

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard Bioethics Collaborative

Thursday, October 17th, 2019 | 10:00am- 3:00pm
Ropes & Gray LLP | 800 Boylston Street, Boston, MA, 02199

Ethical Challenges in Adaptive and Platform Trials Executive Summary

The October 17th, 2019, meeting of the MRCT Center Bioethics Collaborative convened stakeholders from academia, industry, patient advocacy organizations, foundations, and Institutional Review Boards (IRBs) to examine the topic of **Ethical Challenges in Adaptive and Platform Trials**.

Introduction

Adaptive and platform clinical trials are innovative study designs that aim to render research more efficient and ethical but carry their own ethical and practical concerns. **Adaptive designs** modify key features of studies in line with pre-determined criteria on the basis of periodic data analysis. **Platform designs**, which may utilize adaptive elements, test multiple therapies simultaneously with the option to add or drop investigational therapies. While adaptive and platform trial designs may promise greater efficiency and scientific sophistication, they raise questions about foundational research ethics principles of informed consent, clinical equipoise, and justice, in addition to practical challenges. The convened meeting of the Bioethics Collaborative engaged and expanded upon these ethical issues and considered strategies for addressing the theoretical and practical challenges that they raise for investigators, sponsors, IRBs, participants, and other stakeholders.

Meeting Summary

Informed consent is an ethical requirement for research participation. Meeting attendees debated which details of adaptive study design need to be disclosed and explained to research participants to obtain consent that is fully informed. One viewpoint holds that patients do not need to be presented with certain details of adaptive designs, such as the fact that the randomization ratio may change mid-study or arms may be added or dropped, as they are unnecessary for informed consent and may overwhelm and confuse patients. The opposing view holds that research participants should understand adaptive elements of study design, particularly when changes may alter the particular risks and benefits individual participants may experience. An alternative approach could also be considered. Potential participants could be informed that changes may be made during the course of the trial without going into detail about the content of these potential adaptations at the time of initial informed consent. If an adaptive change is going to be implemented during the course of the trial, the details of the change could then be disclosed to

the participant and the participant could be re-consented in light of the new information. This approach may mitigate concerns surrounding withholding information while not inundating participants with unnecessary information from the trial's outset.

Currently, some informed consent documents for platform trials detail the risks and benefits for all of the study's interventions even though an individual participant will only receive one or two interventions. Attendees agreed that the inapplicable information should be removed, and, ideally, the consent document should be tailored to each patient's specific intervention. One attendee described a plan for a two-stage informed consent process for adaptive-platform trials: one consent form at the beginning of the trial that explains the general trial design, and a consent form after the participant is randomized to their specific intervention that explains the benefits and risks, and alternatives, to that particular adaptive intervention.

Clinical equipoise is generally regarded as an ethical requirement for interventional clinical research: there must be genuine uncertainty about which trial intervention is best in order for it to be ethical to randomize participants between or among the alternatives. Attendees considered if this ethical principle is compromised in adaptive trial designs that modify the randomization scheme to favor the "better" arm on the basis of incoming data (e.g. 'play-the-winner' designs) or, alternatively, eliminate an arm that is not faring well. Questions such as how much uncertainty is needed to maintain equipoise and who determines the degree of uncertainty were posed. With regards to maintaining clinical equipoise, it is not clear that changing aspects of design mid-study is any different than updating one's conception of the experimental agent and determining appropriate next steps in between the phases of traditional drug development. It is important to remember that until a trial is completed, there is no determination of 'better' or 'worse' interventions. An interesting opinion was proffered: adaptive and adaptive-platform trials may uphold clinical equipoise more effectively than traditional trial designs by addressing uncertainty more frequently through periodic data analyses. If an adaptive review shows that equipoise is sufficiently disturbed, the trial can be terminated or modified accordingly.

The principle of justice demands fair and equitable treatment for all trial participants. Does an adaptive study design that begins to favor one arm abrogate the principle of justice by letting early participants bear more risk than later participants? Meeting attendees did not find this to be a salient challenge to justice. As long as participants enrolling at the same time bear the same risk, and the informed consent documents are clear about what those risks are, justice is not compromised, even if the risks differ between cohorts. Participants suggested that justice is perhaps more fairly investigated in terms of equal *access* to adaptive and adaptive-platform trials. Adaptive and adaptive-platform trials require greater resources to run and therefore may only be available to people who live near resource-rich research centers. Individuals in other locations may have restricted access to these types of trial. The bridge between ethical considerations and practical implementations was explored through presentations from the designers of several adaptive and adaptive-platform trials, including the Healey Amyotrophic Lateral Sclerosis (ALS) Platform, Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And moLecular Analysis 2 (I-SPY 2), and the Targeted Agent and Profiling Utilization Registry (TAPUR) trials. Review of the features of these and other trials led

attendees to suggest that adaptive and/or platform features are particularly well-suited for certain types of research:

- Research involving rare diseases
- Rapidly progressing diseases
- Disease in which there is low confidence in the standard-of-care (unmet medical need)
- Large drug trial pipeline
- Relatively short and rigorous endpoints
- Therapeutic exploration instead of confirmation

Participants also suggested that efficiency alone is insufficient for implementing adaptive designs in a trial and that adaptive designs do not guarantee increased efficiency. The Healey ALS trial contains several of the elements identified as advantageous for adaptive study design, including a rapidly advancing disease, a surfeit of experimental drugs, and no current effective therapy. Practical recommendations that addressed ethical concerns were discussed by the ALS trial representative. Several concrete examples of design aspects with ethical relevance are listed below:

- Use of a pooled placebo so that the number of participants receiving placebo can be minimized and a majority of participants can receive a potentially active drug, but any intervention can still be compared to placebo for data analysis
 - Pooled placebo example:
 - There are 3 regimens
 - Within a single regimen, participants are randomized to receive intervention to placebo at a 3:1 ratio
 - The placebo data is pooled from each regimen
 - A single regimen is compared to a pooled placebo at a 1:1 ratio
- Choosing investigational therapies that have the same exclusion/inclusion criteria
 - Particularly important and relevant for platform trials of investigational products
- Selecting investigational drugs with similar risks
 - Particularly important and relevant for platform trials of investigational products
- Allowing re-randomization after regimen completion
 - After the trial period is over, the participant may choose to re-enter the trial and be re-randomized to any of the regimens
- Continuing access to the investigational product after trial completion if beneficial to the participant (and working with companies that commit to continued access)
- Creating a support group for patients and caregivers to learn additional information concerning the trial and specific interventions

Attendees also examined the practical challenges of adaptive trials from an IRB perspective. Sponsors and investigators should provide IRBs with clear justification as to why an adaptive or adaptive-platform trial is preferable to a traditional trial design. Participants suggested that central or single IRBs could assist smaller IRBs by reviewing this complex design. Even with

central IRB assistance, educating IRBs on adaptive and platform designs is a time-consuming, but necessary, process. The investigator or a mediator commissioned by the research team should be prepared to invest significant time into helping IRBs understand unfamiliar complex designs. Researchers may be able to ease the approval process by inviting IRB members to a meeting dedicated specifically to understanding the mechanisms of and justifications for adaptive and/or platform designs. One question that remained unanswered was how involved an IRB should be in the decision to close or open an arm of a study or to review planned modifications of randomization schemes. Should the IRB prospectively review each adaptation, or rather be content to approve criteria for changes and decision-processes articulated in the protocol at the time of initial review? How much interaction should the IRB have with independent Data Monitoring Committees (DMCs) or safety committees constituted by the sponsor? How can IRBs ensure that any changes material to participants are reflected in revised consent materials and communicated to participants in a timely way? While individual IRBs may take different approaches to these questions, a basic framework articulating the key issues and decision points may assist IRBs in reviewing complex adaptive and platform trials. Moreover, the research community may be challenged by the vocabulary used to describe complex trial designs. The terms adaptive, platform, basket, umbrella, master protocol, Bayesian, frequentist, are often used incorrectly or interchangeably. A clear and authoritative source for harmonized definitions is needed.

Potential Future Work

To advance and operationalize discussions of adaptive designs in clinical research, the following ideas were suggested as potential next steps:

- Generate an authoritative guide for complex clinical trial design vocabulary
- Create a framework for the factors that render adaptive trial design particularly appropriate to answer the research question
- Characterize the relationship between IRBs and DMCs, creating guidance for communication and the necessary characteristics of DMCs to be trusted intermediaries
- Guidance for researchers to explain adaptive designs in a way that is easily understandable to IRBs and to potential participants
- Explore the impact of non-simultaneous control groups and changes in standard of care over the course of an adaptive trial
- Create guidance for IRBs on the appropriate standards for ICF disclosure in adaptive and platform trials and best practices for prospective review of proposed adaptive changes