ETHICAL CONSIDERATIONS IN ADAPTIVE DESIGN CLINICAL TRIALS

Abstract
An adaptive design clinical study is one that includes a prospectively planned opportunity for modification of one or more aspects of the study design and hypotheses based on interim analysis of study data. The overall objectives of an adaptive design approach are to make clinical trials more efficient, more informative or more likely to demonstrate an effect of the investigational product. While adaptive design is associated with many potential benefits, it may also present challenges to observing the basic ethical principles of research in human subjects.

In this white paper, we review the features of particular clinical trial design adaptations and discuss the ethical obstacles they can present and those they can potentially resolve. Using examples of both published and unpublished clinical studies, we highlight the importance of proper design and planning and appropriate ethical due diligence in the successful conduct of an adaptive design clinical trial.
The Value of Adaptive Design

In today’s drug development and regulatory environment, lengthy research and development programs, high clinical trial attrition rates, and increasing costs all demand a smarter, more efficient approach to drug development. Adaptive designs are clinical trial methodologies that incorporate pre-specified changes in design or analyses guided by examination of the accumulated data at an interim point in the trial. As part of their Critical Path Initiative for driving innovation in the way regulated products are developed, evaluated and manufactured, the U.S. Food and Drug Administration (FDA) has identified adaptive design as one way to improve clinical trial efficiency at all phases of development. Compared to conventional study designs, adaptive design approaches can lead to studies that:

- More efficiently provide the same information,
- Increase the likelihood of achieving the study objective or
- Yield improved understanding of the investigational product’s effect.

Adaptive design may help to address the issue of how to best utilize limited funding to advance knowledge and patient care and how to minimize economic waste in the conduct of clinical trials. In the exploratory phases of drug development, adaptive design can improve resource allocation or result in the combining of development phases, thus saving time. In confirmatory trials, adaptive design may enable:

- Early trial termination for either efficacy or futility.
- Change in the treatment arms included or the treatment group allocation ratios to allocate more subjects to effective treatments and minimize the number of subjects exposed to either ineffective or toxic doses (i.e., a “drop-the-losers” design).
- Reassessment and adjustment of the sample size (i.e., sample size re-estimation) to minimize the likelihood of a trial failing due to lack of statistical power.

Challenges of Adaptive Trial Designs

While adaptive design is generally accepted as an advance in clinical trial methodology, it can present both opportunities and challenges from an ethical perspective. The Belmont Report issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1978 summarizes ethical principles and guidelines for research involving human subjects. The Report identifies three core principles:

- Respect for persons
- Beneficence
- Justice

The Report also states three primary areas of application for these principles – 1) informed consent, 2) assessment of risks and benefits and 3) selection of subjects.

Ethical issues may arise when “justice,” in the form of clinical equipoise, is disturbed by the apparent superiority of one treatment over another, as in cases where treatment differences cannot be fully masked or where there has been extensive off-label use or open label trials. In such situations, investigators may be placed in the position of withholding from ongoing and new participants in a trial information that is necessary to make a considered judgment or give informed consent, raising an issue with “respect for persons.” Moreover, investigators may potentially violate the principle of “beneficence,” which emphasizes minimizing harm and maximizing possible benefits.

The following examples highlight the ethical considerations fundamental to the protection of human subjects in clinical trials with an adaptive design.
Respect for Persons

In the context of progressive disease and morbidity and where trials evolve from initial uncertainty to obvious differences between treatment arms, patient risk from being on placebo or active comparator may not be minimal. When investigators feel compelled to share interim analysis data with trial participants to maintain respect for persons, study adaptations can have unintended consequences, as shown in the following case study.

Case Study: The Big 1-98 Trial

A Potential Pitfall of Adaptation

In this double-blind study, post-menopausal women with operable invasive, receptor-positive breast cancer were randomized to receive either:
- Monotherapy with letrozole or tamoxifen for five years,
- Letrozole for two years followed by tamoxifen for three years or
- Tamoxifen for two years followed by letrozole for three years.

The primary endpoint was disease-free survival, comparing the patients who started with letrozole with those who started with tamoxifen. A planned interim analysis demonstrated that letrozole monotherapy was superior to tamoxifen monotherapy after a median follow-up of 26 months. On the basis of these results, the decision was made to allow patients in the tamoxifen monotherapy arm who were disease-free to selectively cross over to letrozole, introducing a study adaptation that was not pre-specified. Of 2,459 patients randomized to the tamoxifen monotherapy group, 619 (25.2%) selectively crossed over to letrozole, confounding the interpretation of long-term follow-up data and raising the issue of how to best deal with compromised randomization in general.

In this study, therefore, since the investigators felt compelled to share interim analysis data with trial participants, the study adaptation, which was not pre-specified, resulted in difficulties in interpreting the data collected post-adaptation.

Mitigating the Risk

The ethical dilemma presented by an interim analysis is whether to withhold such information to maintain trial integrity or risk compromising the scientific basis of the trial in the interest of the health and survival of the study participants. A well-designed adaptive trial, with adequate pre-specification, including the possibility of adaptive treatment cross-over, may help to avoid some of these dilemmas and minimize the risk of regulatory challenge. Preserving trial validity is an ethical consideration that is equally as important as the health and survival of the participants, and it may be necessary to educate investigators on how to balance these ethical considerations.

Beneficence

One form of adaptive design, the response adaptive trial, may help to minimize harm and maximize possible benefits, preserving the ethical principle of beneficence because these designs allow investigators to:
- Re-size the trial based on blinded or unblinded treatment outcomes using pre-specified rules for adaptation,
- Provide for adjustment and refinement of doses being studied by dropping treatment arms that are deemed ineffective and/or overly toxic and
- Add patients to treatment arms that show early signs of patient tolerance and treatment activity.
An additional benefit to patients is compensation for “therapeutic misconception,” which is deemed to exist when individuals do not understand that the defining purpose of a clinical trial is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the trial.5,6

Case Study: The Birth of Adaptive Randomization – the ECMO trials

Background

After a Phase I trial of extracorporeal membrane oxygenation (ECMO) for newborns with respiratory failure showed promising results, Bartlett et al. designed a trial using the “randomized play-the-winner” method for eligible patients already on optimal/maximal treatment.7,8,9 In this method, the first patient had equal probability of being assigned to either ECMO or the maximal treatment, the next patient had a greater probability of being assigned to a more successful treatment, and so on. Parental consent was obtained only for patients assigned to ECMO. Patients whose parents did not consent to ECMO, or who died before the start of ECMO, were still considered to be in the ECMO group.

The rationale behind this design was that: 1) The outcome of each case would be known soon after randomization, making it possible to use. 2) It was anticipated that most ECMO patients would survive and most control patients would die, so significance could be reached with a modest number of patients. 3) It was a reasonable approach to the scientific/ethical dilemma as the investigators were compelled to conduct a prospective randomized study, but reluctant to withhold a lifesaving treatment from alternate patients simply to meet conventional random assignment technique.7

Twelve patients met randomization criteria: the first was randomized to ECMO and survived and the second to conventional treatment and died. With the odds of assignment to ECMO now 3:1, the third was assigned to ECMO and survived. The plan was to continue in this way until there were ten who had been treated with ECMO or ten control patients who died. When the study was terminated, there had only been the one control patient who had died and 11 ECMO patients, all of whom survived.

The small size of Bartlett’s control group necessitated a second ECMO trial, conducted by O’Rourke et al in 1989, which confirmed the benefits of ECMO using a block randomization design in the first phase and requiring a minimum of 4 deaths in either group before randomization was discontinued and the more successful treatment chosen for the second phase. In phase I of the study, 4 out of 10 babies in the CMT group died and 9 out of 9 babies in the ECMO group survived. Randomization stopped after the fourth death in the CMT group and the next 20 patients were treated in the ECMO group, and 19 babies out of 20 survived.10 In this situation, the adaptive design was able to minimize the number of children assigned to the less effective treatment as the trial progressed, fulfilling the ethical aim of beneficence.

Discussion

It could be argued, as Thall did in 2002, that “outcome-adaptive randomization…provides a compromise between ethical concerns and the scientific goals of obtaining an unbiased treatment comparison…[and] directly addresses the problem that equipoise (justice) is lost as interim data becomes available during the trial.” From this perspective, an adaptive randomization approach helps to more closely align the aims of science, the desires of research participants, and the ethical principles of beneficence and justice.6
On the other side, several authors have argued that outcome-adaptive randomization is unethical in terms of informed consent, justice, and potential investigator bias. Saxman has pointed out that:

- Even while assigning more patients to the ‘superior therapy,’ some patients continue to be assigned to the increasingly likely ‘inferior therapy,’ an active intervention reflecting disturbed equipoise that is ethically problematic.
- Informed consent requires telling patients of the potential imbalance in assignments, its rationale, and their chance of being randomized to what has been calculated as more likely to be the ‘inferior therapy,’ with the additional ethical challenge that most patients have difficulty understanding even standard randomization.
- There may be enrollment (selection of patients) bias, given the risk that patients who enroll later and are thus more likely to be randomized to the ‘superior therapy’ may be qualitatively different from those enrolling earlier.

Interestingly, more recently, Thall presented a radically different perspective on adaptive randomization than he did in 2002:

“Outcome AR [adaptive randomization] has several undesirable properties. These include a high probability of a sample size imbalance in the wrong direction, wherein many more patients are assigned to the inferior treatment arm, the opposite of the intended effect. Compared with an equally randomized design, outcome AR produces less reliable final inferences, including a greatly overestimated actual treatment effect difference and smaller power to detect a treatment difference. This estimation bias becomes much larger if the prognosis of the accrued patients either improves or worsens systematically during the trial.

AR produces inferential problems that decrease potential benefit to future patients, and may decrease benefit to patients enrolled in the trial. These problems should be weighed against its putative ethical benefit. For randomized comparative trials to obtain confirmatory comparisons, designs with fixed randomization probabilities and group sequential decision rules appear to be preferable to AR, scientifically, and ethically.”

Thus, it is important for sponsors to stay abreast of recent studies and research in adaptive design to ensure that the most current thinking is being applied to their proposed study.

**Justice**

Randomization in clinical trials may appear unethical or unjust by virtue of assigning patients with equal needs to receive unequal treatment given the known results of open label trials or anecdotal reports providing preliminary evidence of a drug’s efficacy and/or safety. However, many interventions fail at Phase III, supporting the counter-argument that justice continues to be upheld at Phase III for many investigational agents.

Adaptive designs offer the opportunity to expose fewer subjects to ineffective or toxic treatments while still producing statistically significant results. However, they can also risk operational bias, as interim analyses and trial adaptations may influence an investigator’s sense of justice in the middle of a trial, shifting the selection of subjects to enroll. This is especially true if there is adaptive allocation based on response in studies where it is not possible to fully blind the investigator from the treatments as the trial progresses. The difficulty in predicting or gauging these potential effects is part of the less well understood aspect of some adaptive designs.

**Case Study: Challenges of Confirmatory Trials for Widely-Accepted Treatments**

**Challenge**

Based on numerous retrospective studies and case reports and two small, placebo-controlled trials supporting the efficacy of oral propranolol as a treatment for infantile hemangioma (IH), propranolol was widely considered to be first-line therapy for IH, despite the paucity of evidence from randomized, controlled clinical trials and the previous lack of a pediatric formulation. Léauté-Labrèze et al. designed a multi-center, randomized, double-blind, adaptive, phase II-III trial to assess efficacy and safety of several doses of propranolol (stage 1), followed by an interim analysis to choose a final dose to study for the final efficacy analysis (stage 2). When recruitment started in February 2010, it quickly became apparent that extensive off-label usage of propranolol to treat IH, along with numerous communications concerning the positive benefit vs. risk profile of the drug, made recruitment even more challenging than originally anticipated.
Solution

With regulatory guidance, the study authors adjusted the protocol to reduce the number of subjects assigned to the placebo arms in both stages of the trial, extend enrollment to include non-facial hemangiomas, and include additional trial centers, enabling successful completion of the trial. In order to maintain justice and beneficence, investigators were required to fully inform participants of the availability of propranolol as an off-label treatment, reassuring them that any delay in treatment of IH resulting from placebo randomization would likely be minimally harmful and emphasizing that the purpose of the clinical study was to address remaining uncertainties about the efficacy, safety and timing of propranolol use for IH.\(^\text{17,18}\)

Thinking Outside the Box: Current Trends in Adaptive Design

New paradigms for clinical trials are already supplementing or supplanting the classic single-drug, single-disease model. Notable examples of this shift include the I-SPY 2 breast cancer trial and the BATTLE (NCT01248247) and Lung-MAP (NCT02154490) lung cancer trials.\(^\text{19,20}\) These ‘platform’, ‘umbrella’ or ‘basket trials’, which use multiple drugs and cover multiple disease types, aim to provide speed and efficiency to the clinical trial process. They often employ simulations to model and project the outcomes of different design features and decisions and use response adaptive randomization to progressively improve the outcomes for study participants being treated.\(^\text{21,22}\)

Additional features of the I-SPY 2 trial include the ‘perpetual trial’ concept (with regimens entering and leaving the trial on a continual basis), a ‘master protocol’, a ‘common control arm’ and adaptive sample size re-estimation and randomization in each arm.\(^\text{18}\)

Other examples of innovative adaptive design trials include:

- The European Union’s 2013 Innovative Medicines Initiative calling for proposals to build a European Platform to Facilitate Proof of Concept for Prevention in Alzheimer’s Disease (EPOC-AD)\(^\text{23}\)
- The President’s Council of Advisors on Science and Technology’s 2014 call to action for the development of a “robust standing national clinical trials network for antibiotic testing” that would “develop ‘platform trials’ for antibiotics, where multiple new agents from different sponsors can be evaluated concurrently”\(^\text{24}\)
- The National Cancer Institute’s Molecular Analysis for Therapy (NCI MATCH) II study, which will enroll 1,000 cancer patients in approximately 20 mutation-specific groups in a very large Phase II basket trial using targeted therapies\(^\text{25}\)

Case Study: Innovative Adaptive Design to Address Immediate Threats

In 2015, in response to the 2014 Ebola outbreak, the National Institutes of Health – in collaboration with other organizations – designed a protocol to investigate Ebola treatments that simultaneously evaluated therapies against a best available control group in an adaptive randomized trial. The shared control group would be adaptively modified to include therapies as they revealed themselves to be effective, and the incremental benefit of the treatments under study would continue to be evaluated. Frequent pre-specified Bayesian analysis would be used to identify winners and eliminate losers as soon as possible. This type of adaptive design attempts to credibly answer research questions as quickly as possible with a control group that adapts to what is learned, thus improving the risk/benefit to subjects assigned to the continuously evolving best available therapy.\(^\text{26}\)

Conclusion

Clinical trials and their design face ethical challenges that shift continuously based on a multitude of factors, including underlying disease, phase of development, current scientific knowledge, available alternative therapies, ability to mask the effects of treatment and potential toxicity of the investigational drug. These challenges may be multiplied in adaptive designs, with added cost and complexity and the potential for reduced statistical power, unclear treatment effect size, Type 1 error inflation and operational bias. However, these challenges can be overcome by thoughtful adaptive design, simultaneously promoting efficiencies and serving the three traditional ethical imperatives of research in human subjects.
Adaptive design plays a critical role in the push towards delivering increased product development efficiency and productivity. According to the 21st Century Cures initiative launched in April 2014, “broader application of adaptive trial designs would be an encouraging step in the right direction.” Due to the ethical obstacles that may be inherent in certain forms of adaptive design, the critical importance of careful design, meticulous planning and rigorous ethical review of adaptive design trials on a case-by-case basis cannot be overemphasized.

About Premier Research
Premier Research is a leading contract research organization serving the needs of biotechnology, pharmaceutical and medical device companies worldwide. The company has a wealth of experience in the execution of global, regional, and local clinical development programs with a special focus on addressing unmet needs in such areas as analgesia, CNS, rare diseases, medical device and diagnostics, and pediatric research. Premier Research operates in 84 countries and employs more than 1,000 professionals, including a strong international network of clinical monitors and project managers, regulatory, data management, statistical, scientific, and medical experts. With its mission to improve productivity in clinical development, the company aligns itself with the mission of its customers to bring new medical treatments to patients promptly, accurately, and cost-effectively.

About Thomas Laage, MD, MPH | Director, Product Development Consulting and Regulatory Medical Writing Support
During his tenure at Premier Research, Dr. Thomas Laage has assisted with protocol development, clinical study report finalization, business development, regulatory strategy, and medical monitoring in a variety of CNS areas, both adult and pediatric. He is a member of the DIA Adaptive Design Scientific Working Group and has co-authored papers in this area.

After residencies and board certification in Internal Medicine and Psychiatry and Neurology, Dr. Laage practiced psychiatry in both in-patient and out-patient settings, holding an appointment as Instructor in Psychiatry at the Harvard Medical School for many years. He completed an MPH in Quantitative Methods at the Harvard School of Public Health in 2011.

Prior to joining Premier Research, he worked as an independent contractor for the consulting firm John Lehmann, LLC in medical writing and safety reporting for clinical trials and as an independent medical writer and editor for Edanz Group Ltd in China and Japan, for CE Outcomes LLC in Birmingham, AL, and for the American Physician Institute in Chicago, IL. He is a member of Phi Beta Kappa, Alpha Omega Alpha, the Massachusetts Medical Society, the Regulatory Affairs Professionals Society, and the Drug Information Association.

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Jennifer Nezzer is responsible for the management of biostatistics team members and for providing technical leadership on the biostatistical aspects of numerous development projects in North America and serving as lead statistician on multiple global programs. Prior to her joining Premier Research four years ago, she supported the biostatistical development of numerous global programs at another CRO for more than five years.

Jennifer has supervised the statistical aspects of Phase I through IV clinical trials from design through analysis and reporting for both traditional and adaptive study designs in a broad range of therapeutic areas including oncology, endocrine/metabolic, infectious/parasitic diseases, CNS, genitourinary, hematology, diseases of the musculoskeletal system and connective tissue, congenital anomalies and mental disorders. She has represented the biostatistics department with interactions with sponsor companies, NDA submissions and represented multiple sponsor in both phone and face to face interactions with regulatory agencies.

Prior to her tenure in the pharmaceutical industry, Jennifer served as a senior biostatistician for Signature Science, LLC for eight years providing statistical support for various quality assurance, field testing and environmental projects. She earned her BA in statistics from Kansas State University, and her MS in statistics from New Mexico State University. She is a member of the American Statistical Association, Phi Beta Kappa and Phi Kappa Phi.
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