



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

Thursday, October 13, 2022 | 2:00 – 4:30 PM EST
Virtual Meeting

**Post-Trial Responsibilities: Continued Access to Investigational Medicines and Devices
Meeting Summary**

Background

In November 2017, the MRCT Center published the *Post-Trial Responsibilities: Continued Access to Investigational Medicines* Guidance Document and Toolkit. This framework outlined a case-based, principled, stakeholder approach to evaluate and guide the ethical responsibilities related to providing continued access to an investigational medicine at the conclusion of a patient’s participation in a clinical trial.¹ The workgroup and guidance document converged on several consensus points:

- “Post-trial access is a shared responsibility of sponsors, researchers, and host country governments;
- The plan for continued access should be determined before the trial begins, and before any individual gives their informed consent;
- The protocol should delineate continued access plans; and
- The plan should be transparent to potential participants and explained during the informed consent process”¹

A complete list of the MRCT Center’s Principles of Post-Trial Responsibilities: Continued Access to Investigational Medicine can be found [here](#).

The 2017 Guidance Document identified the four principles of bioethics – autonomy and respect for persons, beneficence, nonmaleficence, and justice – as central considerations in biomedical research in concert with post-trial responsibility (PTR) duties.^{2,3}

As defined in the MRCT Center Guidance Document, “continued access refers to the sponsor’s provision of continuity of investigational medicine (or comparator), and the needed medical



care and health care infrastructure required to appropriately use the investigational medicine to individual participants at the completion of their participation in a clinical trial or at the conclusion of a clinical trial.”¹

Over the past 5 years since its publication, sponsors and investigators have utilized the MRCT Center guidance to create their own internal PTR policies. While the ethical principles and main consensus points remain valid, the application of the principles and implementation continue to challenge clinical research stakeholders and study participants. It is therefore timely to revisit and update the framework.

The October 13 Bioethics Collaborative’s discussion aimed to help identify and address these ethical challenges and areas for further development. Sarah White, MRCT Center Executive Director, introduced the MRCT Center’s past work on PTR and reviewed the current central issues. Six subject-matter experts provided comments thereafter. Questions from meeting participants and discussions were welcomed at the end of each speaker’s commentary.

Defining Benefit

Studies are only initiated if the benefits or potential benefits of the research outweigh the risks. In addition, a positive risk-benefit analysis is required for continued approval of a trial. For the individual participant, considerations of benefit guide assessments of their needs at the end of a trial. While there is substantial literature discussing risk, the topic of benefit has not been given the same attention.

Certain risks are universally considered unacceptable – for example, injecting hepatitis into children with developmental disabilities to understand natural disease progression.^{4,5} It is more difficult, however, to agree on what constitutes benefit and when the possibility of continued benefit supports continued provision of experimental interventions after the study is complete.

In particular, two different types of benefits are relevant for determining the scope and force of PTR: social and individual. Social benefit consists of the knowledge to be gained from the research and the potential future dissemination of interventions that are shown to be effective. Statistical tools are generally utilized to determine whether a drug, biologic, or device meets a predetermined endpoint or outcome, thus deciding the benefit with some statistical confidence of the result. Individual benefit, by contrast, is the benefit that research participants might experience as a result of being in the study.



In some cases, social and personal benefit align: interventions have shown to be effective at the population (or social) level and also benefit the individuals in the study, and thus, strong reasons exist to support the provision of the drug or device after the trial.

In other cases, however, individuals may experience or perceive personal benefit as a result of participating in studies that do not, in the aggregate, succeed in establishing efficacy. Determining post-trial responsibilities in these situations is far more challenging. What level of certainty regarding an individual participant's benefit is needed to give rise to post-trial obligations? How can benefits for individual participants be quantified, and what is the best way to measure them? Who decides which benefits are important? At what point can it be decided that the benefits of an intervention for an individual outweigh the risks? Should the same metrics be used to measure an individual participant's benefit that are used to assess study-level efficacy?

Expectations and Limitations of Stakeholders

Meeting participants noted that the obligation to provide post-trial access to investigational drugs and devices is highly contextual. Providing continued access is obligatory in some situations and supererogatory in others. Many factors influence the distinction between these two categories. These include the severity of the condition, prognosis, the availability of sufficient quantities of the investigational product (allowing for completion of ongoing clinical trials), availability and suitability of alternative treatments, individual participants' response to the investigational drug or device, and the infrastructure needed to continue administering the intervention, among others.

Several participants referenced policies that refer to the seriousness of a condition as a criterion for deciding about the provision of continued access. Some sponsors will only allow post-trial access to interventions aimed at treating conditions that have been established as serious and/or life-threatening. While FDA has defined "a serious or life-threatening condition" in several guidance documents, the definition is subject to clinical judgment. For instance, 21 CFR 312 Subpart I - Expanded Access to Investigational Drugs for Treatment Use (Sec 312.300 (b)) provides definitions that are applicable only to that subpart:

"Immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

Serious disease or condition means a disease or condition associated with morbidity that has a substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.”⁶

The FDA has used a similar definition in the 2014 Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.⁷

Continued access to oncology drugs, for example, is rarely questioned, since the potential consequence of treatment withdrawal is so serious. Chronic, non-life-threatening conditions can be more controversial: it is often difficult for non-affected individuals—including sponsors and researchers—to appreciate the lived experience and burden that patients face. A meeting participant referenced a case where a participant in a migraine-relief drug trial committed suicide following study completion when continued access to the drug was not provided. This incident underscores how important it is to appreciate the participant’s lived experience.

A number of meeting attendees encouraged the group to consider ethical duties beyond the traditional responsibilities of medical oversight that arise in the course of clinical trials. To what extent do researchers incur an obligation to continue access to investigational products and continuity of care once research protocols end? There is more to trial participation than being given an investigational drug or device and going to appointments. In addition to the time and financial resources required for trial participation, there are important psychological and relational aspects that must be considered, and literature suggests that participants may feel distressed or even have a sense of loss at study closeout. This distress may be amplified when patients are asked to return a provisioned device or transition off a drug that has improved their quality of life.^{8,9} Meeting attendees recognized that meaningful relationships may be developed between participants and research staff over the course of trial participation and emphasized that clinical research is a joint endeavor *with* participants; it is not something done on or to them. Discontinuation of an effective drug or removal of a device can be stressful and potentially impact the quality of life significantly. Consequently, questions need to be asked about whether there is a duty to care (which, in the meeting itself, was termed “non-abandonment”) and to what extent that duty exists.

Participants acknowledged the importance of understanding, before a study is initiated, who will be responsible for providing what, under what conditions, and for how long after the conclusion of a trial. To complicate matters, regulatory requirements regarding post-trial access to investigational drugs and devices differ among different countries and regions. While a few countries require post-trial access to investigational products, in many places there are no formal regulations, though guidance or suggestions may exist. A handful of countries, including Finland and South Africa, have regulations explicitly stating that post-trial access is optional, while others, notably Brazil, have regulations requiring it.^{10,11}

In Brazil, regulations require experimental drugs to be made permanently accessible by the sponsor (or individual/organization responsible for the trial), free of charge to trial participants, when the supervising physician evaluating a participant determines that they have benefitted from an investigational product and that there is no reasonable alternative.^{12,13} But even this is complex. If the product is not approved or its development is discontinued, the sponsor nevertheless remains responsible for manufacturing and providing the product. Furthermore, investigators need to dedicate time and effort to the long-term treatment of participants. Both can be expensive, take away resources from other studies, and, depending on the situation, may not be feasible. Since the regulation expects the investigational product to be provided indefinitely, sponsors may choose not to conduct studies in the country as a way to avoid assuming these burdens. One participant with first-hand experience of these dynamics noted that patients sometimes decline post-trial access in favor of local healthcare providers even if the participant benefits from the investigational drug. Another BC member shared the results of a series of informal conversations that suggested that a low percentage of trial participants in Brazil currently utilize the post-trial access mechanism. The reasons for this are currently unknown but may be related to the burden on both the patient and clinician of continuing an investigational treatment. Of note, Brazil is undertaking legislative actions to reduce the duration of continued access to investigational drugs to 5 years. Work must be done to clarify what obligations exist in which circumstances, and to whom those responsibilities fall.

Devices

Additional issues associated with investigational devices, specifically implantable devices were discussed. Device implantation, even in the most experienced surgical hands, is an invasive procedure that carries risks (e.g., infection, bleeding) related to the procedure. Not all risks are quantifiable, particularly with new devices. The implantation of neural devices is particularly



challenging and fraught with high risks such as permanent loss of function. This surgery can be lengthy and requires that the patient remains awake throughout, adding to the burden of participation.

While most drugs can be discontinued on short notice in response to an adverse event or completion of a trial, explantation requires another surgery with accompanying risks. In cases where the device has stopped providing a benefit, the moral calculus shifts to a focus on non-maleficence, as it must now be determined whether leaving the device in or taking it out carries the greater risk. During or immediately after a study, surgeons are available; with time, surgeons familiar with the device may be scarce.

In addition, devices require maintenance, like replacing or recharging batteries. During a trial, this need is anticipated and taken care of; maintenance is more complicated after a trial ends, even if a post-trial maintenance plan was outlined. Finding a surgeon or qualified clinician may be difficult, and there may be supply issues for parts (e.g., batteries, specialized components). Companies can go out of business, and insurance may deny coverage for care, creating another financial barrier. The planned procedures may change if product development plans change. Any number of unforeseen issues may arise.

Meeting attendees raised an additional issue of whether research participants who receive an investigational implantable device will nevertheless be eligible for future studies. If a new and potentially improved device is developed, participants from earlier studies may not be eligible for the new version due to the presence of their implanted device or even prior surgery. What are the obligations that sponsors and investigators must consider under these circumstances? What are the stakeholder responsibilities and decision points related to continued maintenance or explant of an investigational device? Do sponsors bear special obligations to participants who undertook risks and burdens in early-stage research when better technologies become available?

To the extent possible, logistical challenges should be anticipated and addressed proactively, including specifying who is responsible for maintaining the components, repairing accidental damage, and providing follow-up safety monitoring. Meeting attendees even suggested the creation and impact of an industry-wide standard design for components (e.g., batteries). Would standardization resolve or aggravate issues when technology advances and the standard must be updated or changed?

Transparent Communication

When people are enrolled in a trial, they engage in an informed consent process. Sometimes post-trial access plans have been made and can be discussed at that time; even so, many factors are unknown at enrollment. How the product will perform (e.g., safety, efficacy) in aggregate, and how the individual research participant will respond, can only be appreciated with time and experience. Thus, at the end of a participant's time in the study, further discussion is needed. Researchers should again explain the risks and benefits of continuing to use an investigational product in light of the study data and the response to the investigational product, the participant's condition, and available alternatives if they exist.

Meeting attendees noted that, during protocol development, sponsors may be uncertain of post-trial access to the drug and/or duration of availability. Early-stage companies may not be able to commit to post-trial access in good faith. One meeting participant mentioned how difficult it is to convince protocol development teams to use transparent and clear language, noting the desire to keep the commitment 'flexible' given the wide range of contingencies and deep uncertainties over the future trajectory of product development.

Meeting attendees agreed that research participants will also need support in navigating health systems once the trial ends and the product is approved and available on the market to ensure they have access. If, for any reason, the investigator cannot oversee a participant's care, finding a physician who is able and willing to oversee treatment with an investigational product may be difficult. Finally, access to the product after marketing approval is not guaranteed. What should a patient do if the drug is approved, but their insurance will not cover it or they have no insurance at all? The availability of a product does not mean it is accessible to the people who need it, and that is a general issue in healthcare systems. But do sponsors and investigators have a responsibility to continue to provide medicines and other products simply because insurance (or the national health care system) declines coverage or the individual does not have health insurance? How does one balance the tension of commitment to the research participant (and commitment not to abandon the research participant) and the appropriate transfer of responsibility to the healthcare system?

Conclusion

Post-trial responsibilities arise from foundational bioethical principles: beneficence, nonmaleficence, justice, and non-abandonment. Benefit is a central concept in the evaluation



of the provision of continued access, and understanding how to assess, evaluate, and determine the sufficiency of benefit requires further discussion. Understanding the limits of post-trial responsibilities assumed by sponsors and researchers, especially in light of the complexity and costs of these efforts requires multi-stakeholder consideration. Throughout, the participant's perspective must be kept in mind and the patient voice included in this work.

The October 13, 2022 meeting of the Bioethics Collaborative served as a launch for revisiting the MRCT Center's 2017 Guidance Document. The Center plans to initiate monthly task force meetings starting in January 2023 through the Fall of 2023 to (1) define the current issues associated with continued access to investigational drugs and maintenance of implantable devices after trial completion and (2) identify practical and actionable resources and tools needed by stakeholders.

Revisiting the PTR framework provides the opportunity to advance harmonized guidance and practice to our clinical research stakeholders, including industry, government, academia, and patients/participants. In addition, advocating for acceptable standards through wide dissemination can help standardize industry practice and government expectations.

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