Guidance for Industry

Adaptive Design Clinical Trials for Drugs and Biologics

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Adaptive Design Clinical Trials for Drugs and Biologics

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February 2010
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A)-Where there is the opportunity to choose a study result from among the results on many endpoints, study groups, or data time points, it is well recognized that bias is introduced because of the opportunity to choose the successful result from among the multiplicity of options.

In this circumstance an approach to controlling the Type I error rate should always be used.


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The adaptive design in clinical trials: regulatory and research aspects

2nd of February, 2007

11.45-12.30	*The adaptive design: state of the art and paths for future research* Speaker: Raphael Porcher Moderator: Ciro Gallo
12.30-13.00	Floor discussion
13.00-14.00	Break
14.00-14.45	*The adaptive design: issues in current research and implementation* Speaker: Peter Thomas Moderator: Maria Grazia Valsecchi
15.00-16.00	*Roundtable: issues in homogeneity and current evaluation of adaptive designs in clinical studies by the ethical committees* Discussants: Carlo Tomino, Antonella Bacchieri, Bruno Cesana Moderator: Francesco Grigoletto
16-16.15	Final remarks Francesco Grigoletto (SISMEC)

Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

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U.S. Department of Health and Human Services
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September 2018
Clinical/Medical

Clinical trial simulations often play a critical role in planning and designing clinical trials in general, and are particularly important for adaptive trials. Simulations can be used, for example, to select the number and timing of interim analyses, or to determine the appropriate critical value of a test statistic for declaring efficacy or futility. *Simulations can also be useful for comparing the performance of alternative designs.* Finally, a major use of simulations in adaptive trial design is to estimate trial operating characteristics[18] and to demonstrate that these operating characteristics meet desired levels.

18. Trial operating characteristics are properties of the trial with a given design. For example, properties of interest might include Type I error probability; power; expected, minimum, and maximum sample size; bias of treatment effect estimates; and coverage of confidence intervals (the probability the confidence interval would include the true treatment effect if the clinical trial were repeated many times).

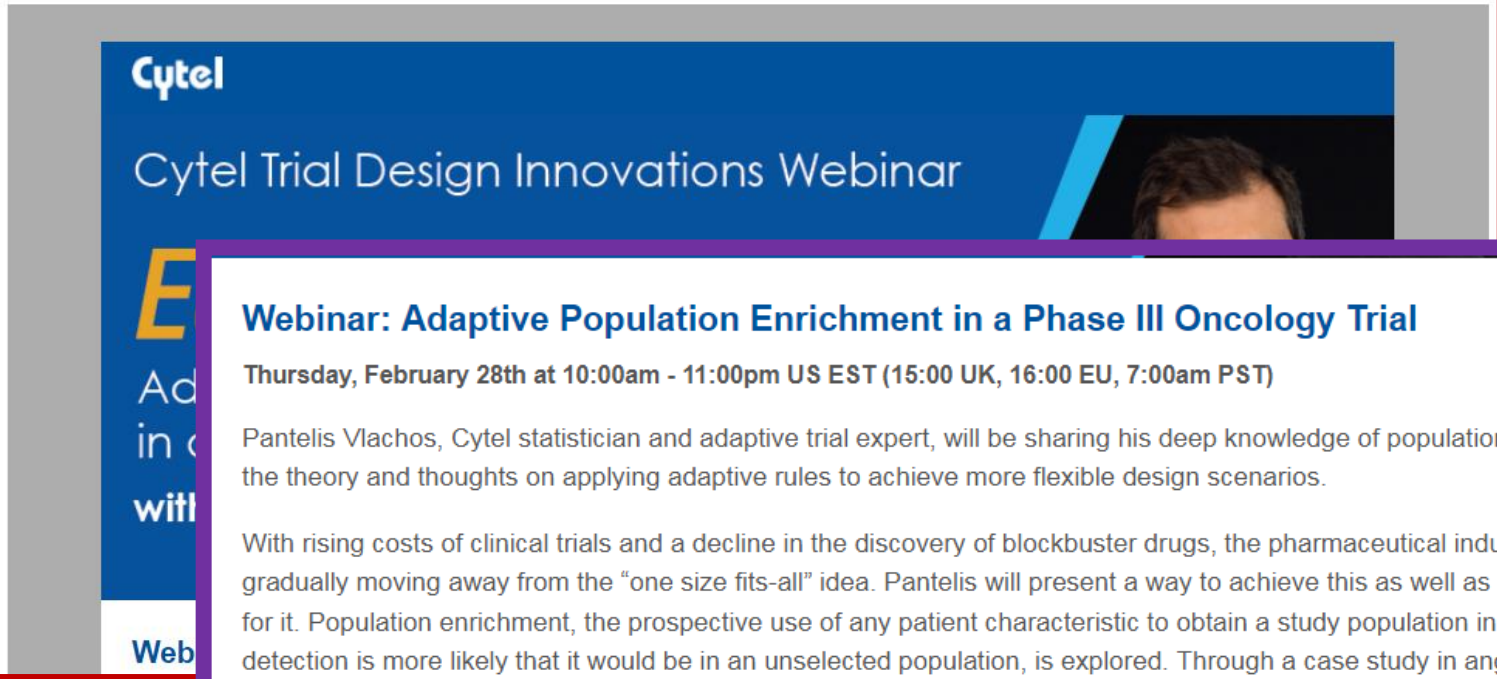
Webinar: Adaptive Population Enrichment in a Phase III Oncology Trial

Posta in arrivo ×

Sean Cronin <sean.cronin@cytel.com> Annulla iscrizione

a me

15 feb 2019, 16:39 (1 giorno fa)



Webinar: Adaptive Population Enrichment in a Phase III Oncology Trial

Thursday, February 28th at 10:00am - 11:00pm US EST (15:00 UK, 16:00 EU, 7:00am PST)

Pantelis Vlachos, Cytel statistician and adaptive trial expert, will be sharing his deep knowledge of population enrichment, the theory and thoughts on applying adaptive rules to achieve more flexible design scenarios.

With rising costs of clinical trials and a decline in the discovery of blockbuster drugs, the pharmaceutical industry is gradually moving away from the "one size fits-all" idea. Pantelis will present a way to achieve this as well as the software for it. Population enrichment, the prospective use of any patient characteristic to obtain a study population in which detection is more likely that it would be in an unselected population, is explored. Through a case study in angiosarcoma (AS) we present a practical design that ultimately leads to greater power, a shorter duration and a smaller sample size.

Register to join Pantelis and learn how the East 6.5 ENRICH module supports the simulation of clinical trial designs with adaptation options for population enrichment. The benefits include:

- Seamless phase 2/3 with Phase 2 objective to select the right patient population and Phase 3 to confirm the effect in the selected population
- Allows adaptation in sample size and patient population
- Mitigate risk of uncertainty around treatment effect and patient population
- Precision medicine to target the right treatment for the right patient population

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Adaptive Designs

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What is Adaptive Design?

To understand adaptive designs it may be easiest to look at a fixed trial design. Traditionally a fixed sample size is specified with fixed allocation and fixed entry criteria. The data is not analyzed until trial completion, which is typically years after the trial began. This 75-year-old design approach creates very restrictive design types – and really forces the design team to guess at the doses, range, patient population, duration and frequency of treatment, etc, because a fixed design requires linear effort spent for each treatment arm.

An adaptive design is like driving with your eyes open! It allows the pre-specification of flexible components to the major aspects of the trial, like the treatment arms used (dose, frequency, duration, combinations, etc), the allocation to the different treatment arms, the patient population used, and the sample size. An adaptive design can learn from the accruing data what the most therapeutic doses or arms are, allowing the design to hone in on the best arms. This allows the design to start with a wider range of doses – say 8 instead of 3 – with using a smaller number of patients. The result is a smart design, using resources (including time) much more efficiently, at the same time increasing the scientific precision. Well constructed adaptive designs can be better for all involved – better learning, more efficient,

NIH Webinar on Adaptive Trials

The one drawback is that adaptive designs are more work to construct. It involves clinical trial simulation to make sure the design works well, meets regulatory scrutiny and is efficient. Creating an adaptive design means getting all parties involved in the process – having statisticians work with clinicians, marketing, regulatory experts, execution teams, drug supply, etc, to construct a highly efficient design.

Adaptive Designs are not restricted to phase I, but rather all stages of development of drugs and devices. The following list of phases/stages is where we have constructed adaptive designs:

Phase I: Sample size, Dose escalation, Combination of arms, Seamless phase I-II.

Phase II/Pilot: Sample size, Dose allocation, Introduce/Drop arms, Histology investigation, Prediction of Phase III, Seamless Phase II-III.

Phase III/Confirmatory: Sample size, Multiple arms, Accrual Interim Analysis, Futility Analyses, Timing of Conclusions.

Phase IV: Sample size, Timing of Conclusions, Indications

Bruno M. Cesana

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- What is Adaptive Design?
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Bayesian ISBA Lecture

Bayesian Approach

Trial Design:

The Bayesian approach provides a mathematically rigorous and principled methodology for making decisions under arbitrarily complex scenarios. It provides a powerful framework for determining optimal behavior in the face of uncertainty. The Bayesian approach is ideal for many adaptive designs because it provides a naturally sequential learning framework, and allows the efficient and transparent integration of complex clinical trial and external data and natural prediction of future events (e.g., clinical trial results).

In contrast to traditional methods, the Bayesian approach itself is very flexible. It is naturally sequential, and can create updated distributions based on the information from a trial – and can be done continuously, without constraints that traditional methods pose. Essentially doing complex adaptive trials from a traditional approach is impossible – whereas from a Bayesian perspective is quite natural and straightforward.

The flexibility of modeling is also a huge advantage in flexible designs. Bayesian methods provide a flexible, coherent, and transparent method for the creation and evaluation of disparate information. The approach has computational advantages, the ability to model early predictors and biomarkers, the ability to incorporate prediction in

ated populations in to combined

strength of the Bayesian approach
reliability of evidence for
egree of evidence integration or
epends on the consistency of
methodology that allows firm
voids such conclusions, capturing

Modeling and Meta-Analysis:

In addition to the advantages of using the Bayesian approach in trial design, a key strength of the Bayesian approach is hierarchical modeling. The approach is critical for evaluating the sufficiency and reliability of evidence for supporting a treatment guideline or a payers reimbursement decision—is that the degree of evidence integration or borrowing across multiple information sources is not defined *a priori* but, instead, depends on the consistency of evidence across the information sources. This provides a quantitative and rigorous methodology that allows firm conclusions to be drawn when the evidence is concordant and, just as important, avoids such conclusions, capturing the increased uncertainty when the heterogeneity in the information is large.

Bayesian methods allow for a formal synthesis of information from clinical trials that ask the same or related questions and are uniquely suited to comparative effectiveness research. There are three important aspects to the modeling. The first is the ability to model study-to-study heterogeneity, the second is the ability to handle indirect treatment comparisons, also called mixed treatment comparisons, and the third is the ability to model nested treatments and combinations of treatments.

Differences between trials include varying study designs, eligibility criteria, patient populations, treatment regimens, and outcome measures. Bayesian hierarchical models view the trials included in the meta-analysis as sampled from a larger population of trials. A Bayesian hierarchical model is a random effects model that explicitly accounts for trial heterogeneity and allows for "borrowing of strength" across the trials. If results of trials are similar, there will be greater borrowing of information and this will increase the precision of the estimates. If trial results differ substantially, then there will be less borrowing and appropriately increased uncertainty regarding the conclusions of the meta-analysis. The amount of borrowing across trials is not specified in advance, but is determined by the heterogeneity of the available data.

STATISTICS IN MEDICINE
Statist. Med. 2009; **28**:1181–1217
Published online 10 February 2009 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/sim.3538

"Inferentially seamless",
vs. "operationally seamless"

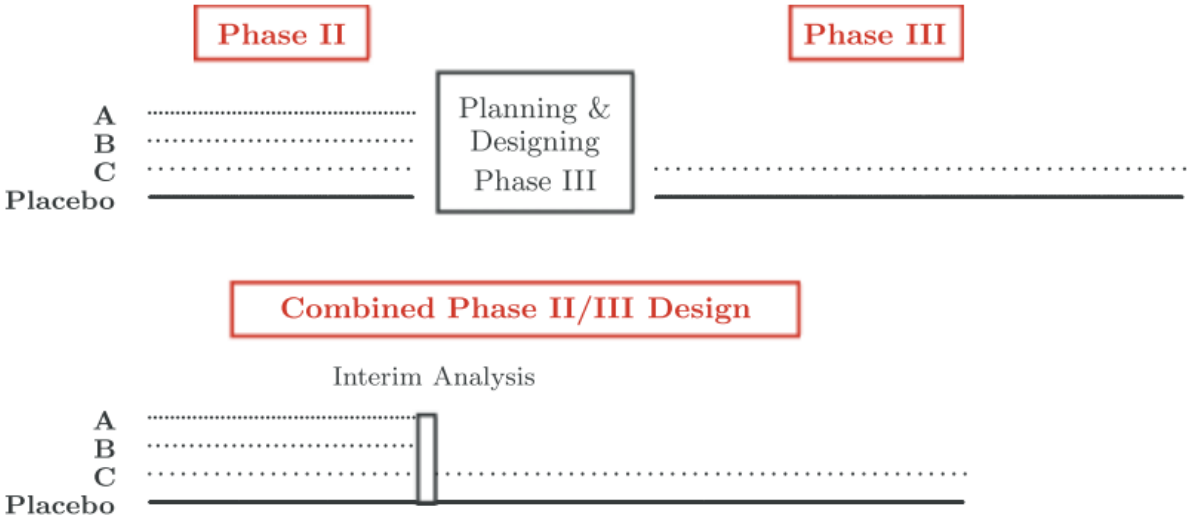

Figure 1. Top: classical development with two sperate studies. Bottom: combined phase II/III design with treatment selection at interim.

dose groups is 6 points of the HAM-A scale. The sample size of the study should ensure that the power for the individual pairwise comparisons is at least $1-\beta=0.8$, assuming a clinically relevant benefit of 2 points over placebo and an overall significance level of $\alpha=0.025$ (assuming one-sided null hypotheses).

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TUTORIAL IN BIOSTATISTICS

Adaptive designs for confirmatory clinical trials

Frank Bretz[1,2,‡], Franz Koenig[3,*,†,‡], Werner Brannath[3], Ekkehard Glimm[1] and Martin Posch[3]

[1]*Novartis Pharma AG, Lichtstrasse 35, 4002 Basel, Switzerland*
[2]*Department of Biometry, Medical University of Hannover, 30623 Hannover, Germany*
[3]*Section of Medical Statistics, Medical University of Vienna, Spitalgasse 23, 1090 Wien, Austria*

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2. A CASE STUDY

This case study refers to the late development phase of a drug for the indication of generalized anxiety disorder. The primary objective is (i) to select the most promising dose levels out of three different dose levels under investigation and (ii) to demonstrate subsequently that the selected dose levels lead to a statistically significant and clinically relevant efficacy as compared with placebo. The primary endpoint of this study is the change from baseline at week 8 of treatment in the total score on the Hamilton Rating Scale for Anxiety (HAM-A, [31]). This psychiatric scale was developed to quantify the anxiety symptomatology. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (severe). It is reasonable to assume that the total HAM-A score is normally distributed. Furthermore, it is assumed based on the outcome of previous studies that the common standard deviation across the dose groups is 6 points of the HAM-A scale. The sample size of the study should ensure that the power for the individual pairwise comparisons is at least $1-\beta=0.8$, assuming a clinically relevant benefit of 2 points over placebo and an overall significance level of $\alpha=0.025$ (assuming one-sided null hypotheses).

[3]*Section of Medical Statistics, Medical University of Vienna, Spitalgasse 23, 1090 Wien, Austria*

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3.1. *Conditional invariance principle*

Adaptive designs follow a common principle called *conditional invariance principle* [5]. Assume a trial with two sequential stages, where design characteristics of the second stage are chosen based on the data from the first stage as well as external information. We consider here the behavior of the trial under a specific elementary null hypothesis H. Let T_2 denote the test statistic for H applied to the second stage data. Due to the data-driven choice of the design characteristics, T_2 will in general depend on the interim data. However, we often can transform T_2 in such a way that the *conditional* null distribution of T_2 given the interim data and the second stage design equals a fixed pre-specified null distribution, and hence is *invariant* with respect to the interim data and mid-trial design adaptations. An invariant conditional distribution is typically achieved by transforming T_2 to a p-value p_2, which is uniformly distributed under H (conditionally on the interim data and the second stage design). Usually, the invariance of the conditional null distribution of p_2 implies that p_2 is stochastically independent of the first stage data. Since the joint distribution of the interim data and p_2 is known and invariant with respect to the unknown mid-trial adaptation rule, we can specify an α-level rejection region in terms of the interim data and p_2. This gives a test that controls the overall type I error rate at level α independently of the interim adaptation. The current most rigorous discussion of this can be found in [33].

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Table I. Summary statistics from the first stage of an adaptive design with dose selection at interim.

i	$\bar{X}_{1,i}$	z-Statistic	$p_{1,i}$
0	0	—	—
1	0.8	0.794	0.2135
2	1.5	1.490	0.0682
3	2.6	2.582	0.0049

O'Brien-Fleming: α_1 =0.0054, α_0 = 0.1

The Bonferroni adjusted *p*-value for the global null hypothesis *H*{1,2,3} at the first stage is *p*1,{1,2,3}=3 min(*p*1,1, *p*1,2, *p*1,3) = 3×0.0049 = 0.0147.

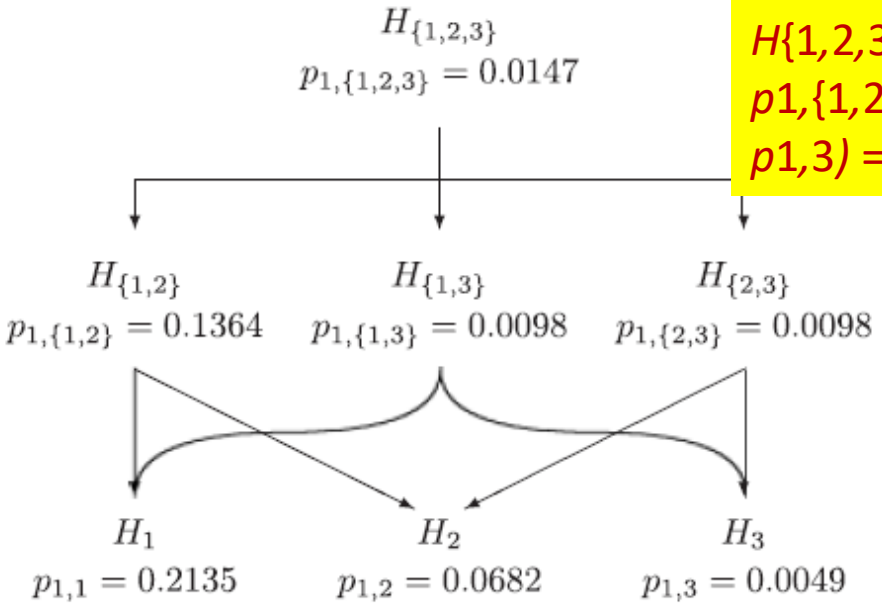

Figure 2. Closed test procedure for the first stage data. Bonferroni adjusted p-values are reported for each intersection hypothesis.

5. A SIMULATION STUDY

In this section, we report the results of an extensive simulation to illustrate some of the methods described previously, motivated by the case study introduced in Section 2 and covering a wide range of practical scenarios. In Section 5.1, we describe the design of this simulation study, including its assumptions and scenarios as well as the performance metrics used to evaluate different statistical operational characteristics of the various methods. The results of the simulation study are summarized in Section 5.2. Because of the large number of scenarios and performance metrics, only a subset of the possible plots is included here to illustrate the key findings. We conclude the simulation study with a few remarks in Section 5.3.

5.1. Design of simulation study

Motivated by the case study from Section 2, consider the comparison of $k=2$ and 3 treatments with a control in the homoscedastic normal model with known common variance σ^2. Let n denote the pre-specified total group sample size. For simplicity we choose n such that the individual treatment-control comparisons have a power of $1-\beta=0.80$ for a one-sided z-test with $\alpha=0.025$. That is, we calculate $n=2(z_{1-\alpha}+z_{1-\beta})^2\sigma^2/\tilde{\theta}^2$, where z_c denotes the c-quantile of the standard normal distribution and $\tilde{\theta}$ is the treatment effect to be detected. For the simulation study we assume $\sigma=6$ and $\tilde{\theta}=2$, resulting in a total sample size of $n=142$ per treatment group. We further assume a two-stage design with one interim analysis. No early efficacy testing in the interim analysis is foreseen. We do, however, investigate the impact of non-binding early futility stopping on power. The subsequent results are obtained by simulating 100 000 trials for each scenario using SAS/IML.

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5. A SIMULATION STUDY

we compute:
(i) the probability to reject correctly at least one of the hypotheses under investigation at the final analysis (disjunctive power) and
(ii) the probability to reject correctly a specific elementary null hypothesis (individual power)

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5.1. *Design of simulation study*

We consider the following decision rules to be adopted in the interim analysis:
(I) Continue with all treatments in the second stage.
(II) Select the best treatment based on the observed first stage mean values.
(III) Select the best treatment only if the mean difference to control is above a threshold.
(IV) Select all treatments where the mean difference to control is above .

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5. A SIMULATION STUDY

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(i)

(ii)

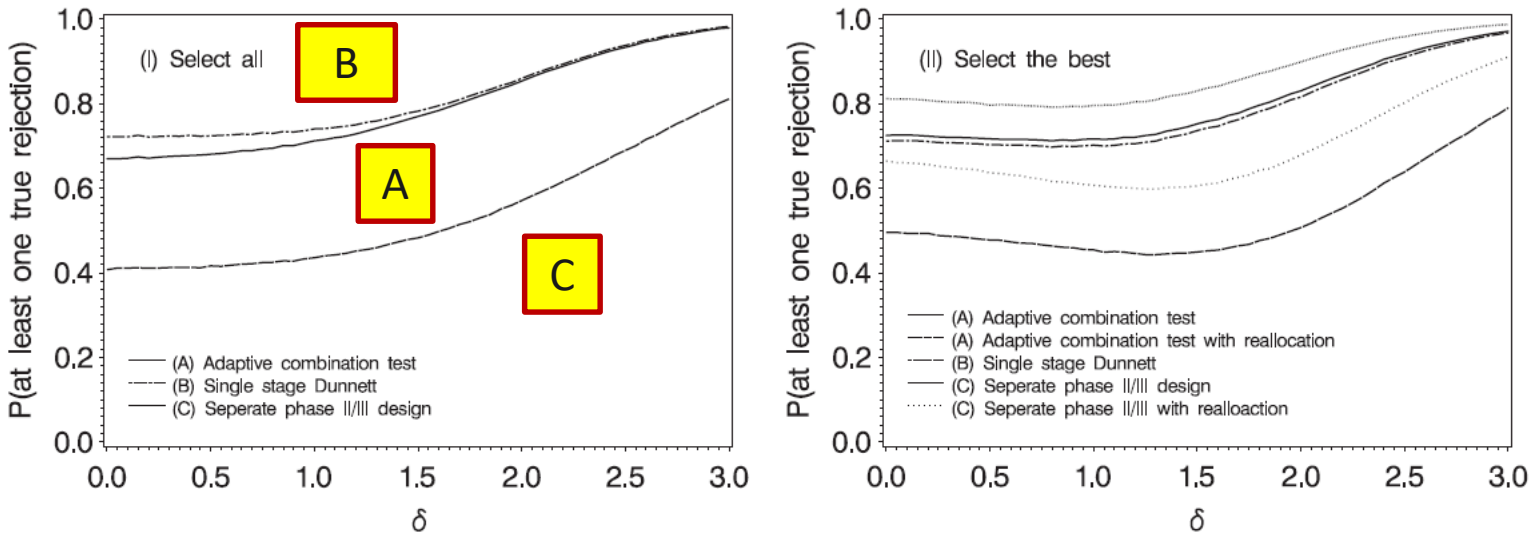

Figure 3. Disjunctive power for comparing $k=2$ treatments with a control using the information fractions $n_1/n=\frac{1}{3}$ (first row) and $n_1/n=\frac{1}{2}$ (second row). The power is the probability to reject correctly at least one of the false null hypotheses at the final analysis for the efficacy profile $(\theta_0,\theta_1,\theta_2)=(0,\delta,2)$ where $\delta\in[0,3]$ is plotted on the abscissa. Left column—decision rule (I): Continue with all treatments in the second stage. Right column—decision rule (II): select the treatment with the larger observed first stage mean value.

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Key design considerations for adaptive clinical trials: a primer for clinicians

Kristian Thorlund,[1,2] Jonas Haggstrom,[2] Jay JH Park,[1] Edward J Mills[1,2]

[1]Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Ontario, Canada

[2]The Bill and Melinda Gates Foundation, Seattle, Washington, USA

Correspondence to: EJ Mills millsej@mcmaster.ca

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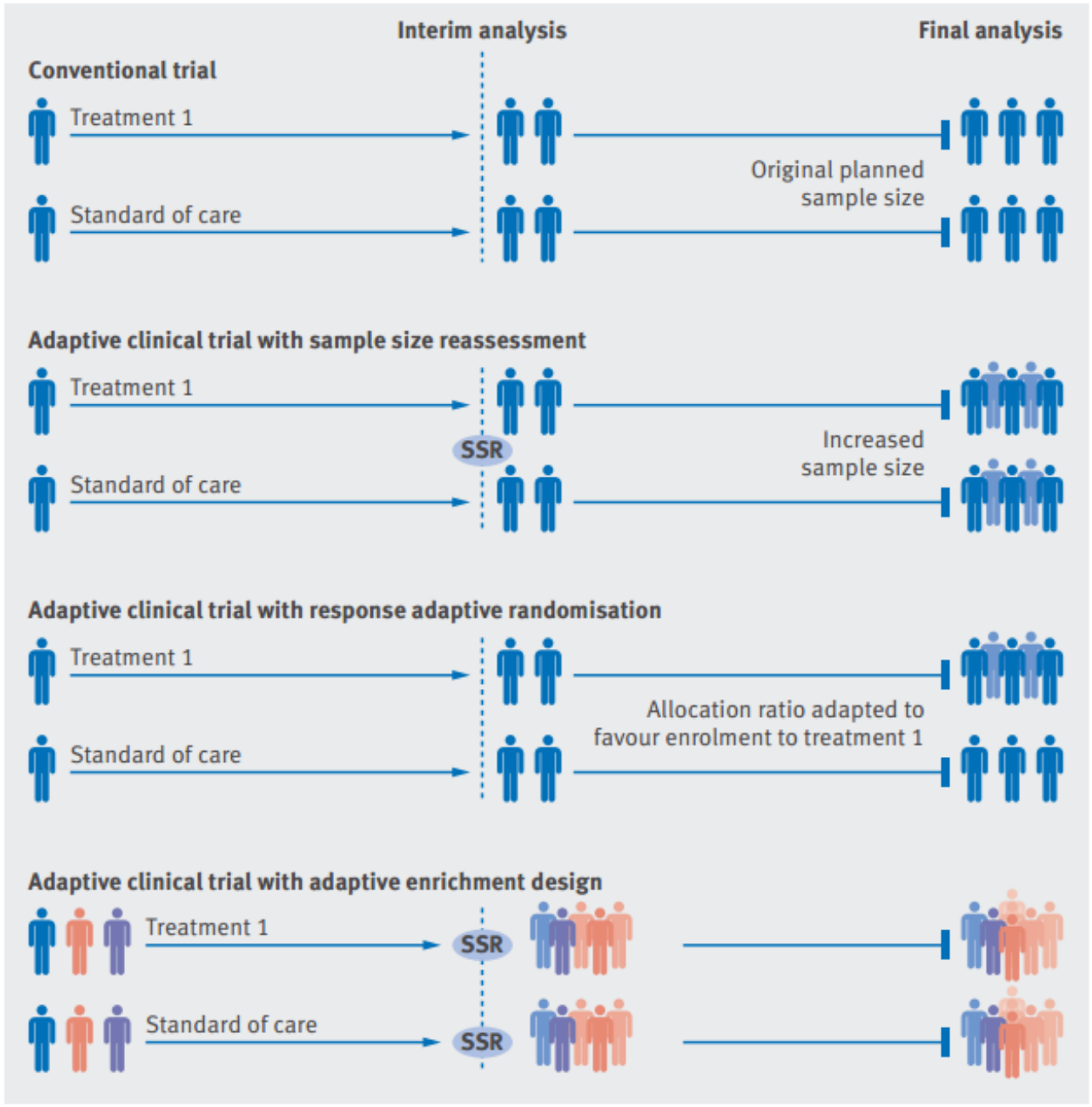
This article reviews important considerations for researchers who are designing adaptive clinical trials. These differ from conventional clinical trials because they allow and even enforce continual modifications to key components of trial design while data are being collected. This innovative approach has the potential to reduce resource use, decrease time to trial completion, limit allocation of participants to inferior interventions, and improve the likelihood that trial results will be scientifically or clinically relevant. Adaptive designs have mostly decision rules that have been rigorously examined via statistical simulations before the first trial participant is enrolled. The authors review important characteristics of adaptive trials and common types of study modifications and provide a practical guide, illustrated with a case study, to aid investigators who are planning an adaptive clinical trial

Adaptive clinical trials can be completed sooner than trials with conventional (non-adaptive) designs. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recently released guidance on adaptive designs for licensing.[1 2]



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REVIEW

Critical concepts in adaptive clinical trials

Clinical Epidemiology 2018:10 343–351

This article was published in the following Dove Press journal:
Clinical Epidemiology

Jay JH Park[1]
Kristian Thorlund[2,3]
Edward J Mills[2,3]

[1]Department of Medicine, University of British Columbia, Vancouver, BC, Canada; [2]Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Hamilton, ON, Canada; [3]The Bill and Melinda Gates Foundation, Seattle, WA, USA

Abstract: Adaptive clinical trials are an innovative trial design aimed at reducing resources, decreasing time to completion and number of patients exposed to inferior interventions, and improving the likelihood of detecting treatment effects. The last decade has seen an increasing use of adaptive designs, particularly in drug development. They frequently differ importantly from conventional clinical trials as they allow modifications to key trial design components during the trial, as data is being collected, using preplanned decision rules. Adaptive designs have increased likelihood of complexity and also potential bias, so it is important to understand the common types of adaptive designs. Many clinicians and investigators may be unfamiliar with the design considerations for adaptive designs. Given their complexities, adaptive trials require an understanding of design features and sources of bias. Herein, we introduce some common adaptive design elements and biases and specifically address response adaptive randomization, sample size reassessment, Bayesian methods for adaptive trials, seamless trials, and adaptive enrichment using real examples.

Keywords: adaptive designs, response adaptive randomization, sample size reassessment, Bayesian adaptive trials, seamless trials, adaptive enrichment

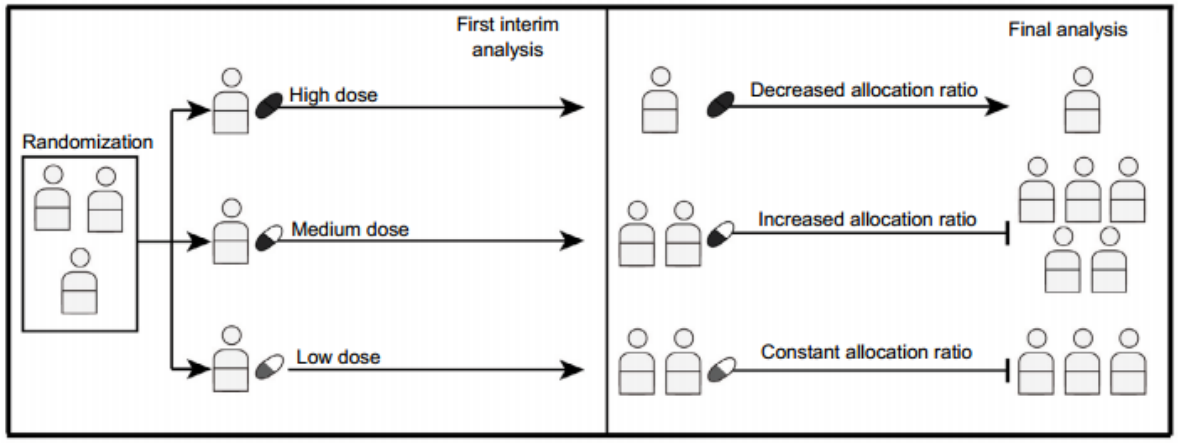

Figure 1 Response adaptive randomization.
Notes: The first interim analysis shows serious toxicity for the high-dose arm and promising results for the medium dose. The RAR design allows the allocation ratio to be changed to zero for the high-dose arm after the first interim analysis, so that patients will no longer be enrolled to this treatment. The allocation ratio for the medium dose, on the other hand, can be increased allowing more patients to be enrolled to this arm. Then, the trial stops after the medium dose demonstrates superiority over the low-dose arm. This example shows how an RAR design can potentially allow for a larger number of patients to be allocated to the superior treatment.
Abbreviation: RAR, response adaptive randomization.

Kristian Thorlund[2,3]
Edward J Mills[2,3]

[1]Department of Medicine, University of British Columbia, Vancouver, BC, Canada; [2]Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Hamilton, ON, Canada; [3]The Bill and Melinda Gates Foundation, Seattle, WA, USA

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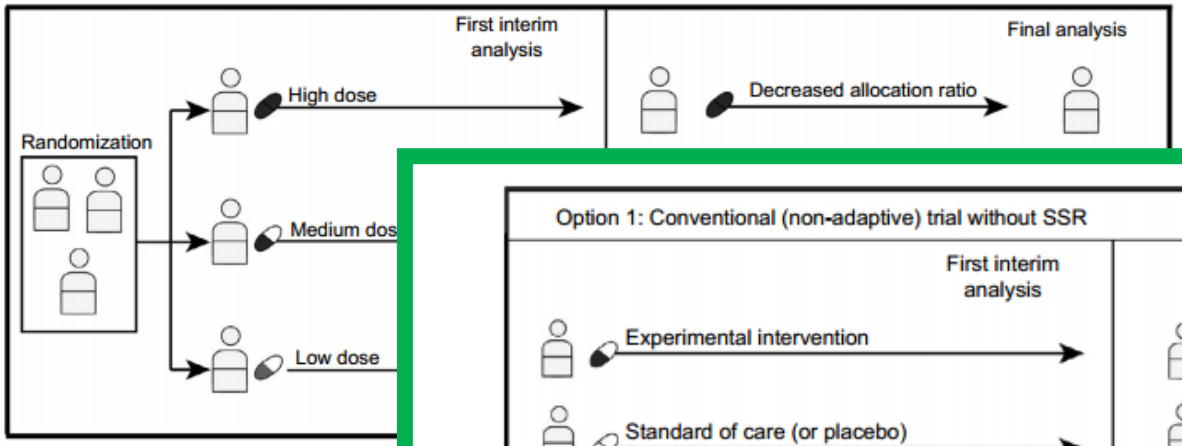
Keywords: adaptive designs, response adaptive randomization, sample size reassessment, Bayesian adaptive trials, seamless trials, adaptive enrichment



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changed to zero for the high-dose arm after the first interi
on the other hand, can be increased allowing more patient
dose arm. This example shows how an RAR design can po
Abbreviation: RAR, response adaptive randomization.

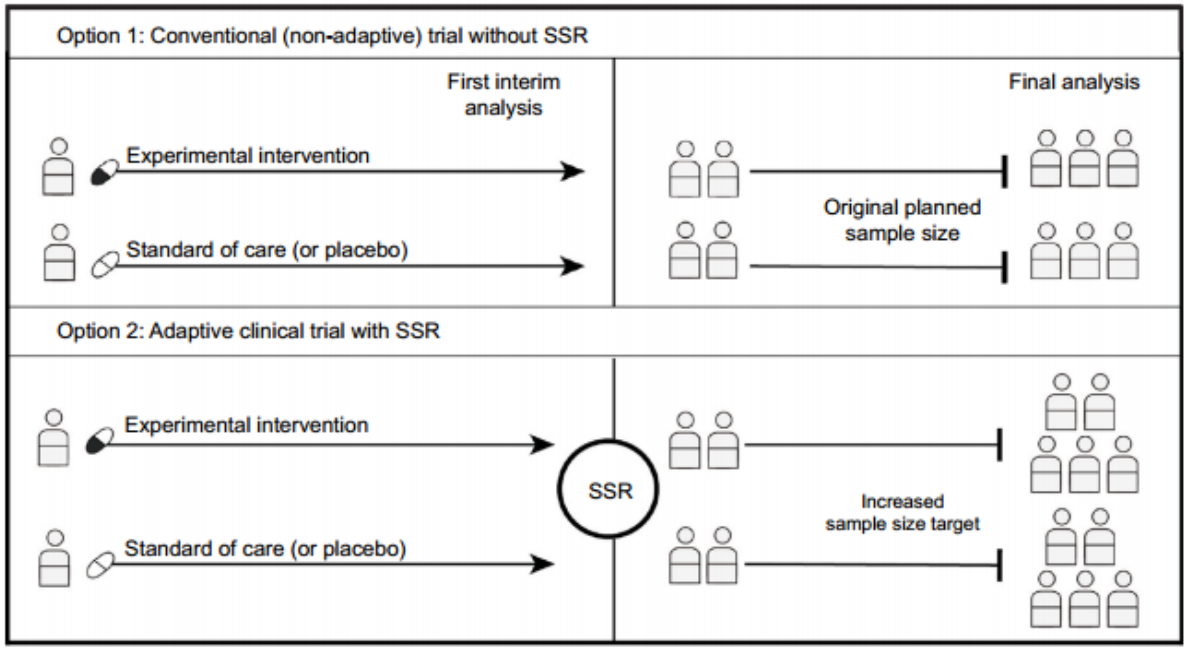


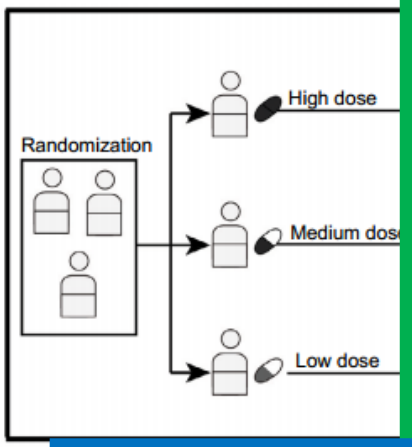
Figure 2 Sample size reassessment.
Notes: If the first interim analysis shows worse results than expected, an SSR can be performed using the interim results. SSR is not permitted in a traditional nonadaptive trial, so even when the original planned sample size is reached, the trial may be underpowered (Option 1). If SSR is permitted, the enrolment target could be increased to ensure that the trial is adequately powered (Option 2).
Abbreviation: SSR, sample size reassessment.

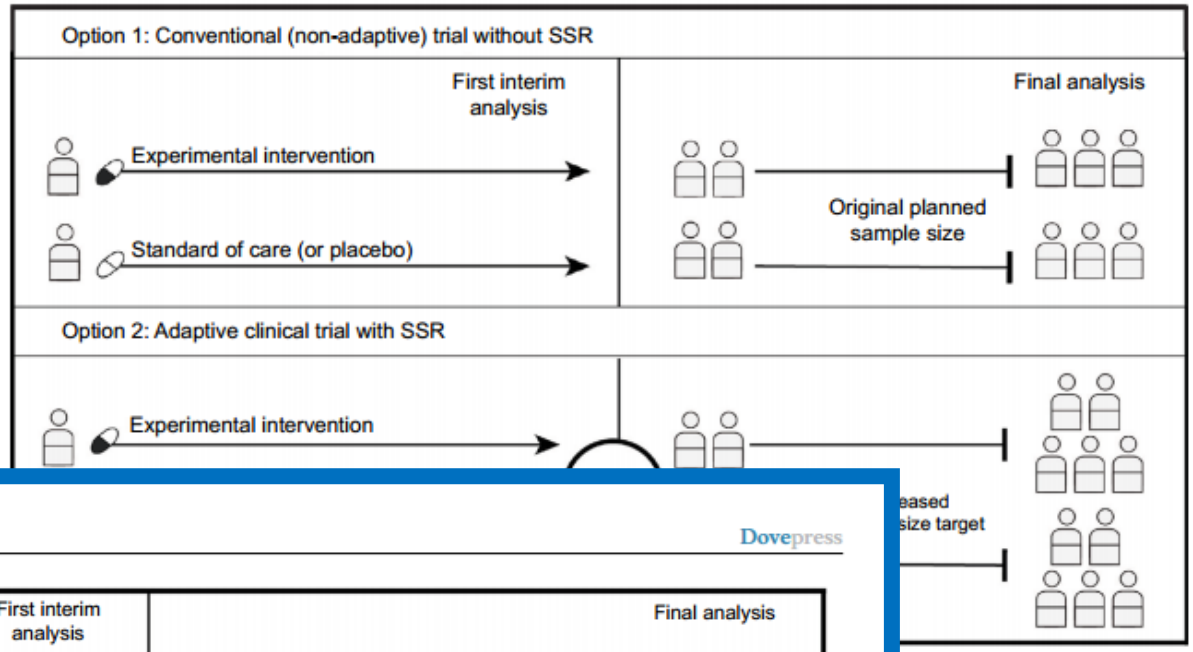
Jay JH Park[1]
Kristian Thorlund[2,3]
Edward J Mills[2,3]

[1]Department of Medicine, Univ
of British Columbia, Vancouver,
Canada; [2]Department of Health
Research Methods, Evidence, a
Impact (HEI), McMaster Univer
Hamilton, ON, Canada; [3]The Bi
Melinda Gates Foundation, Seattle,
WA, USA

the design considerations for adaptive designs. Given their complexities, adaptive trials require an understanding of design features and sources of bias. Herein, we introduce some common adaptive design elements and biases and specifically address response adaptive randomization, sample size reassessment, Bayesian methods for adaptive trials, seamless trials, and adaptive enrichment using real examples.

Keywords: adaptive designs, response adaptive randomization, sample size reassessment, Bayesian adaptive trials, seamless trials, adaptive enrichment





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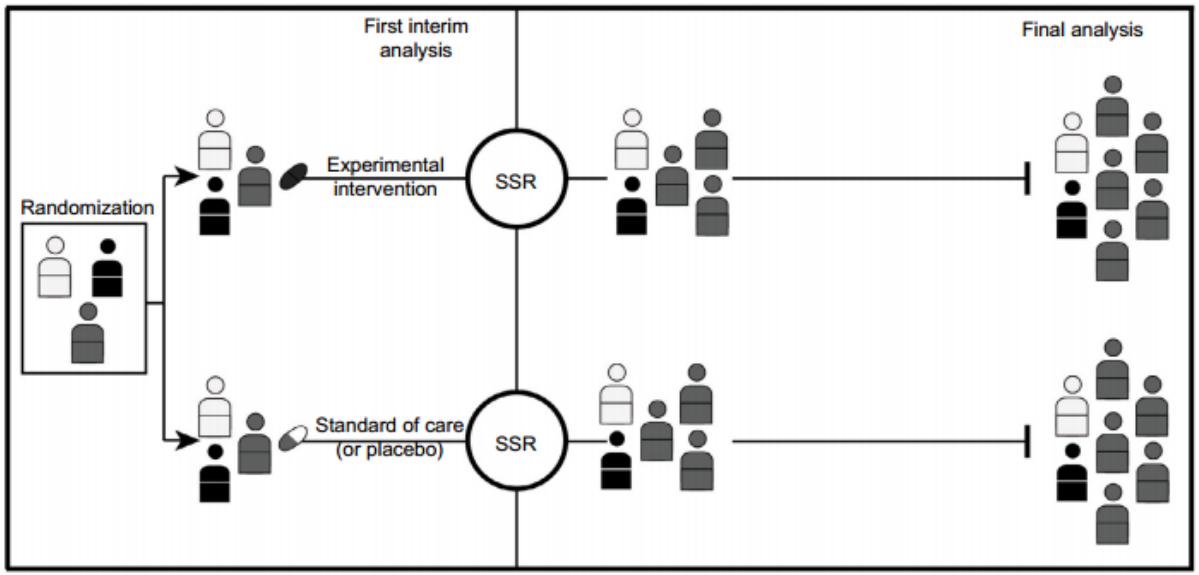

Figure 4 Trial with adaptive enrichment design with SSR.
Notes: In this example, the first interim analysis shows the experimental intervention has more promising results on one subgroup of patients (illustrated in gray), but it is not shown to be effective for other patients. The study eligibility criteria could then be modified to investigate the efficacy of the intervention in the gray subgroup (i.e., an adaptive enrichment design) with an SSR ensuring a sufficient sample size for this subgroup.
Abbreviation: SSR, sample size reassessment.

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Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls

Statist. Med.2016,35 325–347

Peter Bauer,[a] Frank Bretz,[b,c] Vladimir Dragalin,[d] Franz König[a] and Gernot Wassmer[e,f*†]

1. Introduction

2. A brief history of the early days

3. Statistical methodology and new developments

4. Regulatory and industry perspectives

5. Applications

6. Software

7. Summary and discussion

'Multistage testing with adaptive designs' was the ter Bauer that appeared 1989 in the German journal *Biometrie und Informatik in Medizin und Biologie*. The journal does not exist anymore but the methodology found widespread interest in the scientific community over the past 25 years. The use of such multistage adaptive des the publication by Bauer and K h designs faced critical positions regarding their statistical efficiency. Despite, or possibly because of, this controversy, the methodology and its statistics working in ac aptive designs have become the subject of two major regulatory guidance documents in the US and Europe and the field is still evolving aptive designs, including sa signs. In this article, we summarize the developments over the past 25 years from different perspectives. We provide a historical overview of the early days, review the key methodological concepts and summarize regulatory and industry perspect n, we illustrate the application of adaptive designs with three case studies, including unb ssment, adaptive treatment selection, and adaptive endpoint selection. We also discuss the availability of software for evaluating and performing such designs. We conclude with a critical review of how expectations from the beginning were t – discuss potential reasons why this did not happen. © 2015 The Authors. *Statistics in Medic* ublished by John Wiley & Sons Ltd.

Keywords: adaptive design; clinical trials; group sequential desi

VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

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Scott M. Berry, PhD
Berry Consultants LLC, Austin, Texas; and Department of Biostatistics, University of Kansas Medical Center, Kansas City.

Jason T. Connor, PhD
Berry Consultants LLC, Austin, Texas; and University of Central Florida College of Medicine, Orlando.

Roger J. Lewis, MD, PhD
Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, California; and Berry Consultants LLC,

The drug development enterprise is struggling. The development of new therapies is limited by high costs, slow progress, and a high failure rate, even in the late stages of development. Clinical trials are most commonly based on a "one population, one drug, one disease" strategy, in which the clinical trial infrastructure is created to test a single treatment in a homogeneous population.

This approach has been largely unsuccessful for multiple diseases, including sepsis, dementia, and stroke. Despite promising preclinical and early human trials, there have been numerous negative phase 3 trials of treatments for Alzheimer disease[1] and more than 40 negative phase 3 trials of neuroprotectants for stroke.[2] Effective treatments for such diseases will likely require combining treatments to affect multiple targets in complex cellular pathways and, perhaps, tailoring treatments to subgroups defined by genetic, proteomic, metabolomic, or other markers.[3]

There has been increasing interest in efficient trial

benefits when evaluating potentially synergistic combination treatments (eg, treatment A, treatment B, treatment C, and all combinations) if the starting point is the testing of each treatment in isolation.

What Is a Platform Trial?

A platform trial is defined by the broad goal of finding the best treatment for a disease by simultaneously investigating multiple treatments, using specialized statistical tools for allocating patients and analyzing results. The focus is on the disease rather than any particular experimental therapy. A platform trial is often intended to continue beyond the evaluation of the initial treatments and to investigate treatment combinations, to quantify differences in treatment effects in subgroups, and to treat patients as effectively as possible within the trial. Although some of the statistical 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.

Bruno M. Cesana