



Pioneering Statistical Approaches to Accelerate Drug Development through Adaptive Trial Designs

June 2016

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Acknowledgements

The Duke-Margolis Center wishes to thank several individuals for their contribution to the research, development, and preparation of this white paper. This paper would not have been possible without the months-long commitment and participation of the working group of experts listed here. Their thoughtful perspective, content expertise, and diligent input have been critical to the paper's development and we are very grateful for their contributions and support. We would also like to thank those who participated in the conference on which this paper is based – their active and insightful discussion helped illuminate a number of the recommendations contained herein.

Funding for this paper and foundational workshop was provided through a cooperative agreement with the U.S. Food and Drug Administration (FDA). The views expressed in this paper, written conference materials, or subsequent publications do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsements by the U.S. Government.

Authors

Gregory W. Daniel
Deputy Director, Duke-Robert J. Margolis, MD, Center
for Health Policy and Clinical Professor,
Fuqua School of Business, Duke University

Mark B. McClellan
Director, Duke-Robert J. Margolis, MD, Center for
Health Policy and Robert J. Margolis MD Professor of
Business, Medicine and Health Policy, Duke University

Erica Socker
Senior Research Associate, Center for Health Policy, The
Brookings Institution (*former**)

Derek Griffing
Research Associate, Center for Health Policy, The
Brookings Institution (*former**)

Sophie Mayer
Research Assistant, Center for Health Policy, The
Brookings Institution (*former**)

Working Group

Lisa LaVange
Director, Office of Biostatistics, Office of Translational
Sciences, Center for Drug Evaluation and Research, U.S.
Food and Drug Administration

Rajeshwari Sridhara
Director, Division of Biometrics, Office of Translational
Sciences, Center for Drug Evaluation and Research, U.S.
Food and Drug Administration

* These authors' contributions were made during their employment with The Brookings Institution.

Introduction

Recent scientific advances in genomics and our understanding of the underlying causes of disease hold great promise for delivering targeted therapies that could dramatically improve health outcomes. However, it has been challenging to translate such progress into game-changing therapeutics. One challenge is that the costs associated with R&D have been steadily climbing and the average cost of development for a successful product, inclusive of failed products, is now estimated at around \$2.6 billion.¹ While it appears that fewer marginal products are making it through the early stages of development,² up to 40% of all products still fail in phase 3 clinical testing.³ Together, high failure rates, high costs, and lengthy development cycles slow patients' access to effective therapies.

Phase 3 trials that enroll large, heterogeneous patient populations are a key driver of overall development costs. Larger trial patient populations increase statistical power, making it easier to detect significant treatment effects in certain cases, and improve the ability to detect rare adverse events. However, increased heterogeneity may contribute to a trial's failure, and very large trials may also yield statistically significant differences that are not clinically meaningful. Despite the large sample sizes typically required for confirmatory clinical trials, safe therapies effective for treating specific patient subpopulations (e.g., those with a certain cancer subtype or biomarker) may be abandoned if they fail to demonstrate a clinical benefit in the heterogeneous trial population. As our scientific understanding of the biological underpinnings of diseases improves and sponsors leverage this knowledge to develop therapies targeted to specific disease subtypes, modernizing clinical trials to keep pace with these developments is essential. Innovative approaches to clinical trials that take advantage of novel scientific and statistical tools have the potential to improve trial success rates, increase the value and efficiency of clinical research, and speed the availability of effective therapies for the patients most likely to benefit from them.

Adaptive clinical trials are one promising approach that is gradually becoming more widespread. In conventional clinical trials, key parameters such as sample size and study eligibility criteria are fixed throughout the duration of the trial. Adaptive trial designs allow for preplanned, well-defined changes to these parameters in response to data accumulated during the trial without undermining the trial's validity and integrity. Adaptive clinical trial designs can also enable sponsors to conduct mid-term futility analyses or evaluate multiple hypotheses during a single trial, potentially leading to more streamlined trials that allow developers to learn more about the product being tested. Examples include testing multiple products (e.g. the ISPY-II screening trial), dosing regimens, or patient subpopulations (e.g., stratified by biomarker status), and then using the interim results to adjust features of the trial, such as by dropping ineffective doses or therapies or preferentially assigning patients to the most promising treatment arm for them. A shift in the current clinical trial paradigm enabling broader application of adaptive designs could help optimize trial parameters, thereby potentially increasing the odds of success; guard against failures; and expedite the delivery of safe, effective, and more targeted products to patients.

Recognizing the potential advantages of innovative clinical trial designs, the U.S. Food and Drug Administration (FDA) has encouraged greater adoption of adaptive designs and issued draft guidance on "Adaptive Design Clinical Trials for Drugs and Biologics" in 2010. Since the publication of the draft guidance, FDA has seen some changes in the types of trial designs used during therapeutic drug development; however, the use of more complex adaptive designs has been limited primarily to exploratory phase trials (e.g., BATTLE, I-SPY 2), with little innovation occurring in the design of "adequate and well-controlled" trials that are the standard for demonstrating effectiveness for regulatory approval. There is continued interest among FDA, industry, and academia in expanding the use of adaptive designs in confirmatory trials (where the need for improved value and efficiency is greatest), but innovative designs that include adaptations raise a number of statistical and operational concerns that have precluded broader application of these tools to provide evidence for regulatory approval.

This white paper, developed following an expert workshop in March 2014, explores issues related to the broader use of adaptive designs in pivotal phase 3 trials. The workshop was convened through a cooperative agreement with FDA[†] and included participants drawn from industry, contract research organizations, patient groups, academia, and government to discuss statistical and operational issues related to the use of adaptive clinical trials in the curative disease setting and to identify potential strategies to overcome the challenges associated with using adaptive designs in confirmatory trials. A key issue explored during the workshop was trial designs that rely on interim analyses of surrogate or intermediate clinical endpoints as the basis for accelerated approval, with regular approval conditional on confirmation of a product's long-term clinical benefit.⁴ The workshop addressed trial design questions with broad applicability beyond phase III oncology trials; however, it focused primarily on the setting of neoadjuvant treatments for breast cancer to allow for deeper discussion on specific design issues in a single disease area.

This setting was chosen as the focus for the workshop discussion for several reasons. First, increased scientific understanding of disease pathways in oncology and unmet medical need make it an especially active area of drug development with growing opportunities for targeted therapies. Second, the potential benefit of adaptive trials – an increase in the likelihood that an effective treatment makes it to market – is particularly attractive in curative disease settings, such as neoadjuvant therapies for breast cancer. Third, FDA has issued regulatory guidance establishing a pathway for accelerated approval for neoadjuvant treatments in breast cancer based on pathologic complete response (pCR), which is an intermediate clinical endpoint reasonably likely to predict long-term clinical benefit.⁵

Model designs were solicited from participants to further enrich the discussion of adaptive trials with concrete examples. Meeting participants identified potential advantages and disadvantages associated with each of the designs. The main themes from the discussions are summarized below.

Statistical Considerations for Adaptive Trials

The flexibility to change key trial parameters in response to learning that occurs during a clinical trial is a primary strength of adaptive clinical trials. While this flexibility is directly connected to adaptive designs' potential to lead to more efficient clinical trials, it also presents statistical challenges, particularly in confirmatory trials. Workshop participants identified the primary statistical issues associated with adaptive designs, and discussed possible approaches that would maintain the statistical rigor needed for regulatory approval while also allowing for potential efficiency gains.

Bayesian vs. frequentist statistical approaches

Traditional clinical trials to gain regulatory approval for new therapeutics rely on frequentist analyses conducted at the end of the trial and possibly at pre-determined interim time points to estimate the treatment effect and demonstrate effectiveness. While innovative trial designs do not necessarily incorporate Bayesian adaptations or analyses, which rely extensively on model simulations to determine the operating characteristics (e.g., Type I error rate) required by regulatory agencies, some participants thought the Bayesian statistical framework was well-suited to analyzing and learning from the data that accumulate during a clinical trial. Whether and when trial designs should use a Bayesian approach were major topics of discussion throughout the workshop. Participants raised several specific issues related to the use of Bayesian analyses in confirmatory clinical trials, in which making valid and reliable statistical inference is critical.

Use of priors: In frequentist hypothesis testing and statistical inference, results are theoretically derived based on data collected during the clinical trial; prior information is not incorporated into the analysis of the trial data. In contrast, Bayesian inference relies on a combination of trial data and prior probabilities—a priori assumptions about parameters—to estimate the parameters and make probability statements about the size of the treatment effect. Priors can be

[†] At the time of convening, the FDA cooperative agreement was held by the Center for Health Policy at the Brookings Institution. In January 2016, the cooperative agreement was transferred to the Duke-Robert J. Margolis, MD, Center for Health Policy.

“informative” and based on prior knowledge about the product being tested, or “uninformative” and identical for all treatment arms. From one perspective, the ability to incorporate prior knowledge about a therapeutic is an advantage of the Bayesian framework. It can utilize available information from both the current and previous trials, and provides a formal statistical method for combining and optimizing learning from this information.

There are also potential disadvantages to the inclusion of priors. Some participants expressed concern that including priors in the data analysis makes it more difficult to objectively determine whether a treatment is effective. The inferences and decisions made will depend in part on the prior assumptions, but these priors may vary from trial to trial, and more importantly, those conducting and evaluating the trial may not agree on what the priors should be. As the sample size and amount of trial data increase, prior information is weighted less and the results of Bayesian and frequentist approaches converge; however, even large phase 3 trials have relatively small samples in a statistical sense and prior probabilities used for Bayesian analyses are likely to influence the results. Participants generally thought the subjective nature of the Bayesian framework posed greater challenges if used in the final trial analysis to support regulatory approval.

Role of simulations: Another key distinction between frequentist and Bayesian approaches is the reliance on simulation models in Bayesian estimation and inference. Bayesian analyses often use computer-based simulations to quantify trial outcomes, such as estimated size of the treatment effect or the probability of the trial failing to demonstrate effectiveness. Simulation models estimate these quantities and their probability distributions by making repeated draws from a sampling space to determine their statistical properties. Simulations may also be used at other stages to design trials that meet specific criteria, such as strong control of the type I error rate under the model assumptions, and to conduct interim analyses and determine adaptations.

Participants regarded the ease of evaluating inferences and design decisions based on simulated evidence as a potential challenge of implementing Bayesian approaches. Adaptive trials designed and analyzed using frequentist approaches have known operational properties and inferences can be shown to be mathematically valid for the entire sampling space, conditioned on the particular trial design aspects. In contrast, Bayesian approaches rely on simulations to determine the operating characteristics of a trial design and estimate key trial parameters and results. Simulation models allow statisticians to estimate a trial’s operating characteristics for complex trial designs that may not have known analytical solutions, but trial results based on simulations may be more difficult to replicate. Participants generally agreed that using simulations to design and analyze adaptive trials is appropriate and useful in many instances; however, participants also suggested that the Center for Drug Evaluation and Research at FDA should clarify how it will evaluate simulated evidence submitted for regulatory approval. This would involve establishing a transparent review process for reproducing and checking the simulations, including evaluating whether the simulations adequately consider the full range of possible conditions and whether there are conditions under which the inferences do not hold. The need for additional manpower to evaluate simulation results was also mentioned.

Use of Bayesian and frequentist approaches at different stages: Despite the issues participants raised regarding the subjective nature of the Bayesian framework and the challenges associated with using simulation, they did not have fundamental objections to incorporating Bayesian statistical and methodological elements into adaptive trial designs. There was general agreement that Bayesian analysis has some features, such as its formal statistical framework for continuous learning as additional evidence accrues, that make it appealing for interim analyses used to determine parameter changes during an ongoing trial. While Bayesian designs do not increase statistical power in all cases, participants thought they could increase trial efficiency overall because they enable drug developers to ask and answer more questions during a single trial. Some participants supported the use of Bayesian approaches to estimate the final trial statistics; however, there was broader acceptance of using Bayesian methods to design the trials and make decisions along the way, with a frequentist analysis conducted at the end. Trial designs with Bayesian adaptations based on an intermediate outcome but involving traditional survival analysis techniques for the final analysis have been found acceptable by the agency at the protocol review stage for late stage or confirmatory trials, but the number of such cases to date is small.

While many participants were hesitant about using Bayesian analyses at the end of a trial to demonstrate effectiveness, they also noted that issues related to the properties of more complex adaptive designs are not limited to Bayesian approaches. All innovative approaches to adaptive trial design have weaknesses that must be evaluated and weighed—the key question is how often the designs lead sponsors and regulators to draw the wrong conclusions about a treatment’s clinical benefit. Trial designs with multiple or complex planned adaptations will usually require simulations for evaluation and may also introduce statistical bias and/or fail to meet the criteria for adequate and well-controlled trials, even in cases where only frequentist analyses are used. For instance, conducting multiple analyses throughout the trial can increase the probability of a false positive. Designs can include frequentist adjustments to control the type I error rate in many cases; however, some sources of statistical bias may be difficult to account for using frequentist methods. Participants generally felt that more experience with adaptive designs of all types will enable a better understanding of their characteristics, and that acceptance of innovative designs for new drug approvals will increase as this learning occurs.

Operational Challenges in Adaptive Trials

While adaptive trials have the potential to improve the efficiency of the drug development process, the additional complexity of such designs can also make them more challenging to implement. Participants identified key operational challenges that should be addressed when conducting adaptive clinical trials, many of which also have implications for the overall design of the trial, and discussed effective strategies for mitigating these issues.

Managing information leakage

Participants identified the need to perform unblinded interim analyses as one of the primary challenges of conducting adaptive trials. Conducting analyses to determine potential modifications to an ongoing clinical trial requires access to trial data. The release of information about the data or interim results, whether purposeful or not, increases the potential for bias. For instance, conveying even minimal information about the results of the interim analyses through apparent changes to trial parameters or formal announcements can be used to predict whether interim results suggest an experimental treatment is more effective than the standard of care. These predictions can influence the behavior of investigators and lead to unplanned changes to the trial, such as shifts in the trial patient population or subtle changes in the way adverse events are ascertained. If such changes are undetected or unable to be accounted for with statistical adjustments, they can jeopardize the integrity of the trial.

For these reasons, participants emphasized the importance of carefully planning the conduct of interim analyses and access to the data, as well as determining the best approach for communicating the decisions or trial modification made at interim. One key issue is the flow of information between contract research organizations (CROs), data monitoring committees (DMCs), and investigators. Participants stressed that teams conducting the statistical analyses to support interim decisions, usually located at a CRO, should be distinct from those making operational recommendations and decisions about the trial. One model that has been proposed involves establishing two DMCs, one to advise on adaptations and the other to carry out the more traditional DMC role of monitoring data and trial quality and patient safety. Maintaining separation between the two bodies allows the traditional DMC to concentrate on patient safety. Whether one or two DMCs are established, their role is to advise the sponsor on trial continuation and adaptations, if in the adaptive design setting, but not to make those decisions for the sponsor. Another important consideration is the information the resulting adaptations convey to investigators. Certain design features (discussed in the next section) may minimize the impact of interim analyses on investigator behavior and the risk of operational bias. Once a workable plan for managing data and information throughout the trial is developed, the data collection plan, which parties receive what information and when, and the procedures and decision rules for all analyses should be clearly documented in the standard operating procedures and statistical analysis plan to increase regulators’ confidence that the trial meets agency standards.

Number and timing of interim analyses

Participants also discussed the implications of the number and timing of interim analyses for operational bias. Some felt adaptive trials with a single interim analysis might carry a higher risk of bias, as so-called “one-look” designs may make information about the trial, such as its probability of success, easier for investigators to infer from the adaptation (or lack thereof). In contrast, participants indicated that trials with multiple interim analyses could reduce the risk of operational bias. Observers would know whether a trial was continuing, but multiple looks would make it more difficult to guess why the trial was continuing and how close it was to achieving its target endpoint. Additional interim analyses can also lead to larger potential efficiency gains, as they allow for ongoing learning throughout the course of the trial and may enable sponsors to end a trial for futility or success at an earlier point. However, each interim analysis increases trial costs and complexity and may be associated with an alpha penalty (spending some part of the test size or alpha, otherwise reserved for the final analysis), and these factors must be weighed against their potential benefits when determining the optimal trial design.

Patient enrollment and accrual

Some workshop participants indicated that patient recruitment for adaptive trials is often easier because investigators think patients have a higher probability of receiving an effective treatment. But adaptive trials also pose unique challenges related to patient enrollment and accrual. One design question sponsors face is whether to pause enrollment while interim analyses are conducted. Most workshop participants agreed that pausing enrollment during interim analyses could increase the likelihood of information leakage and operational bias, and that in general, interim analyses should be implemented as seamlessly as possible with minimal impact. Shifts in the patient population are particularly difficult to control when enrollment pauses occur, and groups enrolled before or after may diverge in unexpected ways in their composition or trial experience. Pausing enrollment is also logistically challenging because it typically requires retraining and repeated ramp-up efforts. Workshop participants thought there were many advantages to continual enrollment, and that a particularly promising approach to minimize information leakage was achieving full enrollment before making any visible adaptations, although the number and type of adaptations of interest after completing enrollment is reduced. Participants also indicated that overall, timing patient accrual could be hard to predict, particularly when dealing with patient subpopulations whose prevalence may be unknown.

Challenges in the Accelerated Approval Context

One of FDA’s main objectives for this workshop was to evaluate the feasibility of granting accelerated approval based on the results of interim analyses in an adaptive trial setting. Sponsors typically verify the clinical benefit (e.g. event-free survival (EFS) in the setting of neoadjuvant treatments for breast cancer) of a product granted accelerated approval on the basis of a surrogate or intermediate clinical outcome (e.g. pathological complete response or pCR) through a separate confirmatory trial. However, these confirmatory trials are often significantly delayed or may fail to conclusively establish long-term clinical benefit, such as improved EFS, in part because of the difficulty in conducting the trial in the same disease setting as the original trial. A recent FDA analysis of oncology indications approved through the accelerated pathway found that almost 30 percent of products had never been evaluated for long-term clinical benefit, and of the ones that had, more than ten percent had failed to demonstrate benefit in the post-market setting.⁶ Some feel that an adaptive approach could be employed (1) to evaluate a product’s efficacy (on the basis of a surrogate or intermediate clinical endpoint); and if approved, (2) to confirm its long-term clinical benefit in the same trial with longer follow-up. This approach could potentially aid in characterizing the relationship between interim and final endpoints, and represents a more efficient and cost-effective method for conducting confirmatory trials. However, it also raises challenges that have limited the application of this approach thus far.

Characterizing the relationship between pCR and EFS

Though FDA has determined that pCR is reasonably likely to predict clinical benefit and that it can be used for conditional approval, there is uncertainty surrounding the relationship between pCR and EFS. A meta-analysis of pCR across clinical studies with different treatments and patient populations demonstrated a connection between pCR and final clinical endpoints: patients with a pCR are more likely to survive overall and have longer EFS.⁷ However, while pCR appears to be correlated to EFS, it is unclear how observed differential treatment effect in the pCR rate map onto observed treatment effect in EFS.

One approach discussed at the workshop is conducting a single trial for both accelerated and regular approval that models the relationship between the surrogate and final endpoints, incorporates information about the relationship gathered during the trial into this model, and uses the model to make decisions during the trial. Participants thought this approach has several advantages, including considering the final clinical outcome of interest in the same trial used for accelerated approval and explicitly modeling the relationship—including the uncertainty—between the two endpoints for the trial's specific patient population. However, the uncertain relationship between pCR and EFS makes it challenging to design adaptive trials with decision-making rules that consider how a trial is performing relative to both endpoints. For instance, a trial conducted for both accelerated and regular approval that allows for sample size re-estimation must determine the sample size needed to power the trial for approval based on the surrogate and final endpoint. Participants thought addressing this issue would be difficult without more comprehensive information about the relationship between pCR and EFS. But most participants also noted that there are substantial advantages to a seamless adaptive trial that efficiently verifies clinical benefit for the same patient population used for accelerated approval, and stressed that these designs warrant further exploration.

Recruiting patients after accelerated approval

Workshop participants cautioned that regulatory decision-making and data disclosures during an ongoing adaptive trial could significantly impact the conduct of the remainder of the trial for regular approval. Once a product is approved for marketing, it may become impossible or even unethical to recruit additional patients willing to be randomized to the standard of care arm. Furthermore, following approval, public data disclosures, press releases, marketing campaigns, and access issues could influence patients' willingness to participate in an ongoing clinical trial and could significantly alter the trial population (e.g., to include more low-income and/or uninsured patients unable to afford the therapy outside a trial). Participants recommended that if pursuing a seamless adaptive approach to accelerated approval and confirmatory trials, any results from the interim analysis should be kept confidential – and approval delayed – until a trial was fully enrolled in order to avoid altering the trial population.

Participants also discussed an alternative approach employing a matched observational cohort to complete the confirmatory phase of the trial. Participants proposed matching the experimental group, which would continue enrolling new patients following accelerated approval, with patients from a recent observational cohort receiving the standard of care using a set of patient covariates to improve the comparability of the two groups. The analysis would be conducted on the full trial population, including the randomized standard of care group enrolled in the trial prior to accelerated approval. This approach could minimize delays in pursuing accelerated approval (e.g., until a trial is fully enrolled) and avoid the ethical and statistical issues raised by continuing to randomize patients to a control arm after approval. While these statistical techniques have not been used widely in drug development, which relies on randomized controlled trials, they are frequently used and are well-characterized in other data-driven sciences (e.g., sociology, economics). Many participants expressed concern with methods that do not randomize patients across treatment arms, but some thought application of cohort-matching and causal inference techniques to clinical drug development could represent a promising horizon for further exploration within industry, academia, and at FDA once understanding of this methodology improves.

Conclusion and Next Steps

Representatives from industry, academia, CROs, and FDA identified several potential solutions for further exploration to support the use of adaptive designs and other novel statistical and scientific tools in the drug development and regulatory arenas.

Participants felt that the establishment of “standard of care” control cohorts would be a valuable resource for improving the efficiency and cost-effectiveness of drug development efforts in a variety of therapeutic areas. In the application described above, in which the cohort was matched to the experimental patient population, the cohort would likely need to be carefully managed and maintained to ensure its representativeness and usefulness to a variety of research programs. To this end, participants felt that a master protocol to support the development and use of observational cohorts for confirmatory research in adaptive settings would be a promising area for exploration. Master protocols that allow for a “plug-and-play” approach to rapidly test and match a variety of compounds to the most promising trial populations – such as the lung cancer master protocol developed by Friends of Cancer Research and those by TransCelerate BioPharma – are already being used to maximize efficiency and opportunities for collaboration between multiple sponsors and CROs. Participants felt that a broad-based, cross-industry effort could help to diffuse costs and increase value.

Stakeholders also highlighted the need for improved communication and transparency between sponsors and reviewers. FDA indicated that in order to support approval of products studied in an adaptive setting, reviewers would need to critically evaluate the operational characteristics of the design and decision rules. FDA encouraged sponsors to be transparent in providing data and supporting information about simulations, assumptions, and error control techniques so that reviewers are best equipped to make timely and informed decisions. Relatedly, industry representatives indicated that they too would benefit from clarification on FDA’s evidentiary standards for simulated evidence (including those for assumptions, decision rules, and error control) and on what data FDA will require to support product review.

Participants indicated that the further characterization of adaptive trials’ operational characteristics would be a learning process. Collaboration between industry, academia, and regulators was highlighted as a critical component of supporting learning about novel trial designs and products, in addition to developing specific expertise in a given disease area. While to date most adaptive designs have been relatively simple, participants agreed that there were many potential opportunities to improve trial efficiency and value through more complex designs, and that perceived “complexity” is being mitigated with increasing experience, time, and investigation.

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