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

Post-trial, Continued Access Responsibilities to Investigational Medicines Framework: Scenarios that require further consideration.

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Background: In the context of the work, the MRCT Center defines **continued access** as the continued provision of the investigational medicine or continued maintenance of the investigational significant risk (SR) implanted device for any clinical trial participant after participation in the trial. Continued access applies to medicines that are drugs or biologics and excludes vaccines. Some investigational interventions may require specific supportive care that the sponsor, researcher, healthcare systems, or host country governments should consider. Post-trial, continued access is a shared responsibility among sponsors, researchers, and host country governments and should be determined before the trial begins, and before any individual gives their informed consent.

Challenge: Sponsors and Researchers generally agree upon the criteria used to determine post-trial, continued access, the regulatory milestones, and the pathways used to provide continued access to an investigational medicine. The timing between a pivotal trial of an investigational product and its regulatory approval is variable, as is the timing of commercial milestones such as market availability and reimbursement. It is in these windows that decisions about the provision of continued access must be made. There are, however, complex decisions that require further analysis.

The goal of the Framework of Responsibility is to develop a list of considerations that organizations can utilize to make equitable and fair decisions related to continued access to an investigational product. This framework was designed for sponsors and researchers developing investigational products and can be utilized to develop policy or guidance. Please note, that a framework to address considerations that sponsors and researchers can utilize related to *investigational significant-risk implanted devices* can be found here. This framework was developed based on the foundational work[1,2] of the 2017 MRCT Center Post-Trial Responsibilities Workgroup and has been expanded to clarify the current challenges related to post-trial access.

[1] MRCT Center. Post-Trial Responsibilities: Continued Access to an Investigational Medicine: Principles, Interdependent Criteria and Stages of Continued Access. November 2017. https://mrctcenter.org/wp-content/uploads/2023/04/ 2017-11-27-Post-Trial-Responsibilities-Principles-Nov-2017-1_updated-25-3-23.pdf.
[2] MRCT Center. Post-Trial Responsibilities: Continued Access to an Investigational Medicine: Guidance Document. November 2017. https://mrctcenter.org/wp-content/uploads/2023/04/2017-12-07-Post-Trial-Responsibilities-Toolkit-Version-1.1_updated_25-07-01.

Milestones Overview:

(1) Study planning
(2) Ongoing clinical trials
(3) Bridging the gap while awaiting a regulatory decision
(4) Transition I: The investigational product is not approved
(5) Transition II: The regulatory authority approves the investigational product

Milestone 1: Study Planning

The sponsor[3] is responsible for planning before the trial begins. The sponsor should evaluate whether the research trial, in principle, may meet the criteria for continued access given the disease/condition under study, the availability of alternatives, and the investigational product. If so, in discussion with relevant stakeholders, the sponsor should develop a plan, including establishing criteria for when a participant should be transitioned to another pathway of access for continued access or to alternatives. The national legislation/ regulation and local healthcare capabilities should be considered to evaluate continued access in the relevant country in planning multinational clinical trials.

The sponsor should apply interdependent criteria to determine whether continued access will be offered to study participants.

The MRCT Center has defined a set of **interdependent criteria**[4] related to the study program that may lead to continued access. Criteria may include, but are not limited to:

- 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.

[3] The use of the term "sponsor" in this document refers to both sponsors and sponsor-investigators.
[4] MRCT Center. Principles of Post-Trial Responsibilities: Continued Access to an Investigational Medicine, Stages of Continued Access: Stage 1 Study Planning. November 2017. https://mrctcenter.org/wp-content/uploads/2023/04/2017-11-27-Post-Trial-Responsibilities-Principles-Nov-2017-1_updated-25-3-23.pdf

Framework questions and considerations:

- Does the research trial and product meet the organization's interdependent criteria for continued access?
- Do any countries in the planned trial have specific national laws/ regulations regarding continued access that must be considered?
- What pathways for continued access[5] are allowed in the countries where the clinical research study is planned? Would an extension trial or roll-over trial provide a legal pathway for access to investigational products? Could a managed access approach be used? If not, what other pathways are available?
- The informed consent document should explain, in plain and simple language, the post-trial continued access plans, including the ongoing risks, benefits and what research-related care needs they will have after the trial ends (not just whether participants will get to keep the implanted device and what care is supported).
- The study team should plan for the budget, resources, and product manufacturing capacity that will be required if continued access may be provided.
- An equitable rollout of continued access to all similarly situated participants should be planned.

Specific Scenario	**Framework questions and considerations**
Combination (co-administered) drugs for a new indication: Two different drugs may be used in combination (co-administered) to study a new indication as a combination treatment. The trial sponsor may use an investigational product (IP) and a marketed product (non-IP). The marketed product may be from a different sponsor.	• Will post-trial, continued access be considered for the investigational (IP) product only, or the combination treatment (IP + non-IP)? • Is the marketed product (non-IP) reimbursed in the countries where the trial is being conducted? If not, will the trial sponsor compensate the patient for the cost of this non-IP product until the combination treatment regimen is approved? Is commercial procurement or another indirect reimbursement pathway possible?

[5] Accessible in this case means a physician can prescribe the product in the country (the product is 'on the shelf')

Milestone 2: Ongoing clinical trials

The sponsor is responsible for ongoing monitoring throughout the course of the clinical study and drug development program to assess whether there is still an unmet medical need that requires continued access to the investigational product. Alternative products that modify or eliminate the ethical justification to provide continued access may become available. Regulatory requirements or organizational positions on access and/or reimbursement may change.

Interdependent criteria considered at Study Planning continue to be relevant and should be considered.

In addition, the following criteria should be considered:

- 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 accumulating data at a population level.

Framework questions and considerations:

- Does the individual participant meet the organization's criteria for continued access?
  - The sponsor should provide continued access through the pre-established pathway (e.g., extension trial), in line with company policy, and consistent with the commitment in the protocol, ICF, and local laws/regulations.
- The sponsor should continue to monitor whether (1) reasonable alternatives become available, and (2) if the participant is receiving benefit.
- If, during the ongoing trial, a company's intent to launch in a specific region changes due to previously specified criteria, the responsibilities to participants in these regions still exist, and companies must have a pre-determined/planned way to fulfill their responsibilities (also, please see below Stage 4, Product development is discontinued due to business decision)

Milestone 3: Bridging the gap while awaiting regulatory decision or completion of other clinical trials

After data analysis, the sponsor evaluates whether the benefit/risk assessment for the overall study population warrants ongoing continued access to the intervention. In other cases, safety concerns, lack of efficacy, or the emergence of other alternatives may warrant reconsidering the initial decision to provide continued access.

Specific Scenario	Framework questions and considerations
Clinical trials for the investigational product are complete. The product is not yet approved by the regulatory authority.	• The sponsor should provide continued access through the pre-established pathway (e.g., extension trial), in line with company policy, and consistent with the commitment in the protocol, ICF, and local laws/regulations. • If alternative treatments are or become commercially available, participants may be expected to transition to the alternative product unless there is a concern that the research participant could be adversely impacted by switching treatments or the health care professional (HCP) feels that the alternative treatment(s) would not be appropriate given the participant's medical circumstances. • The participant should be informed about expectations that the product will be approved at some point and the continued access will be temporary to bridge the gap between the end of the clinical trial and market approval • The sponsor should continue to monitor whether (1) reasonable alternatives become available, and (2) participant continues to receive benefit (via the health care professional's assessment)?
Planning for legacy programs: Planning for legacy programs or products acquired from other companies should be considered.	• If possible, an understanding of continued access commitments should be identified in the feasibility stage of acquiring a company. If no previous commitment was made, continued access for acquired products should adhere to organizational policy already in place. The organization should not abandon a promise of continued access to a patient that was already made, if able.

Milestone 4: Transition I - The investigational product is <u>not</u> approved.

The responsibility of the sponsor is not of indefinite duration but changes after the regulatory authority has rendered an opinion. Sponsors have an obligation to respect local regulatory authority decisions. Rare exceptions may be made.

Framework questions and considerations common to efficacy or safety decisions:

- Given Health Regulatory Authority (HRA) decision, does the sponsor feel ethically obligated to provide continued access?
- Is an alternative therapy available?
- Can the participant be safely transitioned to the local healthcare system?
- If the investigational product is not approved, will the local HRA permit continued access? This will be assessed in each country.
    - If the benefit-risk assessment supports continuation and no alternative treatments are available or available therapies have failed the patients, and the HRA would allow, continued access should be made available if supply exists or can reasonably be provided.
    - Determine what pathways are allowed in the country (or in the specific situation) for continued access. Would a clinical trial be required, or could a managed access or expanded access approach be used?
- Is a surplus supply available, would additional manufacturing be required? Would stability testing be required to extend shelf-life? If additional manufacturing would be required, how long a commitment is reasonable for a product that will never be commercialized?
- Consider the need for post-trial continued access of the product for the patient verses the potential impact on other development activities that could ultimately benefit a greater number of patients. If there is already surplus supply, post-trial continued access could make more sense than in a situation where additional supply would need to be manufactured, especially depending on complexity and resources required to do so.
- Would post-trial, continued access in this setting impact other development activities including budget, resources, and/or manufacturing capacity?
- The sponsor should provide clear communication about the length of time and other parameters of post-trial, continued access commitment to HCP and require the HCP to communicate with the patient (e.g., set forth that commitment is limited to product availability, but not thereafter.)
- If the participant receives continued access, the sponsor should periodically assess whether the participant is continuing to receive benefit and whether there are reasonable alternatives appearing on the market.

Specific Scenario	**Framework questions and considerations** (*in addition to common considerations above)***:**
The sponsor discontinues the investigational product due to **insufficient evidence of efficacy.**	• Even if group results are negative, if an individual patient is responding, no alternatives are available, and the HCP feels the benefit-risk assessment justifies the continued treatment, the sponsor should consider whether continued treatment is possible with existing supply with or without extending product expiry and whether there is a willingness to continue manufacturing.
The manufacturer/sponsor discontinues the product development due to **safety issues.**	• Consider the significance of the safety issues: do the safety issues identified at the population level alter the benefit-risk assessment so that providing treatment would not or no longer be medically safe or appropriate? o Safety issues would typically be considered a reasonable justification for stopping continued treatment at the population level. Organizations may choose to consider limited scenarios where there are no alternatives options and stopping treatment would clearly be more harmful to the patient than the potential safety risks.
Product development is discontinued due to **business decision**	• Sponsor may be more inclined to provide continued access, depending on the specific drivers of the business decision (i.e., if stopping for reasons other than safety concerns or lack of efficacy) and supply. o What drove the business decision? Is it because there are other reasonable alternatives? Is the product approved for anything else? Is it because physicians are not using the product as expected? o
Marketing application rejected for **2nd indication**; Product is approved for 1st indication.	• The sponsor would generally not provide continued access in this scenario. • Organizations may choose to consider limited scenarios of post-trial continued access where there are no alternatives options and stopping treatment would clearly be harmful to the patient.

Milestone 5: Transition II - Investigational product is approved by regulatory authority

The responsibility of the sponsor is not of indefinite duration but changes after the regulatory authority has rendered an opinion, at which time healthcare systems and host country governments take on more responsibility. In general, in each country, when an investigational product (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 participants attenuates and, after a reasonable amount of time to ensure transition, ends. The local healthcare system and host country government should be responsible for ensuring access to the approved product. In some circumstances, alternate scenarios may arise.

Specific Scenario	**Framework questions and considerations** (*in addition to common considerations above)***:**
The product is not affordable[6] to the patient.	• The sponsor needs to determine at what point they are no longer ethically obligated to continue access to trial participants. For instance, a company may determine that they have made a credible effort to make the product accessible[7] to participants, including providing continued access pre-approval, obtaining marketing approval and availability as clinical supply, and setting up patient support programs. They may decide that if a product is accessible, they no longer have an obligation to provide continued access. The obligation shifts to the local healthcare system.
Heath Technology Assessment (HTA) decision has not yet been made.	• Using accumulated previous data related to time for HTA decision, consider a duration of time for an HTA reimbursement decision. Provide post-trial continued access during that period of time.
Investigational product is not approved for reimbursement.	• Does the sponsor intend to commercialize the product even if not reimbursed? • Has the sponsor considered other legal pathways for access even if not reimbursed? *(Also, see considerations for 'The product is not affordable to the patient')*

[6] Not affordable in this case means a patient cannot afford to pay for the product and usually assumes some/all insurance coverage or reimbursement is insufficient to maintain access.
[7] Accessible in this case means a physician can prescribe the product in the country (the product is 'on the shelf')