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## Novel Designs for Oncology Clinical Trials

Marc Hoffman, MD  
Chief Medical Officer

Mark Penniston, MS  
Executive Vice President, Clinical Analytics  
and General Manager

Howard Grossberg, MD  
Former Senior Scientific Advisor, Oncology

## Introduction

Pharmaceutical innovation is increasingly risky, costly and, at times, inefficient. This has led to a decline in industry productivity. Estimates for the average cost of bringing a new drug to market today range between \$800 million and \$2 billion, in which late-stage failures and the rising costs of Phase II and III trials represent key components. [1]

Despite growing investments in R&D, the number of new molecular entities achieving marketing authorization is not increasing. However, novel approaches to clinical development and trial design could play a significant role in overcoming some of these challenges by improving efficiency and reducing attrition rates.

Clinical development can be made more efficient and effective by adopting an integrated research model that increases flexibility and maximizes the use of accumulated knowledge. Central to this approach to drug development are novel tools, including modeling and simulation, Bayesian methodologies and adaptive trial designs, such as seamless adaptive design and sample-size re-estimation.

Clinical trials of new chemical entities (NCEs) are typically designed to provide evidence of a therapeutic benefit of a particular magnitude over and above that of some reference therapy. However, superior efficacy is not the only possible benefit, and trials may also be designed to show equivalent efficacy but with other advantages, such as improved tolerability or a more favorable dosing regimen. This statistical method, known as “frequentist inference,” works well in situations where there is good reason to believe that the assumptions made about the magnitude of difference at the start are, in fact, correct. In the paragraphs below, we will consider alternatives, Bayesian statistics and adaptive designs, for oncology trials.

## Bayesian Statistical Methods

Bayesian statistical methods have several attractive features that make them ideal for use in clinical trial design and analysis. [2-5] The Bayesian approach allows for: 1) continuous learning as data accumulates; 2) the synthesis of information from sources within and outside of the trial; 3) hierarchical modeling to “borrow” information across therapies or disease subtypes, depending on the homogeneity of the data; 4) calculating probabilities of future outcomes and making inferences using the trial’s currently available data; and 5) direct estimation of evidence for the effect of interest using posterior probability rather than indirect calculation of the probability of observed data.

Bayesian statistical methods, combined with adaptive trial designs, offer the means to make clinical trials dramatically more informative and efficient. The benefits of adaptive trial designs for pharmaceutical development have been gaining interest over the past decade, but scientific and regulatory questions have slowed their adoption by pharmaceutical sponsors despite their widespread use in many other scientific fields. There are three possible reasons for the hesitation: 1) confusion with respect to the definition of an “adaptive design”; 2) controversy regarding the use of sample size re-estimation methods; and 3) logistical barriers that must be overcome in order to use adaptive designs within existing trial frameworks.

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Clinical development can be made more efficient and effective by adopting an integrated research model that increases flexibility and maximizes the use of accumulated knowledge. Central to this approach to drug development are novel tools, including modeling and simulation, Bayesian methodologies and adaptive trial designs, such as seamless adaptive design and sample-size re-estimation.

According to a recent study conducted by the Tufts Center for the Study of Drug Development (Tufts CSDD), 20 percent of clinical trials employ some form of adaptive design at this time, and the adoption of adaptive trial designs in exploratory phase clinical trials is expected to increase significantly over the next few years. The FDA's 2010 draft guidance, Adaptive Design Clinical Trials for Drugs and Biologics, [6] encourages drug developers to expand their use of adaptive designs. An ongoing collaboration among the U.S. Food and Drug Administration (FDA), academia and the industry is applying adaptive design techniques in the I-SPY 2 breast cancer screening trial to streamline the identification of active drugs and predictive biomarkers. [7]

Another FDA initiative, [8] the 2004 Critical Path Initiative report, notes that "the medical product development process is no longer able to keep pace with scientific innovation. Only a concerted effort to apply the new biomedical science to medical product development will succeed in modernizing the critical path." The report calls for innovative clinical trial designs incorporating the application of Bayesian methodology and adaptive designs. Also, the European Medicines Agency (EMA) issued a draft paper in 2006 concerning flexible or adaptive design clinical trials in new drug development. [9]

### Adaptive Trial Design

The purpose of adaptation in clinical trials is to give the investigator flexibility to identify the optimal clinical benefit of the test treatment under study without subverting the validity of the original protocol and study.

Adaptive trials allow researchers to redesign trial procedures at interim stages. This flexibility can enable greater efficiency within the drug development process by reducing the numbers of patients required, allowing earlier decisions to be made to eliminate treatments showing little promise and moving effective treatments to market faster. Adaptive trials are designed to use accumulating information to determine how to modify the trial as it progresses. In order to maintain study validity (providing correct inferences) and integrity (providing convincing evidence), however, it is important to note that the adaptive aspects of the trial are determined before the trial begins, and that they are part of the planned design of the overall study.

In 2005, a Pharmaceutical Research and Manufacturers of America (PhRMA) working group was established to investigate and facilitate the acceptance and usage of adaptive designs in clinical drug development. The group's findings have been reflected in three successive publications between 2006 and 2010, including an entire issue of the Journal of Pharmaceutical Statistics devoted to this topic. [10-12] The group defined an adaptive design as "... a clinical study that uses accumulating data to decide how to modify aspects of a study as it continues, without undermining the validity and integrity of the trial." It was stressed that the changes should be made "by design" and not on an ad hoc basis. The definition makes it clear that adaptive designs are "... not a remedy for inadequate planning," but are meant to enhance the efficiency of studies and utilization of resources. The definition suggests the term "adaptive design" refers to a general set of methods, including adaptive dose-finding studies, seamless Phase II/III designs, adaptive randomization and sample size re-estimation.

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The use of adaptive trial designs allows for more efficient collection of knowledge about dose response and enables better decision making regarding moving drugs into later stage development. These designs address numerous trial goals, allowing patients to be treated in accordance with the best available information and allowing early termination of a study, either from futility of further pursuit or early success. A Tufts CSDD study in early 2013 looked at current adaptive trial design practices and their impact on early study terminations. Applied across a sponsor's portfolio, the study suggests annual savings of between \$100 million and \$200 million in direct and indirect costs, depending on portfolio size and development cycle time savings.

### Oncology and Adaptive Design

Adaptive trial designs can be used across the entire spectrum of oncology trials, from early learning phases of the drug development process to pivotal Phase III trials. Companies employing a comprehensive adaptive design strategy in the earlier stage trials will make better development decisions and increase the probability of success in later trials. For example, in an adaptive dose-finding study, the dose assignment(s) to the next subject or cohort of patients, is based on responses of previous subjects, and the dose assignment is chosen to maximize the information about the dose-response curve. As will be discussed later, this methodology takes on more importance with some of the newer oncologic agents, such as targeted therapeutics.

Adaptive designs use frequent interim analyses of all of the accumulated data, both from within the trial itself as well as any data from external sources, to make decisions as to whether prespecified protocol design changes will be implemented. Interim analyses partition the trial into multiple stages, with subsequent stages being influenced by the data previously generated. Possible adaptations include adjustments to sample size; allocation of treatments; the addition or deletion of treatment arms; inclusion and exclusion criteria for the study population; adjusting statistical hypotheses (such as non-inferiority or superiority) and combining trials or treatment phases. At least five methods exist for implementation of the adaptive design during early stages of drug development. They are:

#### 1. Continuous Reassessment Method (CRM)

This model-based Bayesian method was introduced by J. O'Quigley [13] in 1990. A working model is specified for the dose-outcome relationship and the study begins by dosing the first patient at the "best" dose. The analysis is updated as additional data is obtained. The next patient is then treated at the next estimate of the "best" dose. The sample size for the study (usually 20 to 30 patients) is determined at the outset.

#### 2. Dose-Finding Based on Efficacy (Eff-TOX)

This is a Bayesian procedure described by P.F. Thall [14] that finds a best dose when efficacy must be traded off against toxicity, with the assumption that both are increasing with the dose.

At least five methods exist for implementation of the adaptive design during early stages of drug development. They are:

1. Continuous Reassessment
2. Dose-Finding Based on Efficacy (Eff-TOX)
3. Parallel Design for Combination Therapies (PDCT)
4. Predictive Probability Design (PPD)
5. Adaptive Randomization for Targeted Therapy (ADDT)

3. **Parallel Design for Combination Therapies (PDCT)**  
This technique, as described by X. Huang, [15] allows for the use of multiple drugs in a single clinical trial. In place of separate Phase I and II trials, PDCT uses a parallel Phase I/II clinical trial to simultaneously evaluate the safety and efficacy of combination dose levels in order to select the optimal combination dose.
4. **Predictive Probability Design (PPD)**  
This method is based on Bayesian adaptive randomization and predictive probability monitoring. As described by G. Yin, [16] adaptive randomization assigns more patients to a more efficacious treatment arm by comparing the posterior probabilities of efficacy between different arms. Patients are continuously monitored using the predictive probability. The trial is terminated early when it is shown that one treatment is overwhelmingly superior to others or that all the treatments are equivalent.
5. **Adaptive Randomization for Targeted Therapy (ADDT)**  
In contrast to the frequentist designs that have equal randomization, this Bayesian adaptive randomization as described by X. Zhou, [17] allows for evaluation treatments and biomarkers simultaneously, providing more patients with effective treatments according to the patients' marker profiles. Early stopping rules can be implemented to increase the efficiency of the designs.

In later stage trials, it may be possible to combine a Phase II and Phase III trial into a single confirmatory study to shorten the development time. These seamless Phase II/III trials involve complex interim adaptations, including treatment selection, sample size reassessment and ending a trial for futility.

Adaptive approaches can produce a better understanding of the dose-response relationship without increasing the sample size. Ineffective or unsafe dosage levels can be discontinued early, allowing for more patients to be treated at doses more likely to be effective. Because adaptive designs require data to modify trials in progress, early findings of efficacy can have extreme importance.

Traditional oncology outcomes, such as long-term survival and progression-free survival, are of less benefit in allowing for interim changes. Therefore, the use of biomarkers has become an increasingly important tool for adaptive strategies to become more useful. In this context, biomarkers might range from early responses seen on tumor imaging, to changes in serum markers or molecular markers from tumors measured via biopsy or on circulating cells. Although biomarkers are of considerable interest in oncology studies, they may present significant challenges in their incorporation, measurement and interpretation. Especially in early-stage studies, markers are often not clinically validated as a predictive marker of efficacy. For that reason, it has been recommended<sup>xviii</sup> that these markers be incorporated into early clinical studies cautiously and used prospectively to determine usefulness rather than to prematurely exclude patient subsets from being studied.

Close collaboration between the preclinical scientists, regulatory affairs specialists, statisticians and clinicians is essential to choose the most appropriate trial design to ensure success.

### Bayesian Statistics in Clinical Trials

The Bayesian approach to statistics increases the precision of the information from a current trial by incorporating prior information. When the prior information is based on empirical evidence, such as data from clinical studies, rather than from personal opinion, Bayesian methods are considerably less controversial.

For oncology studies, it is easier to implement adaptive trial designs using Bayesian methods rather than frequentist methods. [19] [20] The CRM Phase I design mentioned earlier was one of the first clinical applications of Bayesian methodology to determine the maximum tolerated dose (MTD) of a drug. Using CRM, doses are determined by historical data, then data obtained from previously dosed subjects is used to determine the range to be explored in subsequent doses. A probability of toxicity is assigned to each dose based on historical data or investigator input; these probabilities represent prior information and are the starting point in the search for the MTD. A model representing the expected dose-response relationship is defined and subjects are treated at the starting dose. Then the dose is increased steadily, dose-limiting toxicities are observed and the next best estimate of the MTD is calculated. With this approach, subjects are treated up to the dose that currently available evidence indicates to be the best estimate of the MTD. CRM is flexible and allows different numbers of subjects to be treated per dose and accommodates specific dose-limiting toxicity rates.

Bayesian methodology can also be profitably applied to Phase II proof-of-concept studies that are carried out to obtain early evidence of clinical efficacy using a small, targeted number of subjects. Traditional designs might unnecessarily expose an excessive number of subjects to an ineffective arm before deciding the dose was suboptimal or the drug was ineffective, and such conclusions can only be drawn once the study is completed. With Bayesian statistics, two-stage Simon designs, three-stage designs, optimal flexible two-stage designs or adaptive two-stage designs can address these limitations. As suggested by their names, these studies are implemented in stages, with data analyzed at each stage. Depending on the results, a decision is made to stop the study early or to enroll additional subjects into the next stage.

In later stage trials, it may be possible to combine a Phase II and Phase III trial into a single confirmatory study to shorten the development time. These seamless Phase II/III trials involve complex interim adaptations, including treatment selection, sample size reassessment and ending a trial for futility. Here, it is important to determine whether frequentist or Bayesian methodologies should be preferred in interim assessments to make the decision-making process more efficient.

### Specific Advantages to Oncology

Although many of these trial design methods are applicable to many therapeutic areas, there are several advantages pertinent to oncology drug development. First, oncology candidate treatments considered for clinical trials have outpaced the number of eligible patients, demanding a focus on greater efficiency in trial design. Second, many of the agents now being developed are targeted therapies, which might only be useful in small groups of patients with a specific cancer subtype, particular genetic mutation or protein overexpression.

Another advantage to Bayesian-based adaptive trial design is that unlike cytotoxic agents for which efficacy and toxicity monotonically increase with dose, biological agents may exhibit non-monotonic patterns in their dose-response relationships. Novel designs that account for both the toxicity and efficacy

of these unique agents are mandatory. A proposed Bayesian dose-finding algorithm was recently published by C. Cai and colleagues [21] with the goal of establishing a set of guidelines for trials of combination biologic agents.

Lastly, patient advocacy groups are extremely valuable in representing the patient perspective in trial design, and such groups have been vocal in their preferences for adaptive designs in oncology studies. [22]

For any number of reasons, the traditional clinical trial process has become cumbersome and inefficient. Novel trial designs, including adaptive design and a Bayesian approach to statistical data, hold the promise of more efficient and effective studies that improve patient care, reduce development costs and timelines and bring beneficial products to market sooner.

### References

1. Adams CP, Brantner VV. Estimating the cost of new drug development: is it really 802 million dollars? *Health Aff (Millwood)*. 2006 Mar-Apr;25(2):420-8.
2. Viele K, Berry S, Neuenschwander B, et al. Use of historical control data for assessing treatment effects in clinical trials. *Pharm Stat*. 2014 Jan-Feb;13(1):41-54.
3. Jaki T, Clive S, Weir CJ. Principles of dose finding studies in cancer: a comparison of trial designs. *Cancer Chemother Pharmacol*. 2013 May;71(5):1107-14.
4. Thall PF, Wathen JK. Practical Bayesian adaptive randomisation in clinical trials. *Eur J Cancer*. 2007 Mar;43(5):859-66.
5. McCarron CE, Pullenayegum EM, Thabane L, Goeree R, Tarride JE. The importance of adjusting for potential confounders in Bayesian hierarchical models synthesising evidence from randomised and non-randomised studies: an application comparing treatments for abdominal aortic aneurysms. *BMC Med Res Methodol*. 2010 Jul 9;10:64.
6. U.S. Food and Drug Administration, February 2010. Draft guidance for industry: adaptive design clinical trials for drugs and biologics. Available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm201790.pdf>.
7. Esserman LJ, Woodcock J. Accelerating Identification and Regulatory Approval of Investigational Cancer Drugs. *JAMA* 2011;306(23): 2608-2609.
8. U. S. Food and Drug Administration. Innovation or stagnation? Challenge and opportunity on the critical path to new medical products. 2004 [2/26/09]. <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>.
9. Reflection paper on methodological issues in confirmatory clinical trials with flexible design and analysis plan. London, UK: EMEA; 2006. European Medicines Agency. Report no: Doc. Ref. CHMP/EWP/2459/02.
10. Gallo P, Chuang-Stein C, Dragalin V, Gaydos B, Krams M, Pinheiro J; PhRMA Working Group. Adaptive designs in clinical drug development—an Executive Summary of the PhRMA Working Group. *J Biopharm Stat*. 2006 May;16(3):275-83.
11. Krams M, Burman CF, Dragalin V, Gaydos B, Grieve AP, Pinheiro J, Maurer W, Gallo P. Adaptive designs in clinical drug development: opportunities, challenges, and scope reflections following PhRMA's November 2006 workshop. *J Biopharm Stat*. 2007;17(6):957-64.
12. Gallo P, Anderson K, Chuang-Stein C, Dragalin V, Gaydos B, Krams M, Pinheiro J. Viewpoints on the FDA draft adaptive designs guidance from the PhRMA working group. *J Biopharm Stat*. 2010 Nov;20(6):1115-24.
13. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics*. 1990 Mar;46(1):33-48.
14. Thall PF(1), Cook JD, Estey EH. Adaptive dose selection using efficacy-toxicity trade-offs: illustrations and practical considerations. *J Biopharm Stat*. 2006;16(5):623-38.

15. Huang X(1), Biswas S, Oki Y, Issa JP, Berry DA. A parallel phase I/II clinical trial design for combination therapies. *Biometrics*. 2007 Jun;63(2):429-36.
16. Yin G, Chen N, Lee JJ. Phase II trial design with Bayesian adaptive randomization and predictive probability. *J R Stat Soc Ser C Appl Stat*. 2012 Mar 1;61(2).
17. Zhou X(1), Liu S, Kim ES, Herbst RS, Lee JJ. Bayesian adaptive design for targeted therapy development in lung cancer—a step toward personalized medicine. *Clin Trials*. 2008;5(3):181-93.
18. Seymour L(1), Ivy SP, Sargent D, Spriggs D, Baker L, Rubinstein L, et al. The design of phase II clinical trials testing cancer therapeutics: consensus recommendations from the clinical trial design task force of the national cancer institute investigational drug steering committee. *Clin Cancer Res*. 2010 Mar 15;16(6):1764-9.
19. Food and Drug Administration. Guidance for Industry and FDA Staff: Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials. 2010 <http://www.fda.gov/ucm/groups/fdagovpublic/@fdagov-meddev-gen/documents/document/ucm071121.pdf>.
20. Chow SC, Chang M. Adaptive design methods in clinical trials - A review. *Orphanet J Rare Dis*. 2008;3:11.
21. Cai C, Yuan Y, Ji Y. A Bayesian Dose-finding Design for Oncology Clinical Trials of Combinational Biological Agents. *J R Stat Soc Ser C Appl Stat*. 2014 Jan 1;63(1):159-173.
22. Katz ML, Archer LE, Peppercorn JM, Kereakoglow S, Collyar DE, Burstein HJ, Schilsky RL, Partridge AH. Patient advocates' role in clinical trials: perspectives from Cancer and Leukemia Group B investigators and advocates. *Cancer*. 2012 Oct 1;118(19):4801-5.

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Wilmington, NC 28412  
USA  
+1 910 338 4760

171 Bath Road  
Slough, Berkshire SL1 4AA  
UK  
+44 (0) 1753 512 000

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