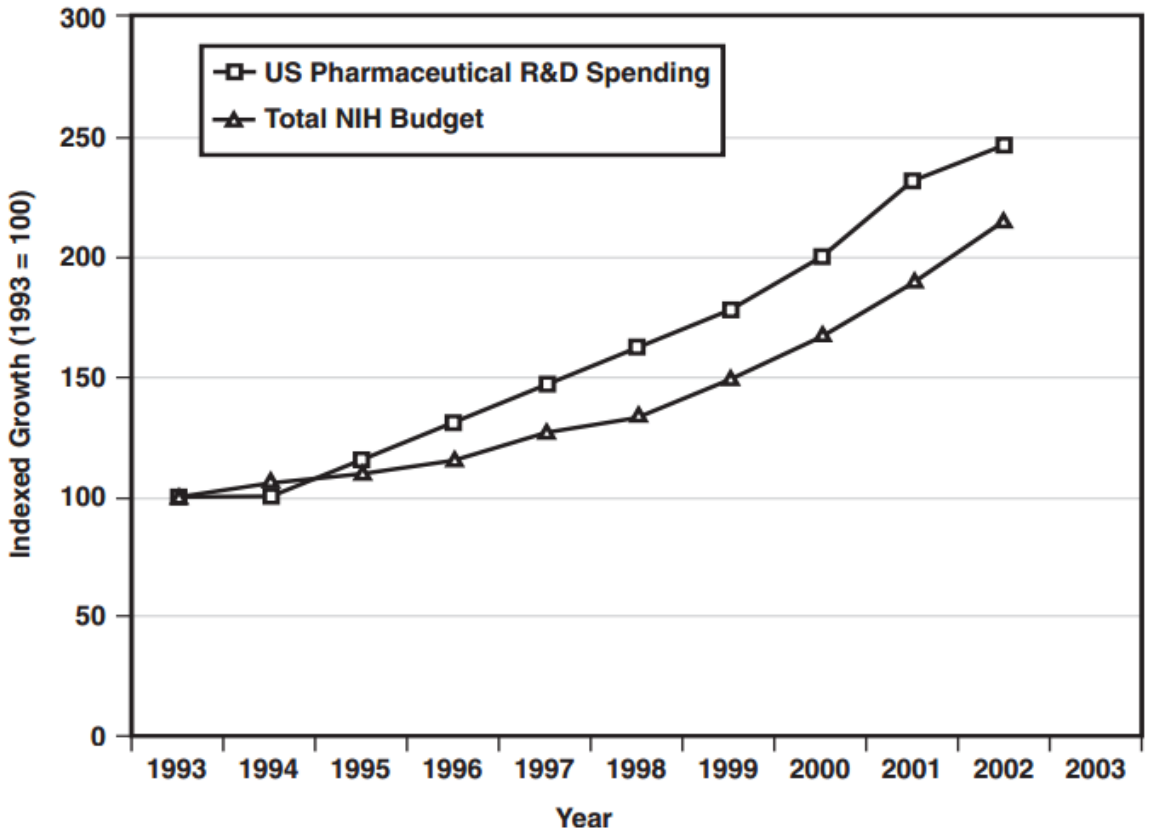
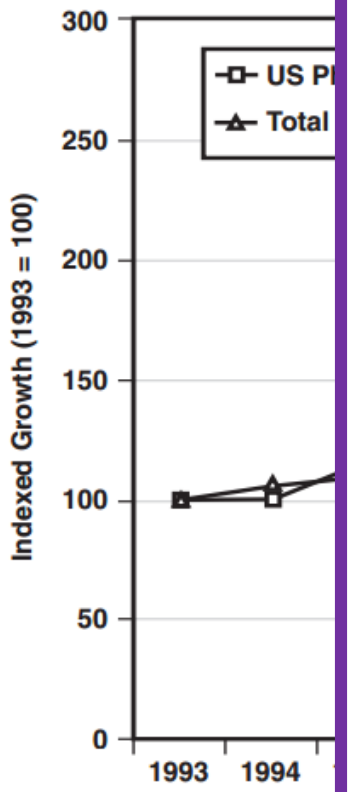
Figure 1: 10-Year Trends in Biomedical Research Spending



The figure shows 10-year trends in biomedical research spending as reflected by the National Institutes of Health (NIH) budget and by Pharmaceutical companies' research and development (R&D) investment.

Figure 1: 10-Year Trends in Biomedical Research Spending



The figure shows 10-ye
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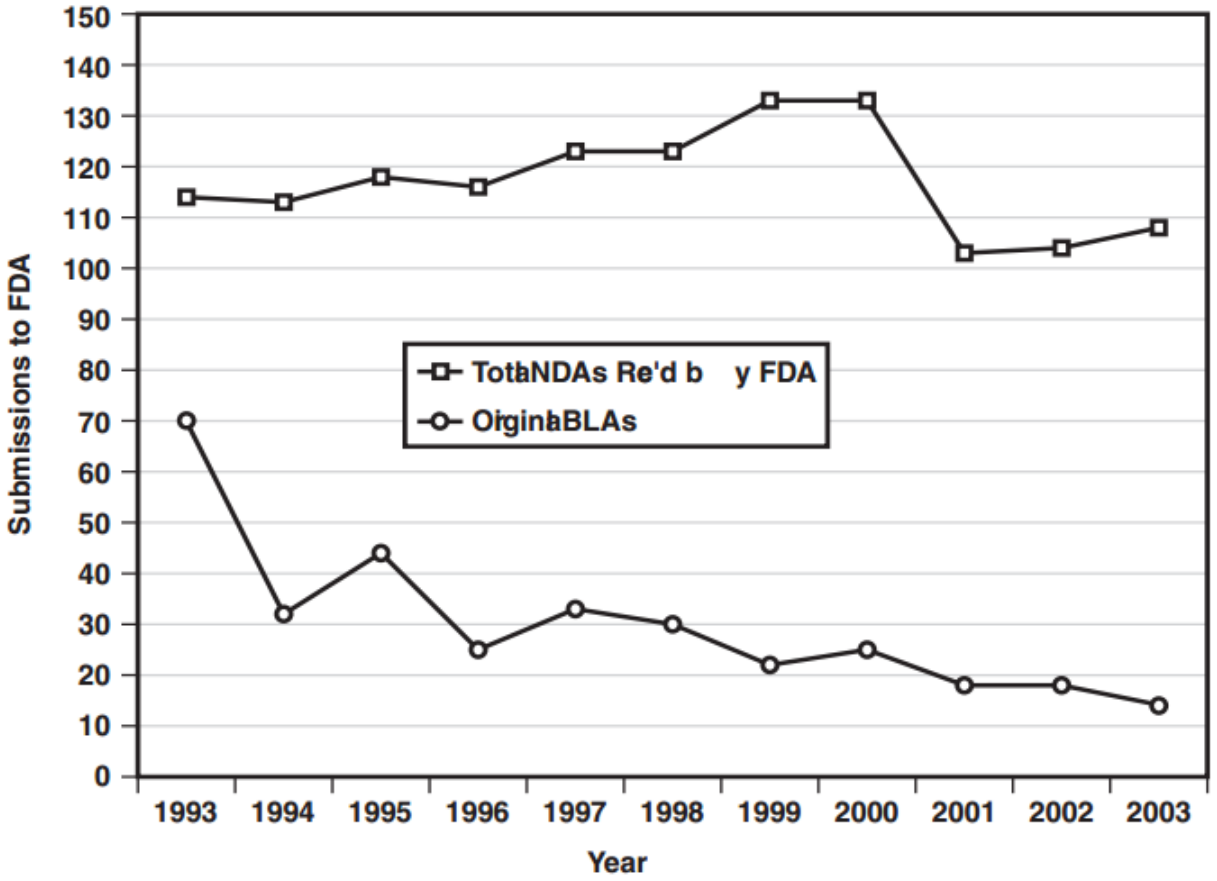
companies' research ar

Figure 2: 10-Year Trends in Major Drug and Biological Product Submissions to FDA



The figure shows the number of submissions of new molecular entities (NMEs) — drugs with a novel chemical structure — and the number of biologics license application (BLA) submissions to FDA over a 10-year period. Similar trends have been observed at regulatory agencies worldwide.

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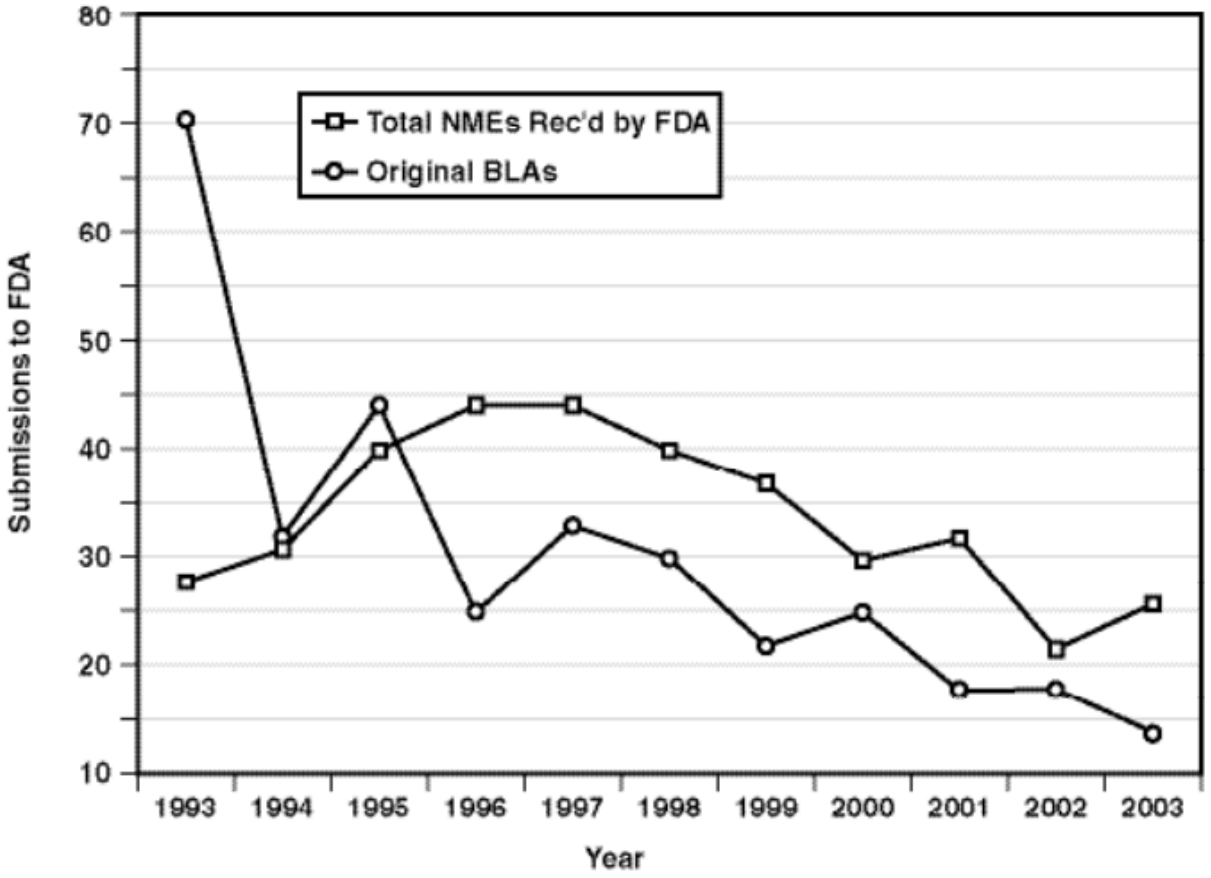
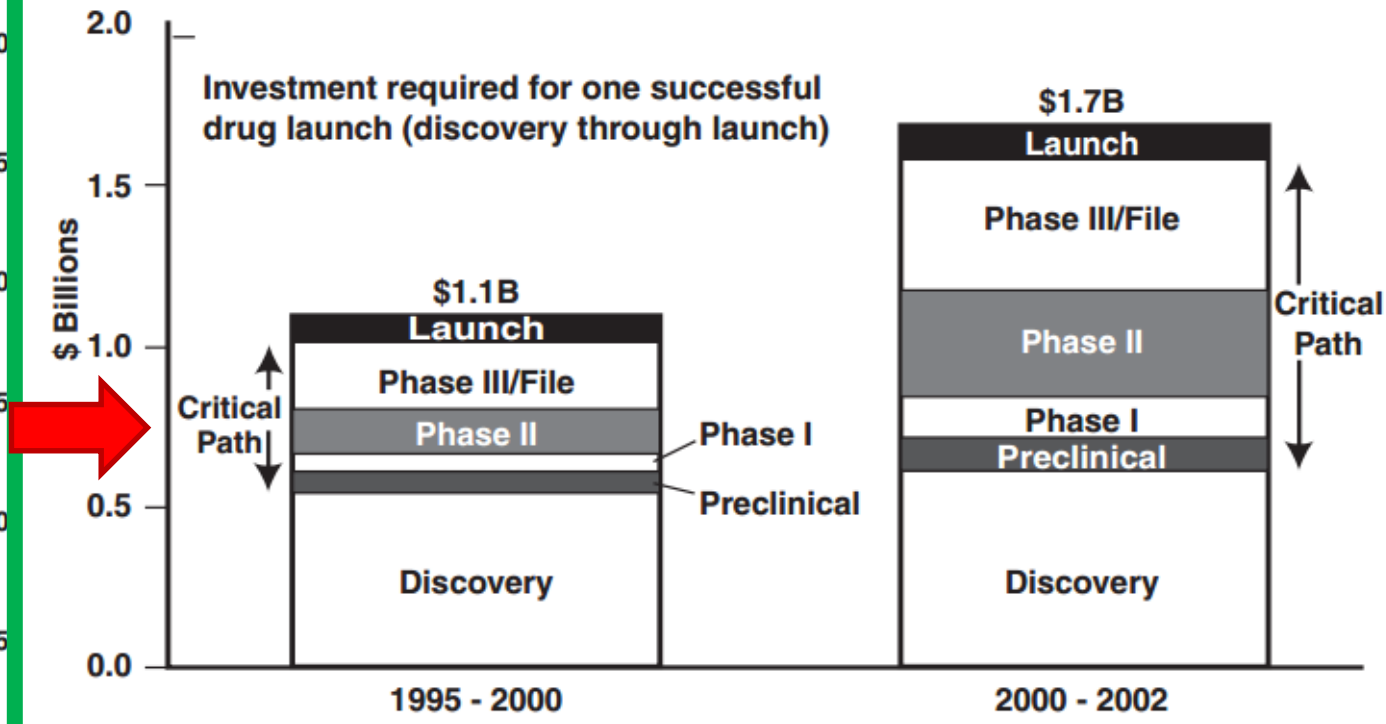


The figure shows the number of submissions of new molecular entities (NMEs) — drugs with a novel chemical structure — and the number of biologics license application (BLA) submissions to FDA over a 10-year period. Similar trends have been observed at regulatory agencies worldwide.

(NMEs)
iologics
Similar
trends have been observed at regulatory agencies worldwide.

Figure 3: Investment Escalation per Successful Compound



SOURCE: Windhover's In Vivo: The Business & Medicine Report, Bain drug economics model, 2003

The figure shows one estimate of the total investment required to "launch" (i.e., market) a successful drug in two time periods. Most of the recent cost increases are within the "critical path" development phase, between discovery and launch.

Indexed Growth (1993 = 100)

30
25
20
15
10
5

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application (BLA) submissions to FDA over a 10-year period. Similar trends have been observed at regulatory agencies worldwide.

Tools for Assessing Safety

For effective development, safety issues should be detected as early as possible, and ways to distinguish potential from actual safety problems should be available. Unfortunately, in part because of limitations of current methods, safety problems are often uncovered only during clinical trials or, occasionally, after marketing. One pharmaceutical company estimates that clinical failures based on liver toxicity alone have cost them more than $2 billion in the last decade — dollars that could otherwise be directed toward new product development.[22] Sometimes, early tests suggest the possibility of safety problems that never materialize, potentially eliminating candidates unnecessarily. Many of FDA's targeted efforts have involved defining more reliable methods for early prediction and detection of significant safety problems. The Agency seeks to prevent harm to patients during clinical development as well as potentially devastating setbacks to a new technology's progress and to public confidence.

Most of the tools used for toxicology and human safety testing are decades old

Tools for safety assessments include product testing (e.g., for contamination), as well as in vitro and animal toxicology studies, and human exposure. Most of the tools used for toxicology and human safety testing are decades old. Although traditional animal toxicology has a good track record for ensuring the safety of clinical trial volunteers, it is laborious, time-consuming, requires large quantities of product, and may fail to predict the specific safety problem that ultimately halts development. Clinical testing, even if extensive, often

Tools for Demonstrating Medical Utility

Better predictive nonclinical screening methods are urgently needed

Predicting and subsequently demonstrating medical utility (also called *benefit or effectiveness*) are some of the most difficult challenges in product development. Currently available animal models, used for evaluating potential therapies prior to human clinical trials, have limited predictive value in many disease states. Better predictive nonclinical screening methods are urgently needed. In many cases, developers must gamble on the results of the large-scale, expensive trials necessary to assess effectiveness in people. Such human trials are currently highly empirical, because most sources of variability in human responses are not understood and thus cannot be controlled for. It is clear to many in the field that new scientific advances have the potential to revolutionize clinical development. However, the path from scientific innovation to usable tool is not clear.

FDA has identified a number of opportunities for targeted efforts in the area of effectiveness (see next section) and, as time and funding permitted, undertaken targeted action. For example, FDA scientists developed statistical methods to control reader variability in trials of imaging devices and made the analysis software publicly available. Use of this method allows the sample size of imaging device trials to

European Medicines Agency

London, 23 March 2006
Doc. Ref. CHMP/EWP/2459/02

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL TRIALS WITH FLEXIBLE DESIGN AND ANALYSIS PLAN

DRAFT AGREED BY THE EFFICACY WORKING PARTY	11 January 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	23 March 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 September 2006

Comments should be provided using this template to line.jensen@emea.eu.int
Fax +44 20 7418 86 13

European Medicines Agency

London, 18 October 2007
Doc. Ref. CHMP/EWP/2459/02

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL TRIALS PLANNED WITH AN ADAPTIVE DESIGN

DRAFT AGREED BY THE EFFICACY WORKING PARTY	11 January 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	23 March 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 September 2006
AGREED BY THE EFFICACY WORKING PARTY	September 2007
ADOPTION BY CHMP	18 October 2007

KEYWORDS	Adaptive Design, Interim Analyses; Design Modifications; Randomised Clinical Trials; Confirmatory Clinical Trials; Biostatistics

EXECUTIVE SUMMARY

In some instances studies can be planned with a so-called adaptive design involving design modifications based on the results of an interim analysis. Such a design has the potential to speed up the process of drug development or can be used to allocate resources more efficiently without lowering scientific and regulatory standards. This is especially welcome if at the same time the basis for regulatory decision-making is improved.

However, in a clinical development plan the purpose of phase III is to confirm the findings from pre-clinical studies, tolerability studies, dose-finding and other phase II studies (CPMP/EWP/2330/99). To argue for design modifications in a phase III trial (or a late stage phase II trial supposed to be part of the confirmatory package) is then a contradiction to the confirmatory nature of such studies and will be rarely acceptable without further justification: adaptive designs should not be seen as a means to alleviate the burden of rigorous planning of clinical trials. Instead, adaptive designs would be best utilised as a tool for planning clinical trials in areas where it is necessary to cope with difficult experimental situations. In all instances the interim analysis and the type of the anticipated design modification (change of sample size, discontinuation of treatment arms, etc.) would need to be described and justified in the study protocol. Adaptations to confirmatory trials introduced without proper planning will render the trial to be considered exploratory.

Using an adaptive design implies that the statistical methods control the pre-specified type I error, that correct estimates and confidence intervals for the treatment effect are available, and that methods for the assessment of homogeneity of results from different stages are pre-planned. A thorough discussion will be required to ensure that results from different stages can be justifiably combined. The body of evidence justifying the final treatment recommendation must be discussed. The need for a change in the study design and the change itself may have implications for the clinical interpretation of the results, which deserve consideration at the planning stage.

KEYWORDS	Adaptive Design, Interim Analyses; Design Modifications; Randomised Clinical Trials; Confirmatory Clinical Trials; Biostatistics

4. MAIN REFLECTION PAPER TEXT

4.1 Interim analyses - general considerations

4.1.1 The importance of confidentiality of interim results

4.1.2 Considerations about stopping trials early for efficacy

4.1.3 Overrunning

4.2 Interim analyses with design modifications

4.2.1 Adaptation of design specifications: minimal requirements

4.2.2 Sample size reassessment

4.2.3 Change or modification of the primary end-point

4.2.4 Discontinuing treatment arms

4.2.5 Switching between superiority and non-inferiority

4.2.6 Randomisation ratio

4.2.7 Phase II / phase III combinations, applications with one pivotal trial and the independent replication of findings

4.2.8 Substantial changes of trial design

4.2.9 Futility stopping in late phase II or phase III clinical trials

4. MAIN REFLECTION PAPER TEXT

4.1 Interim analyses - general considerations

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4.2 Interim

4.2.1 Adap

4.2.2 Samp

4.2.3 Chan

4.2.4 Disco

4.2.5 Switc

4.2.6 Rand

4.2.7 Phas

4.2.8 Subs

4.2.9 Futili

NEW

DEFINITIONS

A study design is called ***"adaptive"*** if statistical [illegible] allows the modification of a design element (e.g. sample-size, randomisation ratio [illegible] of treatment arms) at an interim analysis with full control of the type I error.

NEW

The term ***"difficult experimental situation"*** has been used in this document to describe diseases, indications, or patient populations, where it is common knowled[illegible] clinical trials will be difficult to perform. Examples include situations where (i) placeb[illegible] difficult to predict, even in situations where criteria for inclusion and exclusion o[illegible] to trials are well defined (ii) small populations or orphan diseases with constraints [illegible] maximum amount of evidence that can be provided, and (iii) ethical constraints to expe[illegible]entation.

Confirmatory trial, confirmatory nature of a trial: In section 2.1.2 in ICH-E9 a confirmatory trial is defined as "an adequately controlled trial in which the hypotheses are stated in advance and evaluated. As a rule, confirmatory trials are necessary to provide firm evidence of efficacy and safety".

REFERENCES

Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)

Points to Consider on Multiplicity issues in Clinical Trials (CPMP/EWP/908/99)

Points to Consider on Application with 1.) Meta-analyses and 2.) One Pivotal study (CPMP/2330/99)

Points to Consider on Switching between Superiority and Non-inferiority (CPMP/EWP/482/99)

Points to Consider on Choice of the Non-Inferiority Margin (CPMP/EWP/2158/99)

Guideline on Data Monitoring Committees (CHMP/EWP/5872/03)

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Report on the EMEA-EFPIA Workshop on Adaptive Designs in Confirmatory Clinical Trials

The European Medicines Agency (EMEA) in collaboration with the European Federation of Pharmaceutical Industries and Associations (EFPIA) organised a first joint workshop on Adaptive Designs in Confirmatory Clinical Trials. The workshop was co-chaired by Prof. Bruno Flamion, Chair of the CHMP Scientific Advice Working Party (SAWP) and Dr Solange Rohou Chair of the EFPIA Efficacy Working Party. There was a large attendance from pharmaceutical companies as well as representatives from the regulatory authorities and some academic centres.

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Guidance for Industry

Adaptive Design Clinical Trials for Drugs and Biologics

Contains Nonbinding Recommendations

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