An EC/IRB Guide for Understanding Post-Trial Continued Access

Purpose:
Paragraph 34 of the Declaration of Helsinki (2024)[1] tasks ethics committees with approving exceptions to post-trial provisions of a clinical trial. This document aims to help ethics committee members understand what post-trial access is, why it may be offered, and when it is appropriate not to offer it.

The Role of Ethics Committees in Post-trial Access to an Intervention

Amendments to the Declaration of Helsinki (DoH) in October 2024 by the 75th WMA General Assembly have resulted in changes to Paragraph 34:

> ### Post-Trial Provisions
> 34. In advance of a clinical trial, post-trial provisions must be arranged by sponsors and researchers to be provided by themselves, healthcare systems, or governments for all participants who still need an intervention identified as beneficial and reasonably safe in the trial. **Exceptions to this requirement must be approved by a research ethics committee.** Specific information about post-trial provisions must be disclosed to participants as part of informed consent. *(emphasis added)*

MRCT Center's Resources:

In 2022, the MRCT Center convened the Post-Trial Responsibilities: Continued Access to Investigational Products Task Force to update and add to the original resources released by the MRCT Center in 2017. Implementation and use of this guidance for over 5 years confirmed that the ethical principles and main consensus points remained valid over time. However, additional work was needed to advise on certain practical applications. The MRCT Center updated tools and resources in response to those identified needs.

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[1] 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/

The MRCT Center defines **post-trial continued access to investigational products** as:

> The continued provision of the investigational medicine or continued maintenance of the investigational significant risk device for any clinical trial participant after participation in the trial. Some investigational interventions may require unique supportive care that should be considered by the sponsor, researcher, healthcare systems, or host country governments. Post-trial, continued access is a shared responsibility and should be determined before the trial begins.

Resources created by the MRCT Center and the task force are intended to assist ethics committees in determining whether post-trial provisions are necessary for clinical trials that they review.

Principles of Post-Trial Continued Access to an Investigational Product

The foundation of the MRCT Center's work in Post-Trial Responsibilities: Continued Access to an Investigational Product is grounded in 12 principles:

1. Research participants deserve consideration of continued access to a beneficial investigational product.
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 all stakeholders: sponsor, investigator, site, healthcare provider, healthcare system, and the participant.
3. Provision of continued access is a bounded and limited responsibility of any one stakeholder.
4. The responsibility to provide continued access to the investigational product is generally not 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.
5. Provision of continued access must not inadvertently advantage some and harm others.
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.
7. If there is evidence of benefit exceeding risk in the trial population, and importantly in settings of unmet medical need, individual participants should be evaluated for continued access.

8. Generally, the informed consent document should include language related to continued access to the investigational product.
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.
10. Continued access to an investigational product should always be provided under mechanisms that satisfy local regulatory requirements for investigational products.
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.
12. For the health and safety of an individual participant, responsible transition from the investigational product to other appropriate care 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.

These principles are accompanied by an analysis that should be read and considered in its entirety. Ethics committee members should familiarize themselves with this introductory document to prepare for their new responsibilities enumerated in the Declaration of Helsinki.

Interdependent Criteria

The ethics committees can utilize the MRCT Center's interdependent criteria to inform impartial decisions about the provision of continued access at both a Study Program and Individual Participant level.

Program Level:

- Impact of discontinuation: The disease or condition under study is serious or life-threatening, and the research participant could be adversely impacted if access to the product were discontinued.
- Medical need: The investigational product addresses an unmet medical need in that no suitable therapeutic alternatives are available.
- No Access/Not Accessible: A physician cannot yet prescribe the product for the condition being studied.
- Research viability: The provision of continued access to the investigational product will not affect the viability of the research or the ability to complete the trial or other trials.
- Benefit/risk assessment: A positive overall study population benefit/risk assessment based on data analysis from first interpretable results or full study results.

Individual Participant Level:
In addition, the following criteria should be considered at completion of the trial:

- The eligible participant has completed the clinical trial protocol as intended.
- There is demonstrable evidence of benefit exceeding risk for an individual participant as determined by the investigator, in discussion with the participant and informed by the participant.

Understanding the criteria and how they apply to clinical trials can help ethics committees evaluate which clinical trials may need post-trial provisions.

Additional Resources

The Post-trial, Continued Access Responsibilities to Investigational Medicines Framework contains helpful questions ethics committees may want to use to help sponsors with questions about whether their trial needs post-trial access. For example, ethics committee members can ask sponsors to address:

1. Does the research trial, in principle, meet the criteria for continued access given the disease/condition under study?
2. Are there are alternatives to the investigational product already available on the market in the region where the trial will be conducted?
3. Has the study team included post-trial access in their budget and funding plan?
4. Does the informed consent document explain, in plain language, the post-trial continued access plan, including the ongoing risks, benefits, and medical care needs after the trial ends?

Ethics committee members can find additional actionable and practical tools for post-trial continued access on the MRCT Center's Post Trial Responsibilities: Continued Access webpage.