CONNECTING NON-PROFITS

TO ADAPTIVE CLINICAL TRIAL DESIGNS

Themes and Recommendations from the Scientific Advances

in Adaptive Clinical Trial Designs Workshop

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PRECIS

Adaptive clinical trial designs provide the flexibility to make adjustments to aspects of the design of the trial based on data reviewed at interim stages, and can be particularly helpful in trials examining therapies for rare diseases or when time is short. The potential for adaptive designs to improve clinical research has generated widespread interest in the biomedical research community, and a wide variety of adaptations have been proposed or implemented. Yet specific approaches have met with differing levels of support.

The Scientific Advances in Adaptive Clinical Trial Designs Workshop was organized to give participants from government agencies, industry, non-profit foundations, the patient advocacy community, and academia a forum to discuss the use of adaptive designs in publicly funded research.

After addressing issues of adaptive designs that arise at the planning, design, and execution stages of clinical trials, participants set forth seven recommendations for guiding action to promote appropriate use of adaptive designs.

The ability to overcome real and perceived obstacles to the wider use of adaptive designs will lead to greater efficiencies in the conduct of future clinical trials.

LIST OF ABBREVIATIONS

CONSORT: Consolidated Standards of Reporting Trials

CTSA: Clinical and Translational Science Awards

DSMB: Data and Safety Monitoring Board

EMA: European Medicines Agency

FDA: U.S. Food and Drug Administration

IOM: Institute of Medicine

NIH: National Institutes of Health

PhRMA: Pharmaceutical Research and Manufacturers of America

SCT: Society for Clinical Trials

INTRODUCTION

The biomedical research community's search for dependable and reliable ways to improve clinical research has led to considerable interest in adaptive clinical trial designs, which provide the flexibility to make adjustments to aspects of the design of the trial based on data reviewed at interim stages. Adaptive designs, while useful in many situations, can be particularly helpful in situations in rare diseases or where time is short. Statisticians and clinical investigators have proposed or implemented a wide variety of adaptations in clinical trials, but specific approaches have met with differing levels of support. Within industry, investigators are actively exploring the benefits and pitfalls associated with adaptive designs. For example, a Pharmaceutical Research and Manufacturers of America (PhRMA) working group on adaptive designs has engaged regulatory agencies in discussions about adaptive designs. Many researchers working on publicly funded clinical trials, however, are not yet fully engaged in this discussion.

The 1½-day Scientific Advances in Adaptive Clinical Trial Designs Workshop in November 2009 was organized to begin a conversation about using adaptive designs in publicly funded research. The Workshop offered a forum for participants to address issues of adaptive designs that arise at the planning, design, and execution stages of clinical trials, and to hear the perspectives of influential members of the clinical trial community. The participants also set forth recommendations for guiding action to promote appropriate use of adaptive designs.

This article summarizes the results of the discussions that took place during the Workshop: 1) the definition the Workshop used for an adaptive design; 2) issues related to the initial planning of a trial; 3) important recommendations for broader awareness and use of adaptive designs; and 4) target areas for future activities.

WORKSHOP OVERVIEW

The Scientific Advances in Adaptive Clinical Trial Designs Workshop emerged from QALS, a Phase II clinical trial of high-dose co-enzyme Q10 in ALS, for patients with amyotrophic lateral sclerosis, or Lou Gehrig's disease [1, 2]. The adaptive design of QALS led two members of the trial's Data and Safety Monitoring Board (DSMB), Ms. Christina Clark and Dr. Christopher Coffey, and the trial's senior design biostatistician, Dr. Bruce Levin, to discuss how industry researchers have integrated adaptive designs into ongoing clinical trials more quickly than have researchers conducting National Institutes of Health (NIH) or other non-industry-sponsored trials. The three quickly became aware that the clinical trial community at large was interested in exploring how to advance such designs. The interest was especially strong among researchers supported by NIH because many are searching for ways to reduce the financial cost, number of participants, and time required to conduct clinical trials. Ms. Clark's vision included active engagement of non-profit groups (foundations, advocacy organizations, academia).

The co-chairs of the Workshop, Drs. Levin and Coffey, invited about 50 active representatives in the clinical trial community: NIH staff; the U.S. Food and Drug Administration (FDA); the European Medicines Agency (EMA); patients and non-profit organizations; professional associations; and pharmaceutical companies.

The Workshop had two specific aims:

1) To provide a forum for exploring the potential of adaptive clinical trial designs to achieve reliable results in shorter times and with fewer resources than required by conventional designs.
2) To provide an opportunity for participants to make recommendations regarding next steps toward further research, education, and coordinated activity related to adaptive designs.

The Planning Committee for the Workshop had five members: Ms. Clark, who served as the Workshop coordinating sponsor; Workshop co-chairs Dr. Levin and Dr. Coffey; Mr. Peter Gilbert and Dr. Janet Wittes. Many others contributed to the success of the Workshop.

The first day of the Workshop laid the foundation with presentations on various aspects of adaptive design. The second day was devoted to open-ended dialogue about the use and potential of adaptive designs in clinical trials. (See the supplementary information for the complete Workshop agenda.)

The morning of the first day had five sessions: 1) an introduction to adaptive trial designs, including promises and challenges; 2) three case studies of adaptive designs; 3) an exploration of questions to guide the planning of a clinical trial with an adaptive design; 4) models created by the pharmaceutical industry for adaptive trials that academics and non-profits can draw upon; and 5) challenges of implementing adaptive designs in NIH- and other non–industry-sponsored trials. Discussion followed each session. During the afternoon, a panel of representatives from NIH, FDA, academia, industry, the EMA, international organizations, and the patient community presented their perspectives on adaptive designs.

On the second day, participants divided into three groups to discuss advantages and disadvantages of adaptive trial designs, to explore possible methods for overcoming impediments to wider use of adaptive designs; and to formulate recommendations.

DEFINITION OF AN ADAPTIVE DESIGN

The increasing interest in adaptive designs brings with it a great deal of confusion about what, exactly, “adaptive” means. The term currently applies to a variety of situations. For example, “adaptive” can refer to a broad approach to conducting a trial or to a specific element of a trial’s design. To advance the field, the scientific community must first agree on a definition.

The Planning Committee developed the following definition of an adaptive design:

*"**Adaptive Design:** A protocol that allows certain design features to change from an initial specification based on evolving trial information while maintaining statistical, scientific, and ethical integrity."*

This definition slightly modifies the one used by the PhRMA Adaptive Design Working Group [3]. The Workshop chose various elements of the definition deliberately to reflect the central concepts of an adaptive design:

"protocol": Using an adaptive design does not remove the need for a pre-specified design and statistical analysis plan. Changes should be based on pre-specified rules rather than on ad hoc or post hoc decisions. For example, the protocol might specify: "If [this] occurs, then we will do [that]." Specifying the rules in advance allows statistical evaluation of the operating characteristics of the design.

Analyses and simulations are crucial for determining whether the proposed adaptation introduces bias, for determining how best to correct for bias that occurs, and for comparing the properties of the adaptive design with those obtained from a standard fixed design. (Adaptive designs are not always better.) For these and other reasons, it is necessary to conduct advanced planning for adaptations. Although there may be opportunities to perform simulations with unplanned adaptations, such simulations would generally apply to activity only from the point of adaptation forward. There is no defensible way to go back and capture the randomness of different scenarios that might or might not have led to similar ad hoc changes. Therefore, only planned adaptations can be guaranteed to avoid bias and provide a replicable and, thus, scientifically sound experiment.

"design features that can change": Many design features of a study can be altered, including, but not limited to, the maximum sample size, the stopping time, the allocation ratio between treatment and control groups, dose levels and regimens, the number of treatment arms, the endpoints, or the hypotheses. Alterations to some of these elements are more controversial than others. In fact, altering too many central features of the design of a trial may change the underlying scientific question and render the results uninterpretable.

"evolving trial information": An adaptive design usually consists of at least two stages. At each stage, data analyses are conducted and adaptations implemented on the basis of updated information. Changes may be based on parameters such as the rate of patient recruitment, baseline covariate information, or the rate of information accrual such as endpoint frequencies — all of which can be evaluated without unmasking treatment assignment. Other adaptations might involve parameters that require unmasking, such as the effect of treatment on response. Adaptations based on re-estimated "nuisance" parameters (variables unrelated to the treatment effect) may or may not require the unmasking of treatment assignment.

"maintaining statistical, scientific, and ethical integrity": For a clinical trial to be persuasive, whether the design is fixed or adaptive, it must permit valid statistical analysis, avoid bias, and have the ability to answer the scientific study question. This concept requires an "adaptive by design" approach, as well as careful consideration of how the proposed adaptations could affect patient safety and the integrity of the trial as a whole.

INITIAL PLANNING

During the initial planning of a clinical trial, investigators specify the primary hypothesis to be tested, the patient population, the primary outcome to be measured, a clinically meaningful treatment difference to be detected with desired statistical power, and the assumed values for the nuisance parameters. The magnitudes of these nuisance parameters must be specified because they affect the ability of a trial to answer its study question, even though they are not directly related to the effect of the treatment. Examples of nuisance parameters include the standard deviation of a quantitative measure, the base rate of a categorical outcome, the expected amount of follow-up time per subject for a time-to-event study, and the overall event rate itself. Investigators use the study specifications to design the trial, compute the required sample size, and analyze the results after all participants have been enrolled and evaluated.

Unfortunately, investigators may have limited information to guide their choices at the beginning of a clinical trial. Unlike traditional trials, an adaptive design gives investigators the opportunity to take advantage of knowledge that accrues as the study progresses so they can modify assumptions regarding characteristics of the trial. In many situations, the greater flexibility adaptive designs permit can lead to trials with fewer patients and more efficient use of available resources. The patient community is particularly interested in the potential for adaptive designs to make effective treatments available to patients more quickly or to stop research with ineffective treatments earlier.

RECOMMENDATIONS FROM THE WORKSHOP

Discussions on the second day of the Workshop led to several recommendations. Summaries of the main topics of debate and the recommendations for each follow.

Taxonomy

The Workshop participants felt strongly that more work is needed to define adaptive designs in clinical trials. They debated whether this is best accomplished by developing a taxonomy for adaptive designs or by defining a base set of concepts that all interested parties can use for common discussion, understanding, and education about adaptive designs. One group of participants held that the need for an adaptive design taxonomy stems from the desirability of narrowing the scope and terminology, thus allowing for a better distinction between planned and unplanned adaptations. A second group of

participants held that a taxonomy sets unnecessary boundaries. Because trials differ, even a carefully devised taxonomy would not apply to all circumstances or would evolve over time. This group thought that the emphasis should be on defining useful concepts rather than terms that would constrain researchers.

Recommendation #1: More opinions should be gathered about the need to bring a commonly understood framework to the field of adaptive designs in clinical trial research.

Appropriate Use of Adaptive Design

All participants in the Workshop viewed exploratory settings as highly appropriate for adaptive design. FDA maintains that adaptive designs are acceptable in exploratory studies with the proviso that efficiency and validity are still important. The utility of adaptive designs in confirmatory settings is less clear. The concept of “adaptive by design” is crucial in the confirmatory setting, because implementing too many changes during the course of a confirmatory trial defeats the meaning of “confirmatory.”

Although the Workshop was too short to allow discussion of all types of adaptations, the participants did address several. These discussions confirmed the view that participants considered some adaptations more acceptable than others. For example, nearly all Workshop participants agreed that changing an endpoint during the course of a trial remains controversial and therefore should be avoided. Some participants, on the other hand, expressed the opinion that changing endpoints may be acceptable in certain cases. The participants felt that ad hoc dose modification during a trial is acceptable for assessing safety but not for assessing efficacy. Another acceptable design is one that eliminates the “white space” between studies by merging phases II and III into a single adaptive trial. Even when such a trial is designed, the wise investigator still conducts dosing research beforehand when possible, or builds in dose selection as an initial stage of the design.

Participants spent a great amount of time discussing adaptations in response to an observed interim treatment effect. The final consensus was that planned adaptations in response to an observed effect size that differs from expected are acceptable in some circumstances, but ad hoc changes based on effect size are rarely successful, seldom have a positive outcome, and often lack credibility.

On the contrary, changes based solely on nuisance parameters are generally well accepted and should be planned into clinical trial designs. Many participants encouraged “enrichment designs” in which the trial’s inclusion criteria change over time to increase enrollment of a subgroup of subjects who appear most responsive to treatment.

Recommendation #2: Methodology for trial adaptations should be a priority for future research. In particular, this includes 1) the circumstances in which adaptive designs would benefit patients or save time, effort, and financial resources, and 2) the optimal management of logistical issues in an adaptive trial.

Recommendation #3: For Phase III trials, investigators should minimize ad hoc changes.

Accounting for Adaptive Designs in the Grant Review Process

Participants in the Workshop were particularly concerned with grant review and clinical trials monitoring for adaptive design trials. It is difficult to explain the nuances of an adaptive design within the space constraints of the new NIH grant application. To alleviate this concern, participants suggested applicants use the human subjects section of the application to describe relevant adaptive components of the proposed trial.

Adaptive designs sometimes require adjustments to funding, but such changes take time and often introduce logistical problems. Often, reviewers of grant applications expect investigators to know all the answers in a proposal and are uncomfortable with the unknowns associated with an adaptive design, which can result in a low score. Investigators, reviewers, and funding agencies all find budgetary uncertainty an obstacle.

In February 2010, the FDA published a draft document titled “Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics” [4]. Investigators might find these guidelines useful when writing grant applications. In addition, program officials should familiarize themselves with adaptive trial designs so they may appropriately advise investigators who are developing grant applications.

Recommendation #4: NIH should offer more recognition of adaptive designs and more funding for planning clinical trials that might benefit from them. Suggestions include the following:

- NIH should develop a targeted program for developing tools associated with the use of adaptive designs, such as software for modeling and simulation related to adaptations. More specifically, the group recommended that NIH develop a funding mechanism to examine options for designs of clinical trials.
- NIH should consider implementing flexible mechanisms that address long-term funding of clinical trials and commit to funding adaptively designed trials that follow their approved protocol even with planned variable durations and sample sizes.
- More opportunities for two-way discussions in the NIH grant system should be encouraged. Reviewers of grant proposals should understand how adaptive

design trials work, when they are beneficial, and how evaluating their progress differs from evaluating traditional trials.

- Funders should consider supporting the development of software that can be made accessible to principal investigators considering adaptive designs. This investment could ultimately save resources by encouraging the use of simulations and modeling that lead to carefully planned trials that take less time and fewer resources than traditional trials. Additionally, funders should support data management specialists and systems to allow for early availability of high-quality data.

The Role of Data and Safety Monitoring Boards

The role of DSMBs in adaptive clinical trials was discussed throughout the Workshop. Participants predicted that the role of the DSMB will change as adaptive designs are used more frequently. Specifically, many felt that future adaptive clinical trials have the potential to require a level of involvement from DSMB members that is beyond the current standard. Several participants recommended that investigators develop their studies with that possibility in mind. On the other hand, the DSMB's knowledge of interim results might be perceived as a potential source of bias if the DSMB is given too much leeway in implementing adaptations.

Recommendation #5: The use of adaptive designs may require a different way of thinking about the structure and conduct of DSMBs. Specific modifications include the following:

- For confirmatory adaptive designs, investigators should include decision trees and triggers in the trial design in order to minimize the role of DSMB judgment.
- The statisticians on DSMBs for trials with an adaptive design should be familiar with the theory and practice of adaptation.
- DSMBs should assure the trial has data managers available who are knowledgeable about the special needs of adaptive trials.

Education and Communication

A theme permeating the entire discussion was the need for those involved in clinical trials to understand the methodology of adaptation. The understanding could come directly, through education, or indirectly, through the literature. Training is relevant to reviewers, program officials, potential research participants from the community, academicians, and other investigators. Patient advocacy groups could play a significant role in providing education. Because of the limited resources for training, educating all stakeholders would be challenging.

In an effort to continue and advance the discussion, participants proposed three possible ways forward. Through additional forums, the NIH, advocacy groups, funding organizations, academia, and the pharmaceutical industry could continue the conversation. In addition, the groups represented at the Workshop considered seeking broader representation within existing pharmaceutical industry working groups that are addressing adaptive designs. Another effective way forward would be to combine interested parties under the auspices of an appropriate umbrella group such as the Society for Clinical Trials (SCT).

Another priority participants identified was to document current practice and potential interest in adaptive designs. Participants suggested conducting a survey to see how many of the different clinical trial stakeholders are already using adaptive designs. Findings from such a survey would form the basis of planning future efforts.

One possible next step might be a summary paper that lays out the key elements of adaptive design. NIH study sections also are appropriate venues for further discussions of adaptive designs, as are courses aimed at young investigators and the educational efforts of professional associations.

Another group that must understand clinical trial design is the medical media, including medical and journal editors and reviewers. The media should know that not everything called adaptive design warrants the label according to the Workshop definition.

Finally, information management systems for clinical trials need to evolve to include features necessary for adaptation.

Recommendation #6: An overarching group, such as the Institute of Medicine (IOM) [5], with backing from NIH and participation by biostatisticians, should be approached to develop a means of communicating issues related to adaptive design.

Recommendation #7: It is necessary to educate everyone with a role in clinical trial research about adaptive designs in order for them to be used more frequently. Specific recommendations include the following:

- NIH should develop programs to educate and train researchers, reviewers, and DSMBs about adaptive designs.
- NIH should fund efforts to train young investigators about the appropriate uses of adaptive designs.
- Patient advocacy groups, professional associations, and non-profit organizations should collaborate on ways to educate professionals, patients, family members, and the media about adaptive designs.
- NIH could develop a publication checklist for funded researchers to encourage investigators to disclose the decision-making process in a trial involving adaptation.

- The clinicaltrials.gov registry should incorporate fields for indicating what types of adaptations the trial design allowed.
- The editors of CONSORT (Consolidated Standards of Reporting Trials) should publish definitions and guidelines for reporting adaptive design elements.

Information Processing

Adaptive designs present challenges of information processing and statistical programming. Because adaptive decision making requires high-quality data early in the trial, study statisticians and data managers must have a more active role in trials with adaptive designs than in those with conventional designs. Excellent data management practice is essential for quality control. Uncertainty arises when data are missing or not verified, or when data are analyzed too early or too late. This can lead to inappropriate or untimely adaptations.

Adaptive designs often require exploratory modeling and simulation, which may involve customized software. Drug development in the pharmaceutical industry typically involves modeling disease progression to predict what will happen in clinical trials. Currently, however, researchers funded by NIH, non-profit organizations, and other funding entities often do not have access to the programmers or software to conduct modeling and simulations.

FUTURE DIRECTIONS

From the outset, the Planning Committee felt strongly that this Workshop should serve as a starting point for continued efforts to increase the understanding of adaptive designs in trials funded by public agencies or by foundations. A subset of the Planning Committee has been meeting regularly since the Workshop to discuss possible future directions. This group organized and delivered the collected comments of Workshop participants on the FDA draft guidance document [4] during the 2010 comment period. Some other promising areas of exploration are summarized below.

Publications

A complete summary of the Workshop proceedings appears online at: www.palladianpartners.com/adaptivedesigns/summary. In addition, several manuscripts based on presentations and discussions at the Workshop are in press or scheduled for submission.

Enhancing the Website

A well-maintained website will be a major tool for outreach to interested communities. Work is underway to address how best to meet diverse and ongoing needs. The

website, accessible at www.palladianpartners.com/adaptivedesigns, will emphasize guidance to scientifically valid bibliographies and resources, and already contains a partial bibliography of publications that are directly relevant to the Workshop.

Engaging the Community of Interested Participants

The Planning Committee feels that there may be great promise in continuing to expand the network of organizational leaders who will influence the future of adaptive designs.

Advisory Group for Researchers Developing Adaptive Clinical Trial Designs

NIH-funded researchers considering an adaptive clinical trial design could make immediate use of a group to serve as an advisory resource. While industry uses its resources to conduct extensive modeling prior to submitting a research concept involving an adaptive design, no similar infrastructure exists to support publicly funded researchers. This is particularly problematic because researchers must conduct extensive simulations before submitting a grant proposal, well before they receive any funding to support these activities. There is a strong need for a consortium to support researchers' efforts to apply for NIH grant support for clinical trials with adaptive designs. Such an advisory group might form under its own grant application. Alternative approaches could involve building similar infrastructure within the NIH or incorporating it into existing CTSA networks.

Initiatives for Developing Activities by Non-profit Groups

From the outset, the Planning Committee recognized the potential of including non-profit research and advocacy organizations in deliberative stages of clinical research. Many investigators acknowledge the role of non-profits as adjunct trial funders and, possibly, as portals to trial patients. These organizations have an especially important role to play in educating patient communities and advancing stakeholders' understanding of adaptive designs. The Workshop included 14 representatives from non-profit and advocacy groups as full participants, all of whom were trained in scientific research, public policy, law, or management. The Workshop emphasized the importance of developing understanding by the non-profits and expanding outreach to these organizations on issues of adaptive clinical trials. The model used by the Workshop for the involvement of non-profit organizations was derived from the work of the NIH Public Trust Initiative in partnership with the NIH Director's Council of Public Representatives [6].

The interest and perspectives of the non-profits were viewed as important resources to be incorporated into future activities generated by the Workshop.

SUMMARY

This Workshop on adaptive clinical trial designs brought together a diverse group of NIH researchers, NIH staff, and representatives from regulatory agencies, pharmaceutical

companies, and non-profit organizations. The Workshop offered a forum for exploring ways of improving clinical trial research by reviewing data at critical points during the conduct of an ongoing trial, and making pre-planned adjustments as specified in the study protocol. The participants predict that the ability to overcome real and perceived obstacles to such designs will lead to greater efficiencies in the conduct of future clinical trials.

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5. The IOM is a component of the U.S. National Academies, whose members produce independent recommendations and policy reports to address scientific and technical aspects of some of society's problems. The non-profit IOM operates outside the framework of the U.S. federal government, but the majority of its studies and other activities are funded by the federal government.

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Recommendations from the Workshop

Group discussions on Day 2 of the workshop produced the following recommendations, excerpted from the article:

Recommendation #1: More opinions should be gathered about the need to bring a commonly understood framework to the field of adaptive designs in clinical trial research.

Recommendation #2: Methodology for trial adaptations should be a priority for future research. In particular, this includes 1) the circumstances in which adaptive designs would benefit patients or save time, effort, and financial resources, and 2) the optimal management of logistical issues in an adaptive trial.

Recommendation #3: For Phase III trials, investigators should minimize ad hoc changes.

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