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

Post-trial, Continued Access Responsibilities to Investigational Significant-Risk Device 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) device for any clinical trial participant after participation in the trial. This document uses the U.S. FDA's definition for significant risk:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; **OR**
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.[1]

Please defer to local regulatory guidance for specific interpretations in your region.

Some investigational interventions may require persistent usage, specific supportive care and/or maintenance that the sponsor, researcher, healthcare systems, or host country governments should consider. Continued access is a shared responsibility among sponsors, researchers, healthcare systems, 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 maintenance of an investigational SR device, as well as the clinical care that is needed to ensure the device is working properly. The timing between a pivotal trial of an

[1] U.S. Department of Health and Human Services Food and Drug Administration Center for Devices and Radiological Health (CDRH). *Information Sheet Guidance for Irbs, Clinical Investigators, and Sponsors Significant Risk and Nonsignificant Risk Medical Device Studies*.; 2006. https://www.fda.gov/media/75459/download

investigational SR device 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. These are, however, complex decisions that require further analysis.

The goal of the Framework of Responsibility is to develop a list of considerations that sponsors and researchers can utilize to make equitable and fair decisions related to continued access to an investigational SR device. This framework was designed for sponsors and researchers developing investigational SR devices and can be utilized to develop policy or guidance. Each device may generate unique challenges and should be considered as it relates to the specific use of the specific device. Please note, that a framework to address considerations that sponsors and researchers can utilize related to *investigational medicines* can be found here.

We welcome any user feedback for this Framework. If you would like to send comments, please email us at mrct@bwh.harvard.edu.

Milestones Overview

The MRCT Center outlines 5 milestones related to post-trial, continued access, and the specific scenarios under each milestone that require further considerations regarding continued access to the investigatyional SR device.

(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[2] 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 receive continued access and how that will be achieved. The national legislation/regulation and local healthcare capabilities should be considered to evaluate continued access in the relevant country or specific location in planning multinational clinical trials.

During study planning, the sponsor should apply interdependent criteria to determine whether continued access will be offered to study participants.

[2] The use of the term "sponsor" in this document refers to both sponsors and sponsor-investigators.

The MRCT Center has defined a set of **interdependent criteria**[1] 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.

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 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 continued access to the SR device? Could a managed access approach be used? If not, what other pathways are available?
- The plan should include if and who will be responsible for replacement parts, software upgrades, routine follow-up care by the investigator/clinician, or plans for removal of any implanted device (explant)
- 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 (e.g., life expectancy of the components and how often there may need to be repairs or replacement, not just whether participants will get to keep the device and what care is supported).
- The informed consent document should also list any known device adverse effect and what responsibilities sponsors have after a study finishes.
- An equitable rollout of continued access to all similarly situated participants should be planned.
- The study team should plan for the budget, resources, duration, and equipment needs (component parts of the device) and/or product manufacturing capacity (medicines) that will be required if continued access will be provided.

- The sponsor should assess if discontinuation of continued access, specifically discontinuation of ongoing clinical care, could potentially harm the participant?
- For electrically active *implanted* SR devices, the plan should consider the potential risks of turning the device off without explant.
- If the sponsor determines that an implanted SR device will be removed (explant), planning related to the medical care associated with explant and recovery should be incorporated into the study program.

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

Milestone 2: Ongoing Considerations

The sponsor is responsible for ongoing monitoring throughout the course of the clinical study and device 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.

Specific Scenario	Framework questions and considerations
Planning for legacy programs Planning for legacy programs or products acquired from other companies, as well as companies being acquired by other companies, should be considered.	If possible, an understanding of continued access commitments should be identified in the feasibility stage of acquiring a product or company. If no previous commitment was made, continued access for acquired products should adhere to the acquiring organization's policy already in place. The organization should strive not to abandon a promise of continued access to a participant that was already made, if possible.
Considerations to explant SR implanted device in the following scenarios: 1. Devices that are working 2. Devices that are causing harm 3. Devices that are ineffective 4. Participant preference to have the device explanted 5. The device is recalled due to the potential of causing harm	• A competent participant should never be forced to undergo surgery as it violates personal autonomy. • A sponsor's obligation to explant hinges on the reasoning behind why the explant is necessary. • The sponsor should prospectively comminicate the rationale to, or not to, explant the device. • The consideration to explant the device should consider and communicate the associated benefits and risks to the participant. • The informed consent document and process should clearly explain to the participant any information related to explant of the device (e.g. when explant occurs, who will perform the explant, who will pay for the explant, associated risks). • If the device will not be explanted, the informed consent should clearly explain whether and what long-term care of the device is needed, who will provide the long-term care, and who will be responsible for the cost of long-term care.

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, continued clinical care), 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) participant continues to receive benefit (via the health care professional's assessment)? • If alternative treatments are or become commercially available, participants may be expected to transition to the alternative device 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 sponsor should identify who is responsible and who will cover, the cost of transitioning to an alterative product (sponsor, medical insurance). If the device is implanted, the risk of explanting the device for an alternative implanted device should be weighed with the ongoing effectiveness of the original implanted device. • The participant should be informed about expectations that the product will be approved at some point and the continued maintenance of the device (and associated care) will be temporary to bridge the gap between the end of the clinical trial and market approval.

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.

Specific Scenario	**Framework questions and considerations**
Health Regulatory Authority does not approve the product for **any reason**	**Framework questions and *common considerations* 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? • Is the SR device electrically active? If yes, can the participant be safety transitioned to the local healthcare system for ongoing care? Will insurance pay for this ongoing care? What pathways are in place if the participant is uninsured? • If it is not electrically active and is implanted, can the device remain in the human body? • Can an implanted SR device be safely explanted? • Are investigators (now clinicians) comfortable and trained in providing clinical care for an unapproved device? If patient has been transitioned to a clinician other than the

	investigator of the clinical trial, does this individual have the specialized knowledge and training needed to provide clinical care? • Are replacement parts available? Are interchangeable components with a product that is currently being manufactured available? Would additional manufacturing be required? If additional manufacturing would be required, how long a commitment is reasonable for a product that will never be commercialized? If a participant is dependent on the device, does it change the commitment? • Would post-trial continued access in this setting impact other development activities including budget, resources, and/or manufacturing capacity? Will the company remain in business? • The sponsor should provide clear communication about the length of time and other parameters of post-trial, continued access commitment to investigator and require the investigator 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. This assessment should continue to balance the benefit with the risk of device explant.

The sponsor discontinues the investigational product due to **insufficient evidence of efficacy.**	**Framework questions/considerations** *(in addition to common considerations above)***:** • The sponsor should consider whether it can provide needed hardware or whether there are compatible/interchangeable parts available; investigators should consider whether they want to provide continued clinical care. If an implanted product will be explanted, the sponsor and investigator should coordinate the removal of the device and clinical recovery care.
The manufacturer/sponsor discontinues the product development due to **safety issues.**	**Framework questions and considerations** *(in addition to common considerations above)***:** • Consider the nature and significance of the safety issues: do the safety issues identified at the population level alter the benefit-risk assessment so that providing continued maintenance to an individual would no longer be medically safe or appropriate? ○ Some safety issues would typically be considered a reasonable justification for stopping continued maintenance, or explant of the device at the population level. Sposnors or researchers may choose to consider limited scenarios where there are no alternatives options and stopping/removing the device would clearly be more harmful to the patient than the potential safety risks.

Product development is discontinued due to **business decision**	**Framework questions and considerations** *(in addition to common considerations above)***:** • Sponsor may be more inclined to provide continued maintenance of the device, depending on the specific drivers of the business decision (i.e., if stopping for reasons other than safety concerns or lack of efficacy, there are reasonable alternatives, the physicians are not using the product as intended). • If the sponsor company is at risk of going out of business, participants/patients should be notified and given information about how to get maintenance and spare parts for their device. Investigators and clinicians should also be informed and provided information related to long-term care of the device.
Marketing application rejected for **2nd indication**; Product is approved for 1st indication.	**Framework questions and considerations** *(in addition to common considerations above)***:** • 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 4: Transition II: The 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
The product is not affordable[3] to the patient.	The sponsor needs to determine at what point they are no longer ethically obligated to continue access to trial participants after the device is approved by the regulatory authority. For instance, a sponsor may determine that they have made a credible effort to make the product obtainable[4] to participants, including providing continued maintenance pre-approval, obtaining marketing approval and clinical availability, and setting up patient support programs. They may decide that if a product is accessible, they no longer have an obligation to provide continued maintenance. The obligation shifts to the local healthcare system.
Heath Technology Assessment (HTA) 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 maintenance and clinical care during that period of time.
Investigational product is not approved by the HTA for reimbursement.	• What is the sponsor's role if payors will not reimburse for long term clinical care of an investigational device? ○ Similar to drugs, med tech companies do not provide clinical care.

[3] 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.
[4] Obtainable in this case means a patient can get a product after it has gained regulatory approval in a country. Numerous factors (e.g., affordability, reimbursement considerations, HTA approval if applicable, healthcare facilities and providers equipped and trained to provide the product, etc.) impact obtainability for an individual.