VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

JAMA April 28, 2015 Volume 313, Number 16 1619

Table. General Characteristics of Traditional and Platform Trials[a]

Characteristic	Traditional Trial	Platform Trial
Scope	Efficacy of a single agent in a homogeneous population	Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous
Duration	Finite, based on time required to answer the single primary question	Potentially long-term, as long as there are suitable treatments requiring evaluation
No. of treatment groups	Prespecified and generally limited	Multiple treatment groups; the number of treatment groups and the specific treatments may change over time
Stopping rules	The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment	Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)
Allocation strategy	Fixed randomization	Response-adaptive randomization
Sponsor support	Supported by a single federal or industrial sponsor	The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination

[a] Platform trials and similar trials may also be called basket, bucket, umbrella, or standing trials.

Harbor-UCLA Medical Center, Torrance, California; and Berry Consultants LLC,

ments to subgroups defined by genetic, proteomic, metabolomic, or other markers.[3]

There has been increasing interest in efficient trial

tools used in platform trials are frequently used in other settings and some less so, it is the integrated application of multiple tools that allows a platform trial to address its multiple

The platform design differs from the basket or umbrella designs in that it is not testing a specified hypothesis about matching of drug to genomic alteration.
The platform approach involves an adaptive randomization among multiple drugs for each of several biomarker strata.

https://www.bhdsyndrome.org/forum/bhd-research-blog/genetic-sequencing-approaches-to-cancer-clinical-trials/

Most cancer treatments are established following a traditional clinical trial where new drugs are assessed in patients with the same type of tumour (Figure 1). Advanced understanding and technology have led to the development of targeted treatment clinical trials:

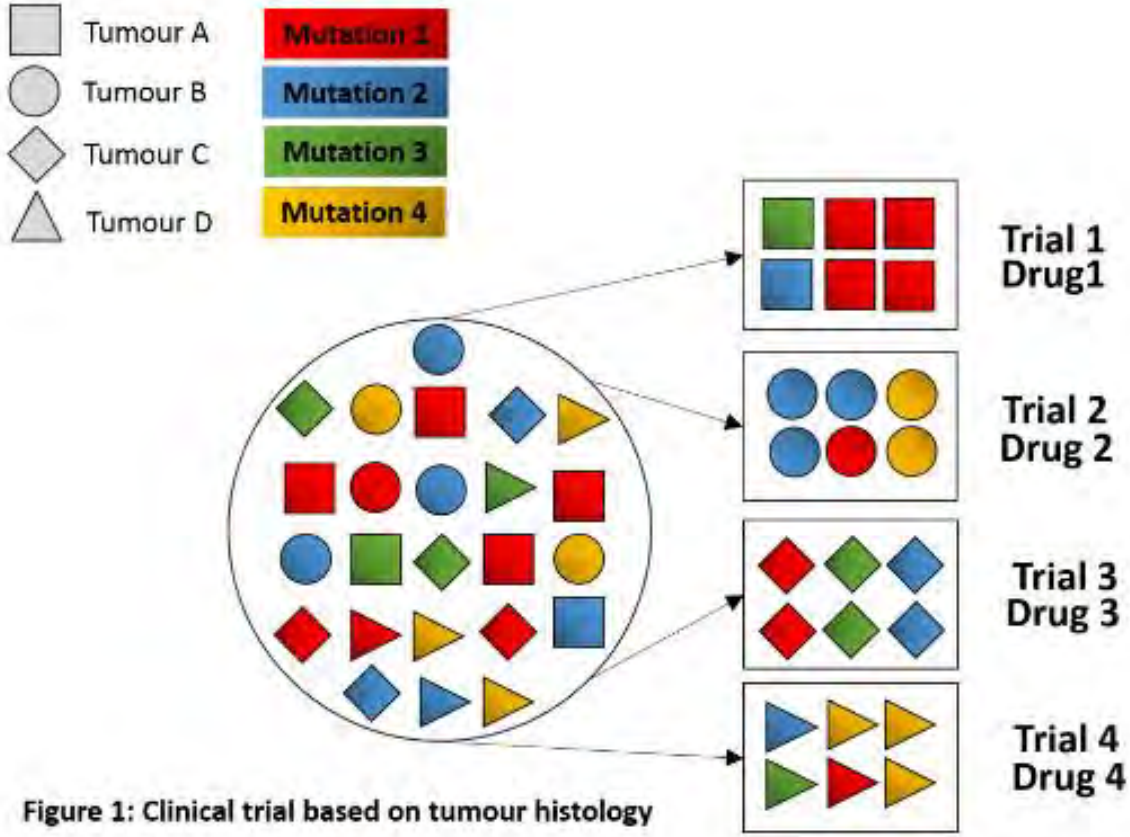


Figure 1: Clinical trial based on tumour histology

https://www.bhdsyndrome.org/forum/bhd-research-blog/genetic-sequencing-approaches-to-cancer-clinical-trials/

Umbrella and basket clinical trials use genetic and molecular data to assess targeted treatments in the right patient cohorts.

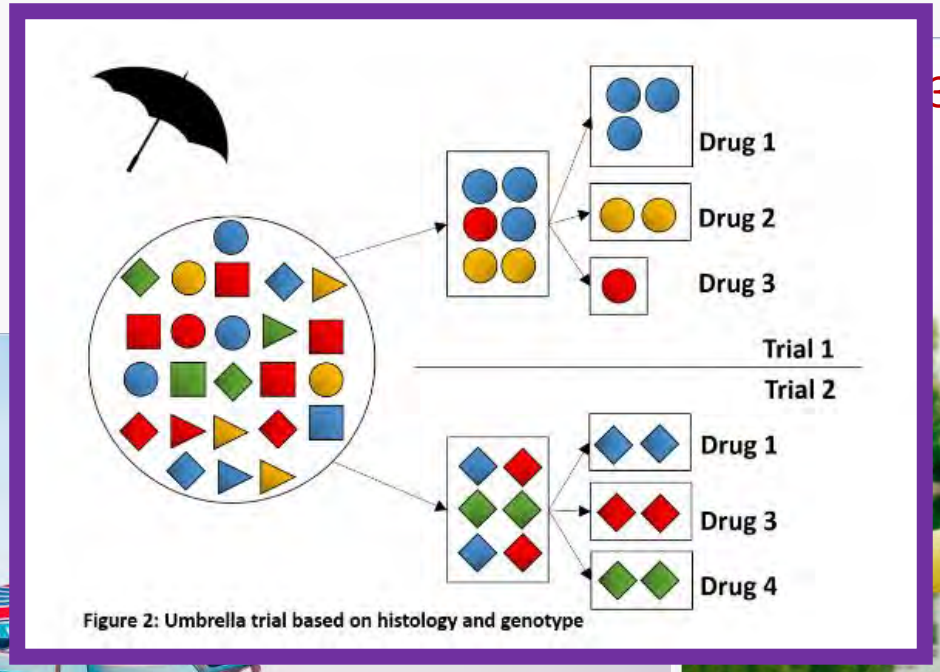
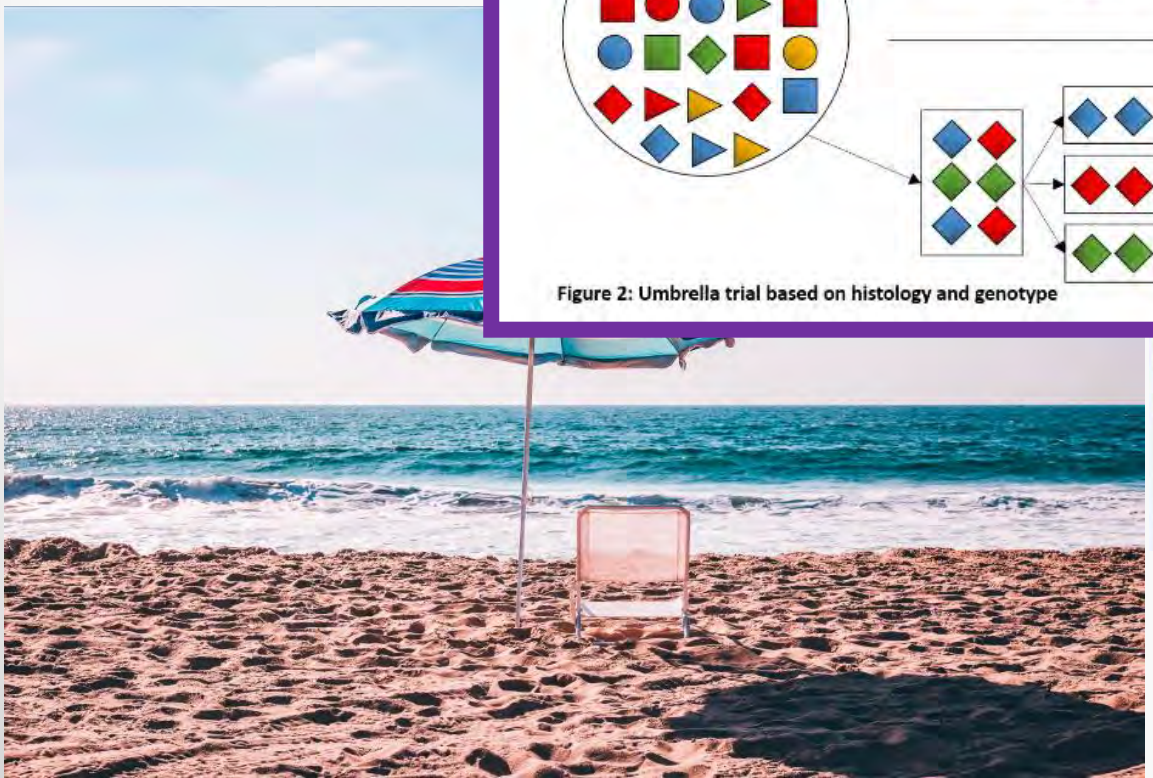
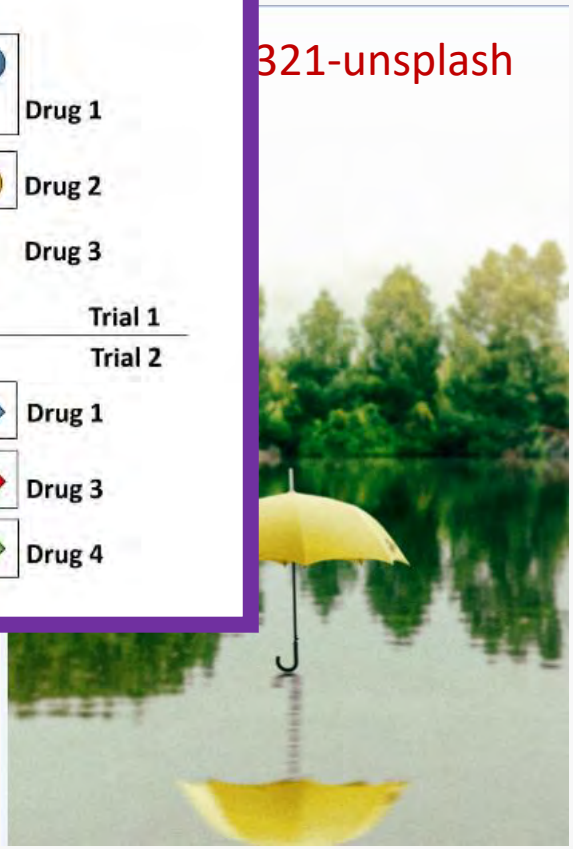


Figure 2: Umbrella trial based on histology and genotype

321-unsplash





https://www.bhdsyndrome.org/forum/bhd-research-blog/genetic-sequencing-approaches-to-cancer-clinical-trials/

Umbrella and basket clinical trials use genetic and molecular data to assess targeted treatments in the right patient cohorts.

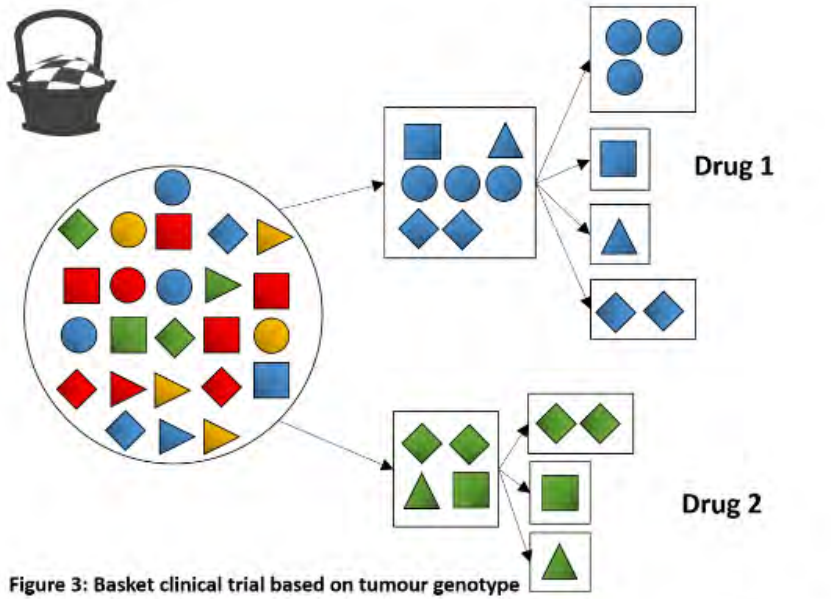
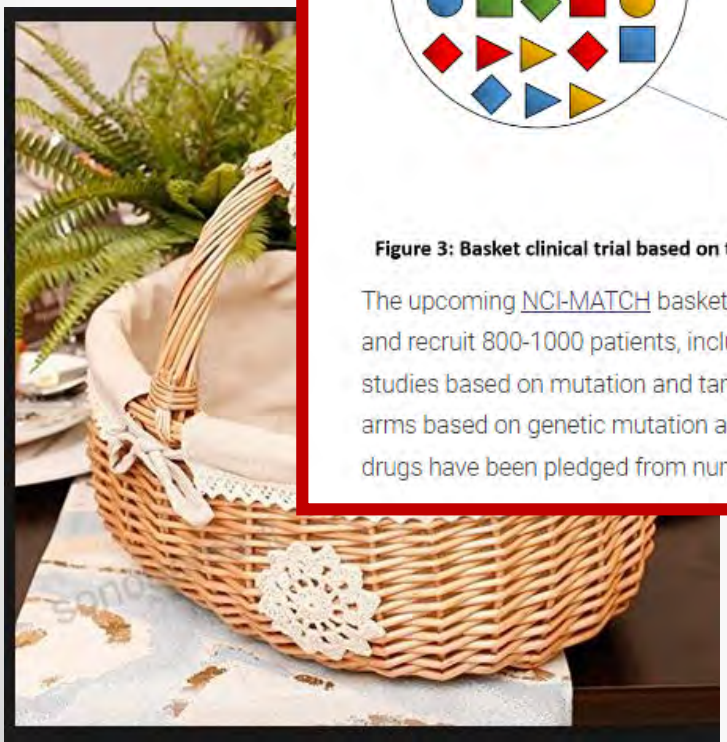


Figure 3: Basket clinical trial based on tumour genotype

The upcoming NCI-MATCH basket trial will screen up to 3000 tumour biopsies and recruit 800-1000 patients, including rare cancer patients, for small cohort studies based on mutation and targeted drugs. There are currently 20 different arms based on genetic mutation and tumour histology and over 40 different drugs have been pledged from numerous pharmaceutical industries.



Cancer Chemother Pharmacol (2009) 63:703–709
DOI 10.1007/s00280-008-0789-4

ORIGINAL ARTICLE

Phase 0 clinical trials in oncology: a paradigm shift for early drug development?

Chris H. Takimoto

Abstract
Purpose To review the potential impact of Phase 0 trials conducted under the United States Food and Drug Administration (FDA) exploratory IND guidance on oncology drug development.
Methods The FDA's exploratory IND guidance document is examined in detail and its practical application to specific first-in-human proof of concept clinical studies called Phase 0 trials is discussed.
Results Phase 0 trials represent a novel strategy for accelerating the development of the next generation of anticancer treatments. Phase 0 studies are conducted prior to conventional toxicity-defined dose-escalation studies and these trials do not explore maximum toxicity levels and by definition are devoid of any therapeutic or diagnostic intent. They require less extensive formulation and non-clinical toxicity testing than conventional first-in-human Phase I trials. This pathway may be valuable in reducing the time and resources required to initiate clinical testing and it may also be useful in guiding the later stages of drug development. Alternatively, the early termination of a less than promising lead compounds could help in selecting the best agents for later clinical development. Possible disadvantages include the ethical challenge of testing non-therapeutic drug regimens in cancer patients and the need to conduct standard dose-escalation Phase I studies later in development.
Conclusions The potential of this novel pathway to accelerate drug development makes it worthy of further exploration, and National Cancer Institute has recently completed a Phase 0 trial demonstrating its applicability to targeted anticancer agents.

Keywords Phase 0 · Exploratory IND · Drug development

The problem: innovation or stagnation?

In 2004, the FDA released an influential white paper entitled "Challenge and Opportunity on the Critical Path to New Medical Products" [2]. This important document highlighted some disturbing trends. First, the number of new chemical entities (NCE) beginning clinical testing in each year from 1996 to 2002 steadily declined instead of increasing. Second, the success rate of new compounds entering into first-in-human testing also decreased. In 2000, a new chemical entity entering into a first-in-human a Phase I clinical trial had an 8% chance of reaching the market, compared with a historical success rate of 14% in 1985. One of the FDA's conclusions was that the "…medical product development process is no longer able to keep pace with basic scientific innovation" [2]. Furthermore, the report conceded that "[w]e must modernize the clinical

PHASE I

In summary, it seems that the idea of the so-called MFDE came up in the NCI in the sixties when the early clinical trials programs started there and was promoted by the scientists mentioned above. They searched for a dose escalation scheme that slows down from doubling the dose to smaller increases within a few steps. The MFDE (Table 1), slowing down the increase from 65% to 33% within the first five steps, seemed reasonable enough to be used in many trials. The method has been successful to the extent that MTDs have been determined through its use. From empirical evidence and the simulation studies performed later, the MFDE seems now to be too conservative in too many cases.

Table 1 Evolution of the Modified Fibonacci Scheme from the Fibonacci Numbers f_n Defined Recursively $f_{n+1} = f_n + f_{n-1}$, $n = 1, 2, \ldots, f_0 = 0, f_1 = 1$

Fibonacci numbers f_n, $n = 1, 2, \ldots$	Fibonacci multiples f_{n+1}/f_n	Modified Fibonacci f_{n+1}/f_n	Smoothed modified Fibonacci
1	—	—	—
2	2.0	2	2.0
3	1.5	1.65	1.67
5	1.67	1.52	1.50
8	1.60	1.40	1.40
13	1.63	1.33	1.30–1.35
21	1.62	1.33	1.30–1.35
34	1.62	1.33	1.30–1.35
55	1.62	1.33	1.30–1.35

MFDE: MODIFIED FIBONACCI DOSE ESCALATION

PHASE I – TRADITIONAL DESIGN 3 + 3

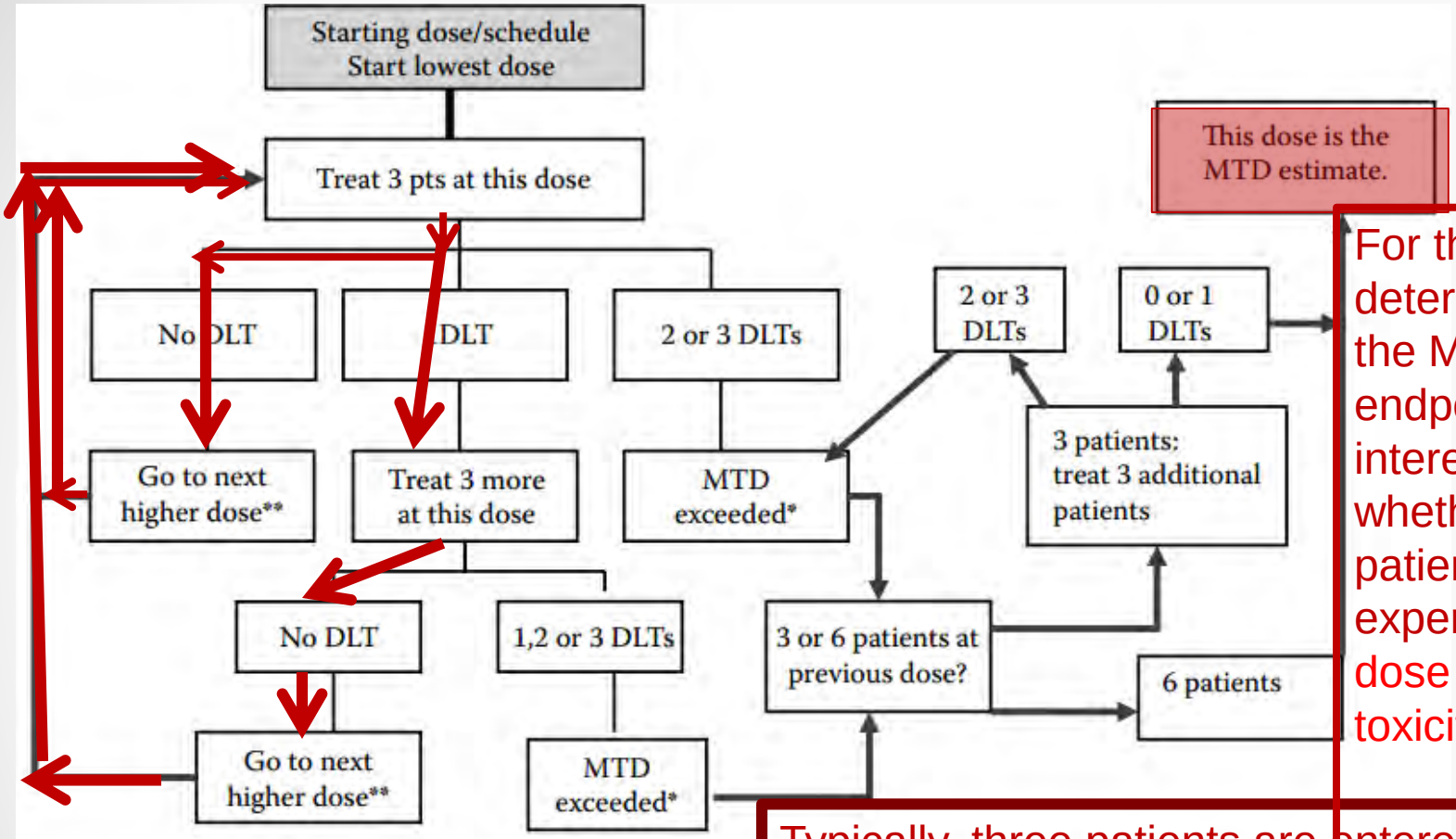


FIGURE 4.1
Schema for traditional Phase I design.

For the determination of the MTD, the endpoint of interest is whether or not patient experiences a dose limiting toxicity (DLT)

Typically, three patients are entered at the first dose level, which is often chosen to be 10% of the mouse LD10 (dose at which 10% of mice die).

Bruno M. Cesana

PHASE I TRIALS

special article

Annals of Oncology 26: 1808–1812, 2015
doi:10.1093/annonc/mdv266
Published online 18 June 2015

Statistical controversies in clinical research: requiem for the 3 + 3 design for phase I trials

X. Paoletti[1,2*], M. Ezzalfani[3] & C. Le Tourneau[3,4]

[1]*Biostatistics and Epidemiology Department, Gustave Roussy, Villejuif;* [2]*INSERM U1018, CESP, Paris-Sud University, Villejuif;* [3]*INSERM/Institut Curie/Mines ParisTech U900, Paris;* [4]*Department of Medical Oncology, Clinical Trial Unit, Institut Curie, Paris & Saint-Cloud, France*

Conclusions: Alternative statistical proposals have been developed to make a better use of the complex data generated by phase I trials. Their applications require a close collaboration between all actors of early phase clinical trials.

Background: More than 95% of published phase I trials have used the 3 + 3 design to identify the dose to be recommended for phase II trials. However, the statistical community agrees on the limitations of the 3 + 3 design compared with model-based approaches. Moreover, the mechanisms of action of targeted agents strongly challenge the hypothesis that the maximum tolerated dose constitutes the optimal dose, and more outcomes including clinical and biological activity increasingly need to be taken into account to identify the optimal dose.

Patients and methods: We review key elements from clinical publications and from the statistical literature to show that the 3 + 3 design lacks the necessary flexibility to address the challenges of targeted agents.

Results: The design issues raised by expansion cohorts, new definitions of dose-limiting toxicity and trials of combinations are not easily addressed by the 3 + 3 design or its extensions.

Conclusions: Alternative statistical proposals have been developed to make a better use of the complex data generated by phase I trials. Their applications require a close collaboration between all actors of early phase clinical trials.

Key words: continual reassessment method, dose finding, efficiency, targeted agents

al article

PHASE I TRIALS

Critical aspects of the Bayesian approach to phase I cancer trials

Beat Neuenschwander*, †, Michael Branson and Thomas Gsponer

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STATISTICS IN MEDICINE
Statist. Med. 2008; **27**:2420–2439
Published online 14 March 2008 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/sim.3230

SUMMARY

The Bayesian approach to finding the maximum-tolerated dose in phase I cancer trials is discussed. The suggested approach relies on a realistic dose–toxicity model, allows one to include prior information, and supports clinical decision making by presenting within-trial information in a transparent way. The modeling and decision-making components are flexible enough to be extendable to more complex settings. Critical aspects are emphasized and a comparison with the continual reassessment method (CRM) is performed with data from an actual trial and a simulation study. The comparison revealed similar operating

Sofisticati approcci metodologici (clinici e statistici) sono necessari per I disegni della Fase I

TITLE:

14/02/2019

6. **STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN**

6.1 **DETERMINATION OF SAMPLE SIZE**

Dose finding will be conducted during the dose-escalation phase of this study. The estimated sample size follows from the dose-escalation rules for a mCRM algorithm, as outlined in Section 3.1. It is anticipated that enrollment of up to five cohorts of 3–6 patients each, for a total of 9–15 evaluable patients, will be required to establish the RP2D during the dose-escalation phase (see Appendix 18 for modeling details and simulation results). Assuming 5 not-evaluable patients (see Section 3.1.2 for the definition of evaluable patients), the expected maximum sample size will be approximately 20 patients.

AML COMPLETE REMISSION

PROTOCOL NUMBER:	GO40800
VERSION NUMBER:	1
EUDRACT NUMBER:	2018-002964-25
IND NUMBER:	117005
TEST PRODUCTS:	Idasanutlin (RO5503781), cytarabine, and daunorubicin
MEDICAL MONITOR:	Yann Nouet, Ph.D.
SPONSOR:	[redacted]
DATE FINAL:	See electronic date stamp below.

PROTOCOL

TITLE: **A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF IDASANUTLIN IN COMBINATION WITH CYTARABINE AND DAUNORUBICIN IN PATIENTS NEWLY DIAGNOSED WITH ACUTE MYELOID LEUKEMIA (AML) AND THE SAFETY AND EFFICACY OF**

14/02/2019

6. **ST**

6.1 **DE**

Dose finding will b
estimated sample
outlined in Sectio
3–6 patients each
RP2D during the
simulation results
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approximately 20

SPONSOR:

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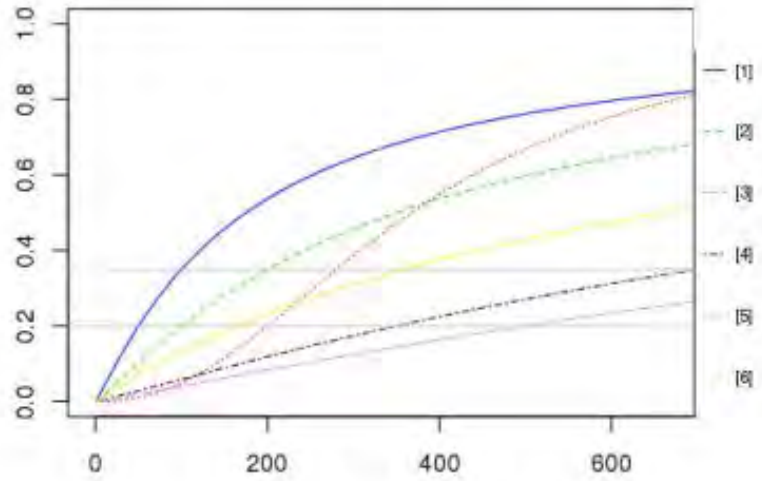

Simulation Results

NOVARTIS

Novartis Research and Development

14/02/2019

HDM201

Clinical Trial Protocol CHDM201A2101

A phase I/II multi-center study of HDM201 added to chemotherapy in adult subjects with relapsed/refractory (R/R) or newly diagnosed acute myeloid leukemia (AML)

Document type:	Clinical Trial Protocol
EUDRACT number:	2018-003107-19
Version number:	00 (Original Protocol)
Clinical Trial Phase:	I/II
Release date:	04-Oct-2018

A Bayesian dual-criterion design will be used and efficacy will be concluded if both of the following criteria are met:

[redacted]

True CR/CRi with ABCR rate	p(success)	p(futility)	p(inconclusive)
N=30, Required # of response for success ≥23 (77%)			
65%	0.12	0.88	0.00
70%	0.28	0.72	0.00
75%	0.51	0.49	0.00
80%	0.76	0.24	0.00
85%	0.93	0.07	0.00
90%	0.99	0.01	0.00

Given the sample size of 30, the probability of observing at least one AE is provided in Table 12-3 for various true AE incidences.

[redacted]

	True incidence			
	p=0.02	p=0.05	p=0.07	p=0.1
Prob (observing at least one AE)	0.455	0.785	0.887	0.958

Optimal Two-Stage Designs for Phase II Clinical Trials

Richard Simon, PhD

Biometric Research Branch, National Cancer Institute, Bethesda, Maryland

ABSTRACT: The primary objective of a phase II clin
determine whether it has sufficient biological
to warrant more extensive development. Su
institution setting where designs of more tha
paper presents two-stage designs that are opti
size is minimized if the regimen has low acti
of the type 1 and type 2 errors. Two-stage
sample size are also determined. Optimum
design parameters are tabulated. These desi
new regimens where toxicity is the endpoint

Contemporary Clinical Trials 33 (2012) 1255–1260

Contents lists available at SciVerse ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

A new adaptive design based on Simon's two-stage optimal design for phase II clinical trials

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ARTICLE INFO

Article history:
Received 25 January 2012
Revised 6 June 2012
Accepted 2 July 2012
Available online 6 July 2012

Keywords:
Phase II clinical trials
Simon's two-stage optimal design
Adaptive design
Conditional type I error
Conditional power

ABSTRACT

Phase II clinical trials are conducted to determine whether a new agent or drug regimen has sufficient promise in treating cancer to merit further testing in larger groups of patients. Both ethical and practical considerations often require early termination of phase II trials if early results clearly indicate that the new regimen is not active or worthy of further investigation. Simon's two-stage designs (1989) are common methods for conducting phase II studies investigating new cancer therapies. Banerjee and Tsiatis (2006) proposed an adaptive two-stage design which allows the sample size at the second stage to depend on the results at the first stage. Their design is more flexible than Simon's, but it is somewhat counter-intuitive: as the response in the first stage increases, the second-stage sample size increases till a certain point and then abruptly becomes zero. In this paper, based on Simon's two-stage optimal design, we propose a new adaptive one which depends on the first stage results using the restrict conditions the conditional type I error and the conditional power. Comparisons are made between Banerjee and Tsiatis' results and our new adaptive designs.

Beard *et al. Trials* (2015) 16:353
DOI 10.1186/s13063-015-0839-2

TRIALS

RESEARCH Open Access

Stepped wedge randomised controlled trials: systematic review of studies published between 2010 and 2014

Emma Beard[1,2*†], James J. Lewis[3,8*†], Andrew Copa
Jennifer A. Thompson[4,8], Katherine L. Fielding[3], Rur

Abstract

Background: In a stepped wedge, cluster randor
and the order in which they received it is randor
documented a steady rise in their use between 1
logistical and analytical advantages. However, the
poorly reported and did not adequately describe
additional stepped wedge trials have been publis
consider what interventions were tested and the

ical Trials 33 (2012) 1255–1260

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mon's two-stage optimal design for phase

HHS Public Access

Author manuscript

Health Psychol. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Health Psychol. 2015 December ; 34(0): 1220–1228. doi:10.1037/hea0000305.

Micro-Randomized Trials: An Experimental Design for Developing Just-in-Time Adaptive Interventions

Predrag Klasnja[1], **Eric B. Hekler**[2], **Saul Shiffman**[3], **Audrey Boruvka**[1], **Daniel Almirall**[1], **Ambuj Tewari**[1], and **Susan A. Murphy**[1]

[1]University of Michigan

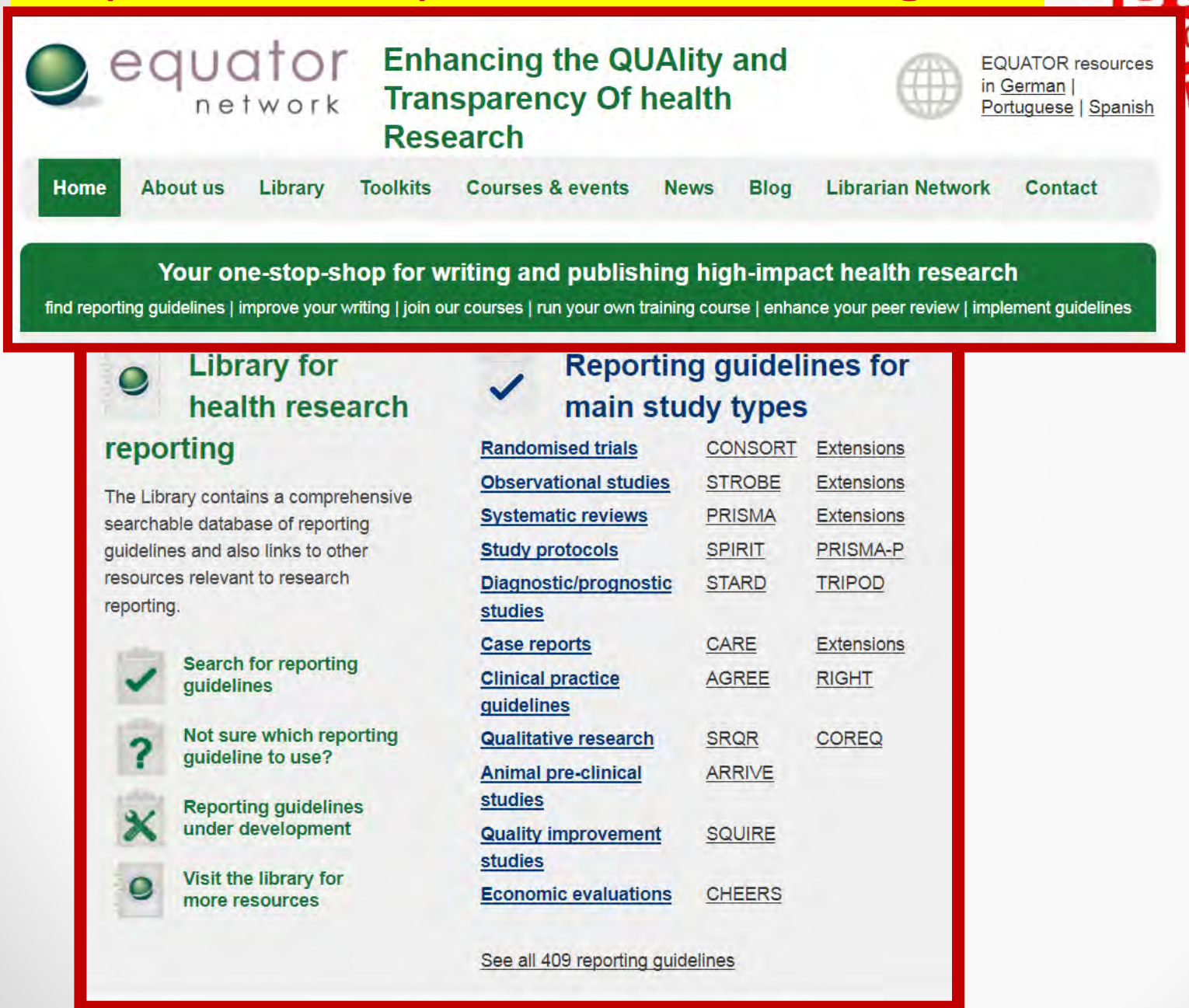
[2]Arizona State University

[3]University of Pittsburgh

Abstract

Objective—This paper presents an experimental design, the micro-randomized trial, developed to support optimization of just-in-time adaptive interventions (JITAIs). JITAIs are mHealth technologies that aim to deliver the right intervention components at the right times and locations to optimally support individuals' health behaviors. Micro-randomized trials offer a way to optimize such interventions by enabling modeling of causal effects and time-varying effect moderation for individual intervention components within a JITAI.

http://www.equator-network.org/



http://www.equator-network.org/

CONSORT Harms 2004; **CONSORT Non-inferiority**: JAMA. 2012; **CONSORT Cluster**: 2012; **CONSORT Herbal**: 2006; **CONSORT Non-pharmacological treatment interventions**: 2017; **CONSORT Abstracts**: 2008; 2008; **CONSORT Pragmatic Trials**: 2008; **STRICTA Controlled trials of acupuncture**: 2010; **CONSORT PRO**: 2013; **CONSORT-CENT**: 2015; **CONSORT for orthodontic trials**: 2015; **TIDieR**: 2014; **Simulation Research**: 2016; **CONSORT for pilot and feasibility trials**: 2016; **CONSORT-CHM formulas**: 2017: **CONSORT for within person randomised trials**: 2017; **CONSORT-SPI**: 2018 **Stepped wedge cluster randomised trials**: 2018;

Hatfield *et al. Trials* (2016) 17:150
DOI 10.1186/s13063-016-1273-9

Trials

REVIEW Open Access

Adaptive designs undertaken in clinical research: a review of registered clinical trials

Isabella Hatfield[1,2], Annabel Allison[2,3], Laura Flight[2], Steven A. Julious[2] and Munyaradzi Dimairo[2*]

Abstract

Adaptive designs have the potential to improve efficiency in the evaluation of new medical treatments in comparison to traditional fixed sample size designs. However, they are still not widely used in practice in clinical research. Little research has been conducted to investigate what adaptive designs are being undertaken. This review highlights the current state of registered adaptive designs and their characteristics. The review looked at phase II, II/III and III trials registered on ClinicalTrials.gov from 29 February 2000 to 1 June 2014, supplemented with trials from the National Institute for Health Research register and known adaptive trials. A range of adaptive design search terms were applied to the trials extracted from each database. Characteristics of the adaptive designs were then recorded including funder, therapeutic area and type of adaptation. The results in the paper suggest that the use of adaptive designs has increased. They seem to be most often used in phase II trials and in oncology. In phase III trials, the most popular form of adaptation is the group sequential design. The review failed to capture all trials with adaptive designs, which suggests that the reporting of adaptive designs, such as in clinical trials registers, needs much improving. We recommend that clinical trial registers should contain sections dedicated to the type and scope of the adaptation and that the term 'adaptive design' should be included in the trial title or at least in the brief summary or design sections.

Keywords: Adaptive design, Clinical trial, Flexible design

Dimairo et al. BMC Medicine (2018) 16:210
https://doi.org/10.1186/s12916-018-1196-2

BMC Medicine

GUIDELINE Open Access

Development process of a consensus-driven CONSORT extension for randomised trials using an adaptive design

Munyaradzi Dimairo[1*], Elizabeth Coates[1], Philip Pallmann[2], Susan Todd[3], Steven A. Julious[1], Thomas Jaki[4], James Wason[5,14], Adrian P. Mander[5], Christopher J. Weir[6], Franz Koenig[7], Marc K. Walton[8], Katie Biggs[1], Jon Nicholl[1], Toshimitsu Hamasaki[9], Michael A. Proschan[10], John A. Scott[11], Yuki Ando[12], Daniel Hind[1] and Douglas G. Altman[13^]

Abstract

Background: Adequate reporting of adaptive designs (ADs) maximises their potential benefits in the conduct of clinical trials. Transparent reporting can help address some obstacles and concerns relating to the use of ADs. Currently, there are deficiencies in the reporting of AD trials. To overcome this, we have developed a consensus-driven extension to the CONSORT statement for randomised trials using an AD. This paper describes the processes and methods used to develop this extension rather than detailed explanation of the guideline.

Methods: We developed the guideline in seven overlapping stages:

1) Building on prior research to inform the need for a guideline;
2) A scoping literature review to inform future stages;
3) Drafting the first checklist version involving an External Expert Panel;
4) A two-round Delphi process involving international, multidisciplinary, and cross-sector key stakeholders;
5) A consensus meeting to advise which reporting items to retain through voting, and to discuss the structure of what to include in the supporting explanation and elaboration (E&E) document;
6) Refining and finalising the checklist; and
7) Writing-up and dissemination of the E&E document.

The CONSORT Executive Group oversaw the entire development process.

http://www.sciencemag.org/news/2019/02/major-medical-journals-don-t-follow-their-own-rules-reporting-results-clinical-trials

Major medical journals don't follow their own rules for reporting results from clinical trials

By Jocelyn Kaiser | Feb. 15, 2019 , 4:45 PM

It's a well-known problem with clinical trials: Researchers start out saying they will look for a particular outcome—heart attacks, for example—but then report something else when they publish their results. That practice can make a drug or treatment look like it's safer or more effective than it actually is. Now, a systematic effort to find out whether major journals are complying with their own pledge to ensure that outcomes are reported correctly has found many are falling down on the job—and both journals and authors are full of excuses.

When journals and researchers were asked to correct studies, the responses "were fascinating, and alarming. Editors and researchers routinely misunderstand what correct trial reporting looks like," says project leader Ben Goldacre, an author and physician at the University of Oxford in the United Kingdom and a proponent of transparency in drug research.

Starting 4 years ago, his team's Centre for Evidence-Based Medicine Outcome Monitoring Project (**COMPare**) project examined all trials published over 6 weeks in five journals: *Annals of Internal Medicine*, *The BMJ*, *JAMA*, *The Lancet*, and *The New England Journal of Medicine* (*NEJM*). The study topics ranged from the health effects of drinking alcohol for diabetics to a comparison of two kidney cancer drugs. All five journals have endorsed long-established Consolidated Standards of Reporting Trials (CONSORT) guidelines. **One CONSORT rule** is that authors should describe the outcomes they plan to study before a trial starts and stick to that list when they publish the trial.

RESEARCH Open Access

COMPare: a prospective cohort study correct trials in

Ben Goldacre[1*]
Anna Powell-Sm

(Continued from previous page)

Conclusions: All five journals were listed as endorsing CONSORT, but all exhibited extensive breaches of this guidance, and most rejected correction letters documenting shortcomings. Readers are likely to be misled by this discrepancy. We discuss the advantages of prospective methodology research sharing all data openly and pro-actively in real time as feedback on critiqued studies. This is the first empirical study of major academic journals' willingness to publish a cohort of comparable and objective correction letters on misreported high-impact studies. Suggested improvements include changes to correspondence processes at journals, alternatives for indexed post-publication peer review, changes to CONSORT's mechanisms for enforcement, and novel strategies for research on methods and reporting.

Keywords: Outcomes, Misreporting, Trials, CONSORT, Audit, ICMJE, Editorial conduct

Abstract

Background: Discrepancies between pre-specified and reported outcomes are an important source of bias in trials. Despite legislation, guidelines and public commitments on correct reporting from journals, outcome misreporting continues to be prevalent. We aimed to document the extent of misreporting, establish whether it was possible to publish correction letters on all misreported trials as they were published, and monitor responses from editors and trialists to understand why outcome misreporting persists despite public commitments to address it.

Methods: We identified five high-impact journals endorsing Consolidated Standards of Reporting Trials (CONSORT) (*New England Journal of Medicine*, *The Lancet*, *Journal of the American Medical Association*, *British Medical Journal*, and *Annals of Internal Medicine*) and assessed all trials over a six-week period to identify every correctly and incorrectly reported outcome, comparing published reports against published protocols or registry entries, using CONSORT as the gold standard. A correction letter describing all discrepancies was submitted to the journal for all misreported trials, and detailed coding sheets were shared publicly. The proportion of letters published and delay to publication were assessed over 12 months of follow-up. Correspondence received from journals and authors was documented and themes were extracted.

Results: Sixty-seven trials were assessed in total. Outcome reporting was poor overall and there was wide variation between journals on pre-specified primary outcomes (mean 76% correctly reported, journal range 25–96%), secondary outcomes (mean 55%, range 31–72%), and number of undeclared additional outcomes per trial (mean 5.4, range 2.9–8.3). Fifty-eight trials had discrepancies requiring a correction letter (87%, journal range 67–100%). Twenty-three letters were published (40%) with extensive variation between journals (range 0–100%). Where letters were published, there were delays (median 99 days, range 0–257 days). Twenty-nine studies had a pre-trial protocol publicly available (43%, range 0–86%). Qualitative analysis demonstrated extensive misunderstandings among journal editors about correct outcome reporting and CONSORT. Some journals did not engage positively when provided correspondence that identified misreporting; we identified possible breaches of ethics and publishing guidelines.

(Continued on next page)

Table 1 Summary statistics on outcome reporting discrepancies

	Journal name	*Annals*	BMJ	JAMA	*Lancet*	NEJM	Total
Basic information	Number of trials included	5	3	13	24	22	67
	Journal listed as "endorsing CONSORT"	Yes	Yes	Yes	Yes	Yes	All
Protocol availability	Pre-trial protocol with pre-specified outcomes available?	0	0	7	3	19	29
	Percentage of pre-trial protocols available	0.0%	0.0%	53.9%	12.5%	86.4%	43.3%
Missing primary outcomes	Trials with any unreported primary outcomes	4	2	2	4	1	13
	Percentage of trials with any unreported primary outcomes	80.0%	66.7%	15.4%	16.7%	5.0%	19.4%
Primary outcomes	Total number of primary outcomes pre-specified	9	4	22	34	28	97
	Number of primary outcomes correctly reported as primary outcomes	4	1	18	24	27	74
	Percentage of primary outcomes correctly reported	44.4%	25.0%	81.8%	70.6%	96.4%	76.3%
	Number of primary outcomes reported anywhere	7	1	18	24	28	78
	Percentage of primary outcomes reported anywhere	77.8%	25.0%	81.8%	70.6%	100.0%	80.4%
Secondary outcomes	Total number of secondary outcomes pre-specified	49	36	111	218	404	818
	Number of secondary outcomes correctly reported as secondary outcomes	15	26	78	141	190	450
	Percentage of secondary outcomes correctly reported	30.6%	72.2%	70.3%	64.7%	47.0%	55.0%
	Number of secondary outcomes reported anywhere	15	26	78	142	190	451
	Percentage of secondary outcomes reported anywhere	30.6%	72.2%	70.2%	65.1%	47.0%	55.1%
Novel outcomes	Number of novel outcomes reported without declaration	32	25	53	192	63	365
	Mean number of novel outcomes reported without declaration, per trial	6.4	8.3	4.1	8	2.9	5.4 (95% CI 1.2–10.6)
	Percentage of novel outcomes declared as novel	5.9%	0%	39.1%	9.4%	3.1%	13.7% (95% CI 0.0–42.5%)

Abbreviations: *BMJ British Medical Journal*, *CI* confidence interval, *CONSORT* Consolidated Standards of Reporting Trials, *JAMA Journal of the American Medical Association*, *NEJM New England Journal of Medicine*

ORIGINAL ARTICLE

Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer

H.S. Rugo, O.I. Olopade, A. DeMichele, C. Yau, L.J. van 't Veer, M.B. Buxton, M. Hogarth, N.M. Hylton, M. Paoloni, J. Perlmutter, W.F. Symmans, D. Yee, A.J. Chien, A.M. Wallace, H.G. Kaplan, J.C. Boughey, T.C. Haddad, K.S. Albain, M.C. Liu, C. Isaacs, Q.J. Khan, J.E. Lang, R.K. Viscusi, L. Pusztai, S.L. Moulder, S.Y. Chui, K.A. Kemmer, A.D. Elias, K.K. Edmiston, D.M. Euhus, B.B. Haley, R. Nanda, D.W. Northfelt, D. Tripathy, W.C. Wood, C. Ewing, R. Schwab, J. Lyandres, S.E. Davis, G.L. Hirst, A. Sanil, D.A. Berry, and L.J. Esserman, for the I-SPY 2 Investigators*

ABSTRACT

BACKGROUND

The genetic and clinical heterogeneity of breast cancer makes the identification of effective therapies challenging. We designed I-SPY 2, a phase 2, multicenter, adaptively randomized trial to screen multiple experimental regimens in combination with standard neoadjuvant chemotherapy for breast cancer. The goal is to match experimental regimens with responding cancer subtypes. We report results for veliparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, combined with carboplatin.

METHODS

In this ongoing trial, women are eligible for participation if they have stage II or III breast cancer with a tumor 2.5 cm or larger in diameter; cancers are categorized into eight biomarker subtypes on the basis of status with regard to human epidermal growth factor receptor 2 (HER2), hormone receptors, and a 70-gene assay. Patients undergo adaptive randomization within each biomarker subtype to receive regimens that have better performance than the standard therapy. Regimens are evaluated within 10 biomarker signatures (i.e., prospectively defined combinations of bio-

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Esserman at the UCSF Carol Franc Buck Breast Care Center, University of California, San Francisco, 1600 Divisadero St., Box 1710, San Francisco, CA 94115, or at laura.esserman@ucsf.edu.

*A complete list of participating centers and investigators in the Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2 (I-SPY 2 TRIAL) is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2016;375:23-34.
DOI: 10.1056/NEJMoa1513749

ORIGINAL ARTICLE

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Carbo

H.S. Rugo, O
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A.J. Chien, A.M
M.C. Liu, C. Is
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RESULTS

With regard to triple-negative breast cancer, veliparib–carboplatin had an 88% predicted probability of success in a phase 3 trial. A total of 72 patients were randomly assigned to receive veliparib–carboplatin, and 44 patients were concurrently assigned to receive control therapy; at the completion of chemotherapy, the estimated rates of pathological complete response in the triple-negative population were 51% (95% Bayesian probability interval [PI], 36 to 66%) in the veliparib–carboplatin group versus 26% (95% PI, 9 to 43%) in the control group. The toxicity of veliparib–carboplatin was greater than that of the control.

CONCLUSIONS

The process used in our trial showed that veliparib–carboplatin added to standard therapy resulted in higher rates of pathological complete response than standard therapy alone specifically in triple-negative breast cancer. (Funded by the QuantumLeap Healthcare Collaborative and others; I-SPY 2 TRIAL ClinicalTrials.gov number, NCT01042379.)

Box 1710, San Francisco, CA 94115, or at laura.esserman@ucsf.edu.

*A complete list of participating centers and investigators in the Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2 (I-SPY 2 TRIAL) is provided in the Supplementary Appendix, available at NEJM.org.

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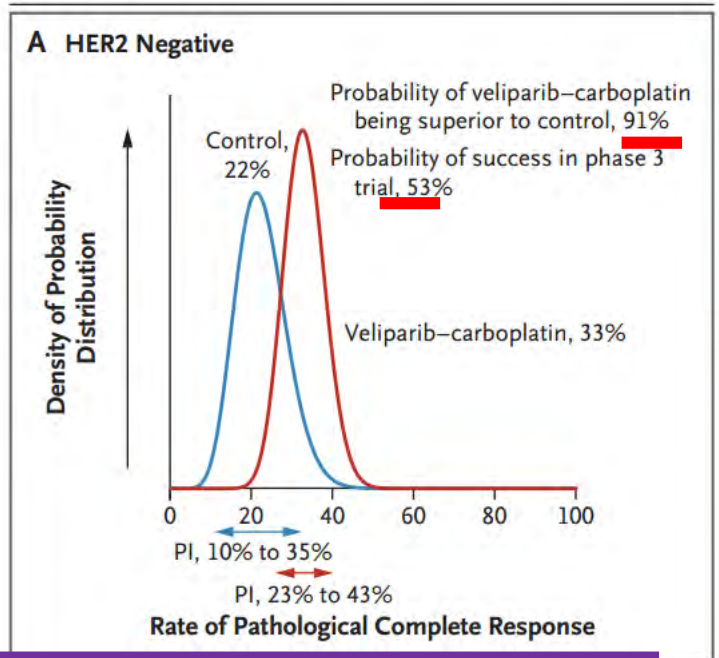
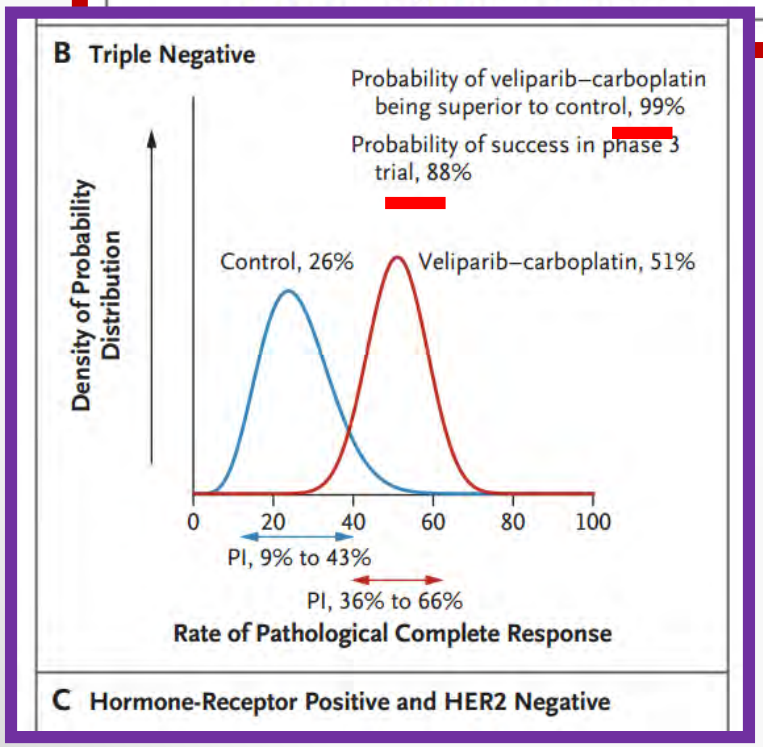
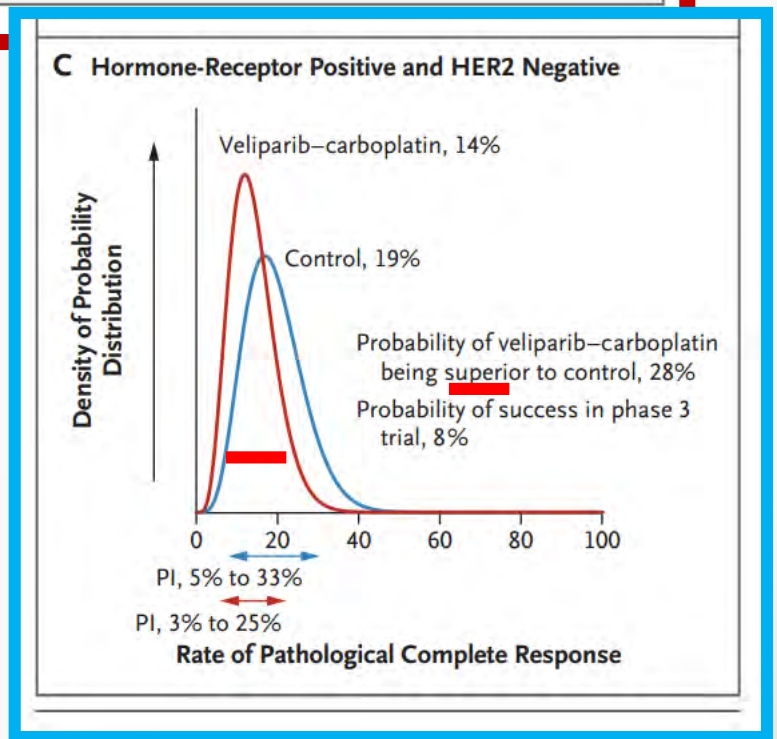


Figure 2. Estimated Rate of Pathological Complete Response with Veliparib–Carboplatin versus the Concurrent HER2-Negative Control.

Panel A shows the probability distribution for all patients with HER2-negative disease, Panel B the probability distribution for patients with hormone-receptor–negative and HER2-negative (triple-negative) disease, and Panel C the probability distribution for patients with hormone-receptor–positive and HER2-negative disease. The red curves represent patients treated with veliparib–carboplatin plus paclitaxel followed by doxorubicin–cyclophosphamide, and the blue curves represent concurrent controls. The corresponding 95% probability intervals (PIs) (represented by the arrows) are shown for each. The mean of each distribution is the estimated rate of pathological complete response.





Another goal of the trial is to specifically improve the drug-development process by predicting the potential success of a given regimen in a future phase 3 trial and by accurately assessing the patient population that has a response to the regimen. Predicting outcomes in a future trial that has a substantial chance of being successful establishes a high bar for continued development. Achieving significance in a phase 2 trial is not enough. The target sample size of 300 patients for a future confirmatory trial of neoadjuvant therapy is consistent with our goal of identifying sufficient signal in the current trial (i.e., a rate of pathological complete response approximately 20% higher than that with the control) such that a moderately sized phase 3 trial involving patients with cancer of the biomarker subtype of interest would be successful.

Non si riporta:

1)-La baseline del controllo su cui si aggiunge questo 20% (effect size)

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

3)-la potenza del test di significatività

4)-il tipo di test di significatività usato o dettagli sulla procedura Bayesiana

Another goal of the trial is to specifically improve the drug-development process by predicting the potential success of a given regimen in a future phase 3 trial and by accurately assessing the patient population that has a response to the regimen. Predicting outcomes in a future trial that has a substantial chance of being successful establishes a high bar for continued de-

Table 2. Final Predictive Probabilities.*

Biomarker Signature	Estimated Rate of Pathological Complete Response (95% PI)		Probability of Veliparib–Carboplatin Being Superior to Control	Predictive Probability of Success in Phase 3 Trial
	Veliparib–Carboplatin	Control		
			percent	
All HER2 negative	33 (23–43)	22 (10–35)	91	53
Hormone-receptor positive and HER2 negative	14 (3–25)	19 (5–33)	28	8
Triple negative	51 (36–66)	26 (9–43)	99	88

* HER2 denotes human epidermal growth factor receptor 2, and PI probability interval.

However, there is no requirement in I-SPY 2 for a future trial.

JAMA Network Open

JAMA Network Open.2018;1(8):e186076

December 21, 2018 1/12

Original Investigation | Critical Care Medicine

Effect of Levocarnitine vs Placebo as an Adjunctive Treatment for Septic Shock

The Rapid Administration of Carnitine in Sepsis (RACE) Randomized Clinical Trial

Alan E. Jones, MD; Michael A. Puskarich, MD, MS; Nathan I. Shapiro, MD, MPH; Faheem W. Guirgis, MD; Michael Runyon, MD, MPH; Jason Y. Adams, MD; Robert Sherwin, MD; Ryan Arnold, MD; Brian W. Roberts, MD, MSc; Michael C. Kurz, MD, MS; Henry E. Wang, MD, MS; Jeffrey A. Kline, MD; D. Mark Courtney, MD; Stephen Trzeciak, MD, MPH; Sarah A. Sterling, MD; Utsav Nandi, MD; Deepti Patki, MS; Kert Viele, PhD

Abstract

IMPORTANCE Sepsis induces profound metabolic derangements, while exogenous levocarnitine mitigates metabolic dysfunction by enhancing glucose and lactate oxidation and increasing fatty acid shuttling. Previous trials in sepsis suggest beneficial effects of levocarnitine on patient-centered outcomes.

OBJECTIVES To test the hypothesis that levocarnitine reduces cumulative organ failure in patients with septic shock at 48 hours and, if present, to estimate the probability that the most efficacious dose will decrease 28-day mortality in a pivotal phase 3 clinical trial.

DESIGN, SETTING, AND PARTICIPANTS Multicenter adaptive, randomized, blinded, dose-finding, phase 2 clinical trial (Rapid Administration of Carnitine in Sepsis [RACE]). The setting was 16 urban US medical centers. Participants were patients aged 18 years or older admitted from March 5, 2013, to February 5, 2018, with septic shock and moderate organ dysfunction.

INTERVENTIONS Within 24 hours of identification, patients were assigned to 1 of the following 4 treatments: low (6 g), medium (12 g), or high (18 g) doses of levocarnitine or an equivalent volume of saline placebo administered as a 12-hour infusion.

MAIN OUTCOMES AND MEASURES The primary outcome required, first, a greater than 90% posterior probability that the most promising levocarnitine dose decreases the Sequential Organ Failure Assessment (SOFA) score at 48 hours and, second (given having met the first condition), at least a 30% predictive probability of success in reducing 28-day mortality in a subsequent traditional superiority trial to test efficacy.

RESULTS Of the 250 enrolled participants (mean [SD] age, 61.7 [14.8] years; 56.8% male), 35, 34, and 106 patients were adaptively randomized to the low, medium, and high levocarnitine doses, respectively, while 75 patients were randomized to placebo. In the intent-to-treat analysis, the fitted mean (SD) changes in the SOFA score for the low, medium, and high levocarnitine groups were −1.27 (0.49), −1.66 (0.38), and −1.97 (0.32), respectively, vs −1.63 (0.35) in the placebo group. The posterior probability that the 18-g dose is superior to placebo was 0.78, which did not meet the a priori threshold of 0.90. Mortality at 28 days was 45.9% (34 of 74) in the placebo group compared with 43.3% (45 of 104) for the most promising levocarnitine dose (18 g). Similar findings were noted in the per-protocol analysis.

(continued)

Key Points

Question Do 1 or more doses of levocarnitine reduce organ failure in septic shock at 48 hours, and, if so, what is the likelihood of success in a phase 3 trial?

Findings In an adaptive randomized, blinded clinical trial of 250 adults, the most efficacious dose of levocarnitine (18 g) demonstrated a posterior probability of efficacy of 0.78, which did not reach the a priori threshold of 0.90.

Meaning Levocarnitine did not meaningfully reduce organ failure at 48 hours in patients with septic shock.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

JAMA Network Open

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Abstract (continued)

CONCLUSIONS AND RELEVANCE In this dose-finding, phase 2 adaptive randomized trial, the most efficacious dose of levocarnitine (18 g) did not meaningfully reduce cumulative organ failure at 48 hours.

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 24, 2018 VOL. 378 NO. 21

Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

A. Combes, D. Hajage, G. Capellier, A. Demoule, S. Lavoué, C. Guervilly, D. Da Silva, L. Zafrani, P. Tirot, B. Veber, E. Maury, B. Levy, Y. Cohen, C. Richard, P. Kalfon, L. Bouadma, H. Mehdaoui, G. Beduneau, G. Lebreton, L. Brochard, N.D. Ferguson, E. Fan, A.S. Slutsky, D. Brodie, and A. Mercat, for the EOLIA Trial Group, REVA, and ECMONet*

ABSTRACT

The NEW ENGLAND JOURNAL of MEDICINE

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A. Combes, D. H
E. Maury, B. Levy,
N.D. Ferguson,

RESULTS

At 60 days, 44 of 124 patients (35%) in the ECMO group and 57 of 125 (46%) in the control group had died (relative risk, 0.76; 95% confidence interval [CI], 0.55 to 1.04; P=0.09). Crossover to ECMO occurred a mean (±SD) of 6.5±9.7 days after randomization in 35 patients (28%) in the control group, with 20 of these patients (57%) dying. The frequency of complications did not differ significantly between groups, except that there were more bleeding events leading to transfusion in the ECMO group than in the control group (in 46% vs. 28% of patients; absolute risk difference, 18 percentage points; 95% CI, 6 to 30) as well as more cases of severe thrombocytopenia (in 27% vs. 16%; absolute risk difference, 11 percentage points; 95% CI, 0 to 21) and fewer cases of ischemic stroke (in no patients vs. 5%; absolute risk difference, −5 percentage points; 95% CI, −10 to −2).

CONCLUSIONS

Among patients with very severe ARDS, 60-day mortality was not significantly lower with ECMO than with a strategy of conventional mechanical ventilation that included ECMO as rescue therapy. (Funded by the Direction de la Recherche Clinique et du Développement and the French Ministry of Health; EOLIA ClinicalTrials.gov number, NCT01470703.)

Table 2. End Points.*

End Point	ECMO Group (N=124)	Control Group (N=125)	Relative Risk or Difference (95% CI)†	P Value
Primary end point: mortality at 60 days — no. (%)	44 (35)	57 (46)	0.76 (0.55 to 1.04)	0.09
Key secondary end point: treatment failure at 60 days — no. (%)‡	44 (35)	72 (58)	0.62 (0.47 to 0.82)	<0.001
Other end points				
Mortality at 90 days — no. (%)	46 (37)	59 (47)	−10 (−22 to 2)	
Median length of stay (interquartile range) — days				
In the ICU	23 (13–34)	18 (8–33)	5 (−1 to 10)	
In the hospital	36 (19–48)	18 (5–43)	18 (6 to 25)	
Median days free from mechanical ventilation (interquartile range)§	23 (0–40)	3 (0–36)	20 (−5 to 32)	
Median days free from vasopressor use (interquartile range)§	49 (0–56)	40 (0–53)	9 (0 to 51)	
Median days free from renal-replacement therapy (interquartile range)§	50 (0–60)	32 (0–57)	18 (0 to 51)	
Prone position — no. (%)¶	82 (66)	113 (90)	−24 (−34 to −14)	
Recruitment maneuvers — no. (%)¶	27 (22)	54 (43)	−21 (−32 to −10)	
Inhaled nitric oxide or prostacyclin — no. (%)¶	75 (60)	104 (83)	−23 (−33 to −12)	
Glucocorticoids — no. (%)¶	80 (65)	82 (66)	−1 (−13 to 11)	

* No missing data were observed for patients' outcomes, except for the total duration of hospital stay, for which data were missing for 13 patients in the ECMO group and 14 in the control group. ICU denotes intensive care unit.

† The relative risk for the primary end point with the 95% confidence interval and the P value were corrected for the triangular test. The width of confidence intervals for median differences and absolute risk differences was not adjusted for multiple comparisons and should not be used to infer definitive treatment differences. Difference values for the other end points are presented in percentage points for differences between rates or in days, as appropriate.

‡ The key secondary end point of treatment failure at 60 days was defined as death in patients in the ECMO group and as crossover to ECMO or death in patients in the control group.

§ The number of days free from a particular intervention were calculated with the use of the assignment of 0 days free from the intervention in patients who died during the follow-up period.

¶ Data included the period from randomization to day 60.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2018.06.001359

Bruno Mario Cesana. Biomed J Sci & Tech Res

BIOMEDICAL Journal of Scientific & Technical Research

Review Article Open Access

What p-value must be used as the Statistical Significance Threshold? P<0.005, P<0.01, P<0.05 or no value at all?

Bruno Mario Cesana*[1,2]

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Received: June 20, 2018; **Published:** July 06, 2018

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For example if we carry out a simple x^2 analysis of the 44/124 vs. 57/125 proportions of events in the ECMO and control group, respectively as the Table 1 of Combes et al. [64] shows, we obtain: Chi-Square = 2.6423 with p = 0.1041 and a Continuity Adjusted Chi-Square = 2.2393 with p = 0.1345, very different from the p = 0.09 reported. Finally, at the Fisher's exact test the two-tailed p is 0.1217. Of course, also the relative risk is different: 0.7782 95%CI: 0.5736 - 1.0556 instead of: 0.76 (0.55 to 1.04) shown in Table 1.

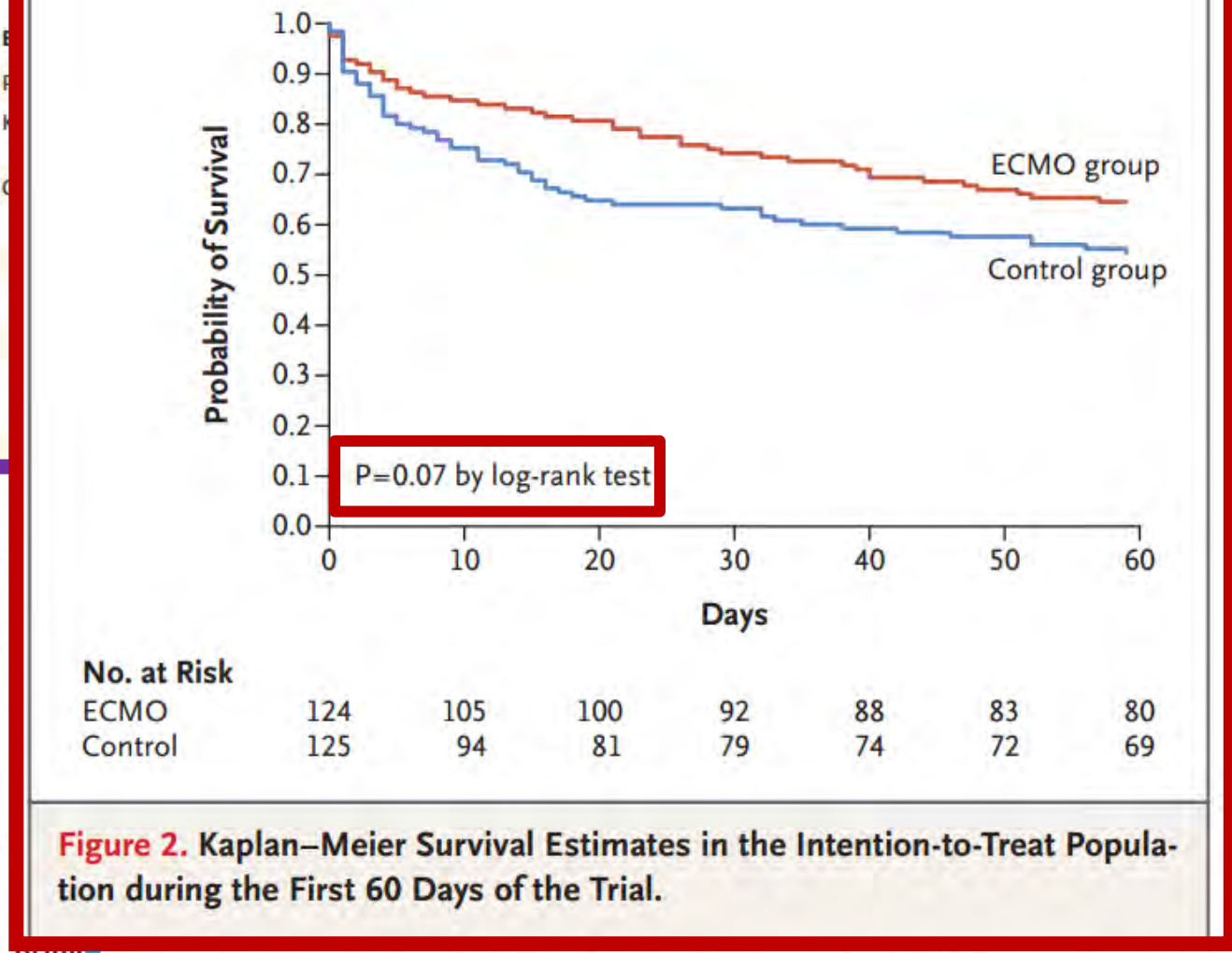

Figure 2. Kaplan–Meier Survival Estimates in the Intention-to-Treat Population during the First 60 Days of the Trial.

P Value
0.09
<0.001

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