MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Principles of Post-Trial Continued Access to an Investigational Product

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The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) Post-Trial Responsibilities: Continued Access to an Investigational Product outlines a principled and practical approach to identify the ethical responsibilities that can, in turn, guide action to provide continued access to an investigational product at the conclusion of a patient's participation in a clinical trial. The foundation of the MRCT Center's work is grounded in 12 principles. The principles, accompanied by an analysis, should be read as a whole.

In the context of the work the MRCT Center defines **continued access** as the continued provision of the investigational medicine[1] or continued maintenance of the significant risk (SR) implanted device for any clinical trial participant after participation in the trial. Some investigational interventions may require specific supportive care that the sponsor, researcher, healthcare systems, or host country governments should consider.

1. Research participants deserve consideration of continued access to an investigational product to which they receive benefit.

Research participants are exposed to the risks and inconveniences inherent in clinical trials to potentially benefit themselves, future patients, the sponsor,[2] and society as scientific knowledge advances. Research participants deserve consideration of continued access based on the following three ethical principles: (1) Following the reasoning of justice as reciprocity, research participants deserve consideration of continued access to a beneficial investigational product in return for their contributions. (2) The ethical principle of non-maleficence supports continued access if withdrawing an investigational product or not offering maintenance of a device at the end of a trial would cause known participant harm or long-term complications. (3) While research does not guarantee benefit to a participant, the principle of beneficence supports the consideration of continued access if the participant is benefiting from the intervention.

References:

- *PTR Guidance document, excerpt from section 3.3.2 Non-Maleficence*
- *PTR Guidance document, excerpt from section 3.3.4 Justice, Justice as Reciprocity*

[1] Continued access applies to medicines that are drugs or biologics and excludes vaccines.
[2] The use of the term "sponsor" in this document refers to both sponsors and sponsor-investigators.

2. The responsibilities of post-trial continued access of an investigational product to a trial participant (patient) after completion of a clinical trial are shared among the sponsor, investigator, site, healthcare provider, healthcare system, and the participant.

The responsibilities to provide continued access to an investigational product at the end of trial participation, including provision to the medicine or maintenance of the device, medical care, and infrastructure, are context-dependent and may shift depending on the trial phase, the underlying and current illness(es), local regulatory landscape, product development path, and the local healthcare system. For example, during clinical trials and before regulatory approval, the sponsor and investigators bear the responsibility to provide continued access to the product as well as medical infrastructure and care (e.g., administration of the investigational product, safety monitoring, equipment replacement). After regulatory approval, the responsibilities should transition to the government, payors, and healthcare providers. Complexities may exist that may complicate the transition into the healthcare system. Ideally, these responsibilities should be understood by and aligned among all involved parties, including participants, at the beginning of the trial to reduce potential problems and misunderstandings at the end of the trial.

References:

- *PTR Guidance Document, Excerpt from Section 4.2.4*
- *PTR Toolkit, Table 2: Responsibility Grid by Stage and Role*
- *PTR Toolkit, Table 3: Scenarios for Continued Access to Investigational Medicine*
- *World Medical Association. (2024). WMA Declaration of Helsinki: Ethical principles for medical research involving human subjects. Retrieved from* https://www.wma.net/policies-post/wma-declaration-of-helsinki/

3. Provision of continued access is a bounded and limited responsibility of any one involved party.

The responsibility to provide continued access to an investigational product is a bounded and limited responsibility for the following reasons:

- Resources (including financial, human, product, and infrastructure) to provide such access are never limitless.
- Those who hold resources must be good stewards of those resources and take into consideration whether providing continued access to some may inadvertently disadvantage or harm others, either directly or indirectly.
- Different involved parties serve different roles and have different functional and societal obligations and, therefore, should and will assume different responsibilities.
- Medical providers have fiduciary responsibilities to the individual trial participants.

There is no requirement to provide continued access indefinitely unless required under local laws. Each decision is based on assessing the absence or presence of relevant factors and should last as long as the reasons that justify the duty persist, and the participant benefits from and consents to continue treatment.

References:

- *PTR Guidance Document, Excerpt from Section 4.1*
- *PTR Guidance Document, Excerpt from Section 4.3.2 Access to the Investigational Medicine, Responsibilities over the time course of a clinical trial*
- *Section 4.3.3.1: Access to Accompanying Medical Care, Distributed Responsibilities*
- *Section 4.3.4.2: Access to Required Infrastructure, Duration of Responsibilities*

4. **The decision to provide continued access to the investigational product should be based on objective criteria and not be influenced by whether the sponsor is a for-profit, not-for-profit, governmental agency, or sponsor-investigator and whether the trial is conducted in a well- or low-resourced setting.**

   The sponsor organization and sponsor-investigators should establish a policy using the interdependent criteria to assess and make decisions about continued access, including the severity of the disease being studied, the impact of discounting the medicine or impact/risk of removing the device, medical need, availability of alternative therapies, research viability, and the benefit/risk assessment. Because continued access can impact the supply of the investigational product, the unique hardware and software associated with the device, and/or may require local support to implement (e.g., cooperation of health authorities, local officials, and other health services), sponsors should consider continued access issues as early as possible in the product development and before a trial begins. The sponsor should routinely revisit considerations of continued access based on evolving data and/or patient response and notify participants if there are any changes to what was initially stated in the informed consent process. Investigator-initiated trials should also consider continued access in advance and determine upfront how potential requests will be addressed.

   References:

   - *PTR Guidance Document, Excerpt from Section 3.3.4*
   - *Excerpt from Section 4.3.1*

5. **Provision of continued access must not inadvertently advantage some and harm others.**

   Continued access decisions should be consistent, fair, based on transparent reasoning, and follow a rigorous assessment to understand the landscape throughout the life cycle of a trial. An equitable plan for implementation of continued access to all similarly situated patients should be created. Sponsors should ensure equitable implementation based on the assessment of transparent criteria at the population level (e.g., medical need, risk of harm if access is discontinued, available alternatives in the country, country requirements, etc.).

References:

- *PTR Guidance Document, Excerpt from 3.3.4*

6. The plan to offer or not to offer continued access to an investigational product should be determined before a trial begins and appropriately communicated to investigators, ethics committees, and participants.

A plan should be developed in advance of the initiation of the clinical trial to determine the circumstances and conditions for which continued access will be considered, including established criteria for the transition of a patient to another therapeutic alternative if available. At the end of trial participation, the investigator should assess the experienced benefit during the trial and the potential risks of removing the product. All participants should know, in advance, what to expect and have the ability to make informed decisions about their healthcare. Knowing what is to be expected in terms of access to the investigational product after the trial allows participants to make an informed decision and demonstrates the ethical principle of respect for persons.

Criteria under which the investigational product will be made available or maintained are likely based on evolving data, participant response (e.g., efficacy, safety, tolerability), available alternatives, and marketing status. Should the product prove helpful for some patients, then research teams should be aware of regional regulations, how long the product will be provided, and how participants will be transitioned to the country's healthcare system to continue the product or to an alternative treatment at the end of sponsor-supported continued access. Evolving data, as they are relevant to the decisions to provide continued access, should be continuously communicated to the investigator and participant throughout the trial.

During the period between completion of clinical trials and a regulatory decision ("Bridging the Gap"), there should be a legally compliant path to provide the medicine to the participant or provide maintenance for the device and care for the participant after the clinical trial. Local legal pathways may include open-label trial extensions, rollover studies, protocol amendments, or separate clinical trial protocols. In most settings, the sponsor will continue to collect data in the continued access period.

Continued access requires significant planning and resources; having a plan before a trial begins helps identify downstream barriers and challenges. New information may become available (e.g., adverse events) that could impact continued access plans. In addition to receiving new information, the sponsor should define, and the protocol should clarify, the time duration for routine review and assessment of the continued access plan (e.g., annual assessment). Modifications to the continued access plan should be updated in the protocol and informed consent documents throughout the trial lifecycle and communicated to all parties.

There may be reasons not to offer continued access (i.e., investigational product is in very early stages of development, available alternative therapies, availability in the marketplace, seriousness of the disease under study), but the decision about whether or not to offer, should some participants benefit, should be made and documented before

the trial begins and communicated clearly in the protocol and the informed consent document.

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References:

- *CIOMS*
- *World Medical Association. (2013). WMA Declaration of Helsinki: Ethical principles for medical research involving human subjects. Retrieved from https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/*
- *PTR Guidance Document, Excerpt from Section 4.2.1 Stages of Continued Access to an Investigational Medicine, Stage 1: Study Planning*
- *PTR Guidance Document, Excerpt from Section 4.3.1 Planning Stage of a Clinical Trial*

7. In settings of unmet medical need, individual participants should be evaluated for continued access, particularly if there is evidence of benefit exceeding risk in the trial population.

The sponsor is responsible for determining if continued access to an investigational product will be made available for the trial population as well as the mechanism for supplying the continued access. An organizational policy and objective criteria should be developed to make consistent determinations. Decisions regarding the provision of continued access to a participant are made on a case-by-case basis, influenced by the patient's clinical condition, the benefit/risk assessment and response to the intervention, what is known about the investigational product at the time of the decision, and availability of an alternative treatment.

The investigator is responsible for evaluating, determining, and communicating (to the participant and sponsor) whether the individual's benefit/risk assessment warrants continued access to the intervention(s) received during the trial in accordance with research program. Participants should also be aware of the trial program and individual criteria that the research team is using to determine their eligibility for continued access, and decisions should be clearly communicated to them.

There may be instances when the individual has benefited, but the trial population has not. If trial data suggest benefit data are unfavorable, but individual participants have benefited, continued access must be evaluated on a case-by-case basis, according to organizational policy.

References:

- *PTR Guidance Document, Sections 4.2.2, Paradigm for Framework, Stage 3: Decision Point 1*
- *PTR Guidance Document, Excerpt from section 4.3.2 Access to the Investigational Medicine*
- *PTR Guidance Document, Excerpt from section 4.3.2.2, Responsibilities of Sponsors After the Trial Results are Analyzed and Known*

- *PTR Guidance Document, Excerpt from section 3.3.2, Non-Maleficence*
- *PTR Toolkit, Table 1: Criteria and Rationales for Continued Access to Investigational Medicine*

8. The informed consent document should include language related to continued access to the investigational product.

To the extent possible, the informed consent form should define under what conditions the participant may or may not receive continued access to the investigational product at the end of their participation in the trial. Additional information regarding for what costs they may be responsible (e.g., cost of surgery to replace battery or cost of blood tests to assess blood test of efficacy of drug) and the risks that the participant may incur with continued access (e.g., long-term safety data, risks of having the implant in the body long term.

References:

- *PTR Guidance Document, Excerpt from section 4.3.1 Planning Stage of a Clinical Trial: Informed Consent Document and Process*

9. If continued access to an investigational product is offered, medical care, infrastructure, and long-term maintenance specifically necessary for the appropriate provision of the investigational product should be considered.

The provision or maintenance of an investigational product alone can be futile or even risky for participants when accompanying medical care is necessary but not available. The availability of medical care necessary for the continued administration or maintenance of the investigational product is an important factor to consider when planning for continued access. The duration of medical care should be concordant with the provision or maintenance of continued access to the investigational product. While sponsors generally develop the continued access plan, it is equally important for investigators to ensure they have the infrastructure to support the continued access plans.

For the safe provision of an investigational product, it is often necessary to make investments in local infrastructure. In addition, capital investment is sometimes necessary to provide medical equipment necessary for trial procedures, laboratory equipment for data or biospecimen acquisition, equipment (hardware/software), and equipment to maintain the physical and chemical properties of the medicine (e.g., cold storage facilities and cold chain transport from distribution location to local site). Many of these needs will be provided for the primary clinical trial. Sponsors and clinical sites should consider, plan, and negotiate proper arrangements and define roles and responsibilities for the duration of post-trial continued access and maintenance phase.

References:

- *PTR Guidance Document, Excerpt from section 4.2.3, Criteria for Providing Medical Care and Infrastructure*
- *PTR Guidance Document, Excerpt from 4.3.3, Access to Accompanying Medical*

Care

- *PTR Guidance Document, Excerpt from section 4.3.4, Access to Required Infrastructure*
- *Section 4.3.3.1: Access to Accompanying Medical Care, Distributed Responsibilities*
- *Section 4.3.4.2: Access to Required Infrastructure, Who is Responsible*
- *Toolkit, Table 4: Scenarios for Continued Access to Medical Care*
- *Toolkit, Tale 5: Scenarios for Continued Access to Infrastructure*

10. Continued access to an investigational product should always be provided under mechanisms that satisfy local regulatory requirements for investigational products.

For each trial, decisions regarding continued access must comply with laws and regulations in the countries in which they occur. Thus, an analysis of the local legal and regulatory requirements, balanced by the ethical obligations to provide continued access should be made prior to finalizing the choice of the site and before the initiation of the trial in a specific region or country.

References:

- *PTR Guidance Document, Excerpt from section 4.3.1, Planning Stage of a Clinical Trial*
- *PTR Guidance Document, Excerpt from section 4.3.2, Access to the Investigational Medicine*
- *PTR Guidance Document, Excerpt from section 4.4.1, National Laws and Regulations*

11. The sponsor is responsible for continuously assessing whether there is an ongoing unmet medical need for the investigational product during the clinical trial and product development program.

During the course of the clinical trial, other treatments, therapies, or interventions may become available that modify or eliminate the ethical justification to provide continued access. The trial sponsor is responsible for ongoing monitoring throughout the clinical trial and the overall product development program to assess whether an unmet medical need persists and justifies the plans for continued access to the investigational product. If alternative treatments are available, the trial sponsor should discuss with the investigator whether the new treatment would be appropriate for their individual patient(s). The investigator is ultimately responsible for determining if the newly available treatments are appropriate for the individual patient given the specific medical situation. Even if new treatments become available, patients for whom the alternative treatment is not appropriate may exist.

References:

- *PTR Guidance Document, Excerpt from Paradigm for the Framework, Decision Stages of Continued Access, Stage 2: Monitoring of available*

alternatives

- *PTR Guidance Document, Excerpt from 4.2.1, Stages of Continued Access to an Investigational Medicine*
- *PTR Guidance Document, Section 4.2.2 Criteria for Continued Access to an Investigational Medicine*

12. For the health and safety of an individual participant, the responsible transition from the investigational product to other appropriate care and treatment may be, and is often, necessary. The responsible transition of the participant to the marketed product following regulatory approval should also be anticipated and planned.

The responsibilities of the sponsor, investigator, and participant extend through the analysis of the data, determination of benefit/risk of the trial population, and regulatory submission, approval, and commercial availability of a product.

The conditions of transition from the investigational product to alternative treatment or the marketed product should be communicated to all sites, investigators, and relevant involved parties as required by law. The responsibility of the sponsor is not of indefinite duration but changes after regulatory authority approval. The conditions of continued access and/or transition to appropriate care should be clearly stated in the informed consent document.

If the participant will not continue to receive access to the investigational product (via either long-term extension trial or other mechanism), the investigator is responsible for transitioning the participant to a medical provider and responsibly terminating the relationship, as appropriate.

In each country, when an investigational medicine (1) receives regulatory approval for the indication under study, and (2) is commercially available in that country, the sponsor's responsibility for providing the product to former trial participants attenuates and, after a reasonable amount of time to ensure transition, ends. Sponsors should utilize available and historical data to objectively determine what a reasonable amount of time is (e.g., data related to length of time for National Health Authority decisions, Health Technology Assessment decisions, etc.).

References:

- *PTR Guidance Document, 4.3.2.1 Responsibilities of Investigators in pending regulatory review.*
- *PTR Guidance Document, 4.3.2.2 Responsibilities of Sponsors After the Trial Results are Analyzed and Known*
- *PTR Guidance Document, 4.3.3 Access to Accompanying Medical Care*
- *PTR Guidance Document, 4.3.4 Access to Required Infrastructure*