

***MRCT Center  
Post-Trial Responsibilities Framework:  
Continued Access to Investigational Medicines  
II. Toolkit***



**MULTI-REGIONAL  
CLINICAL TRIALS**

THE MRCT CENTER of  
BRIGHAM AND WOMEN'S HOSPITAL  
and HARVARD

**June 26, 2017**

**Version 1.0**

# Post-Trial Responsibilities (PTR) Toolkit

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## Section 1: Introduction

The *Toolkit* and an accompanying [\*Guidance Document\*](#) were developed by the PTR Workgroup organized by the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center). The diverse workgroup included more than 40 stakeholders representing industry, academia, non-profit institutions and patient/patient advocate organizations.

This *Toolkit* was designed to be a practical yet flexible mechanism for planning, decision making and implementing post-trial responsibilities (PTR), as outlined in the *Guidance Document*, regarding continued access to investigational medicines. The user is advised to adapt the content as needed to best fit their particular situation and the country regulations in effect.

Together, the Guidance Document and Toolkit comprise the *MRCT Center Post-trial Responsibilities Framework for Continued Access to Investigational Medicines*. While the *Guidance Document* elucidates the ethical principles, approach and rationale for the key recommendations, this *Toolkit* provides useful conceptual diagrams, decision-making tools, points to consider, examples, case studies, and current country regulations.

The *Framework* addresses stakeholder responsibilities to research participants for:

- Clinical Trial Planning
- Continued Access to Investigational Medicine
- Continued Access to Medical Care
- Continued Access to Infrastructure

This *Toolkit* includes a checklist and scenario tables for specific scenarios that may be encountered once a decision for continued access has been made. In Section 2 B you will find:

- Figure 3: Clinical Trial Planning Checklist
- Table 3: Scenarios for Continued Access to Investigational Medicine
- Table 4: Scenarios for Continued Access to Medical Care
- Table 5: Scenarios for Continued Access to Infrastructure

In Section 3 you will find case studies.

In Section 4 you will find:

- Table 6: Pre-commercialization mechanisms
- Table 7: Selected country regulations

## A. Keys to Using this Toolkit

The Toolkit is organized into four sections including:

- Introduction
- Decision-making Tools
- Case studies
- Resources

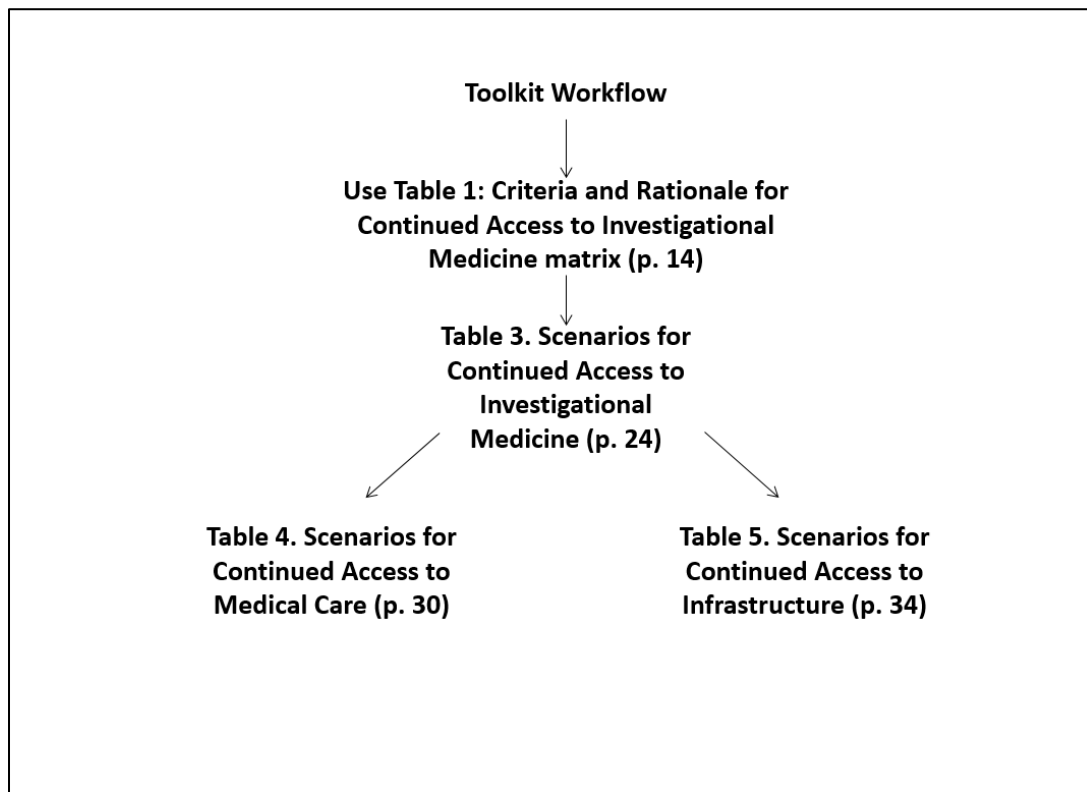


Key to Use	Tool
<b>Key Concepts and Decision-Making Tools (Sections 1 &amp; 2)</b>	
<b>Concepts:</b> Conceptualizing the lifecycle of post-trial responsibilities and transition points.	Figure 2: Spectrum of PTR
<b>Decision-Making Tools:</b> Assessment of the rationale for PTR – the strength of the ethical rationale to fulfill the responsibilities. Does the ethical foundation for PTR constitute an obligation or an elective offer?	Table 1: Criteria and Rationale Table 2: Responsibility Grid
<b>Scenarios:</b> Elucidation of specific scenarios in which it is necessary to decide who is responsible, for how long and through what mechanism PTR should and could be satisfied.	Overview, Points to Consider, Examples, and Scenario Tables for: <ul style="list-style-type: none"> <li>• Figure 3: Clinical Trial Planning</li> <li>• Table 3: Continued Access to Investigational medicine</li> <li>• Table 4: Continued Access to Medical Care</li> <li>• Table 5: Continued Access to Infrastructure</li> </ul>
<b>Case Studies (Section 3)</b>	
<b>Application of the Framework to Real-Life Cases:</b> Examples of how the rationale and scenario tools may be applied to specific case studies.	Case Studies
<b>Resources (Section 4)</b>	
<b>Post-Trial Mechanisms:</b> Descriptions of common mechanisms for providing post-trial access	Table 6
<b>Regulatory Landscape:</b> Current country regulations regarding post-trial responsibilities that should be factored into decision-making.	Table 7 Representative Country Regulations



We suggest the following workflow through the Toolkit:

**Figure 1: Toolkit Workflow**



If the matrix on page 14 indicates that continued access should be provided, then proceed to Scenario Tables 3, 4 and 5 to determine more specific recommendations. Case studies and Resources in Sections 3 and 4 include supporting information.

## **B. Key Concepts**

### **The Lifecycle of Post-Trial Responsibilities**

It is critical to ensure that there are no gaps in the care of study participants, including access to investigational medicines, ancillary and necessary medical care or infrastructure, most particularly if they suffer from serious or life-threatening illnesses or an unmet medical need. Figure 2 (below) summarizes the changing ethical responsibilities of various stakeholders during the transition from clinical trials to the post-trial period. Who is responsible for provision of access shifts over time (e.g., from early phase clinical trial to registration trial, market authorization, availability, reimbursement) and with the circumstances compelling provision of continued access (see Figure 2). The diagrammatic representation is not intended to be prescriptive but rather to allow for flexibility and discretion consistent with fact-based considerations. Rendering the underlying principles of decision-making explicit will ultimately assist stakeholders to assess relevant options.

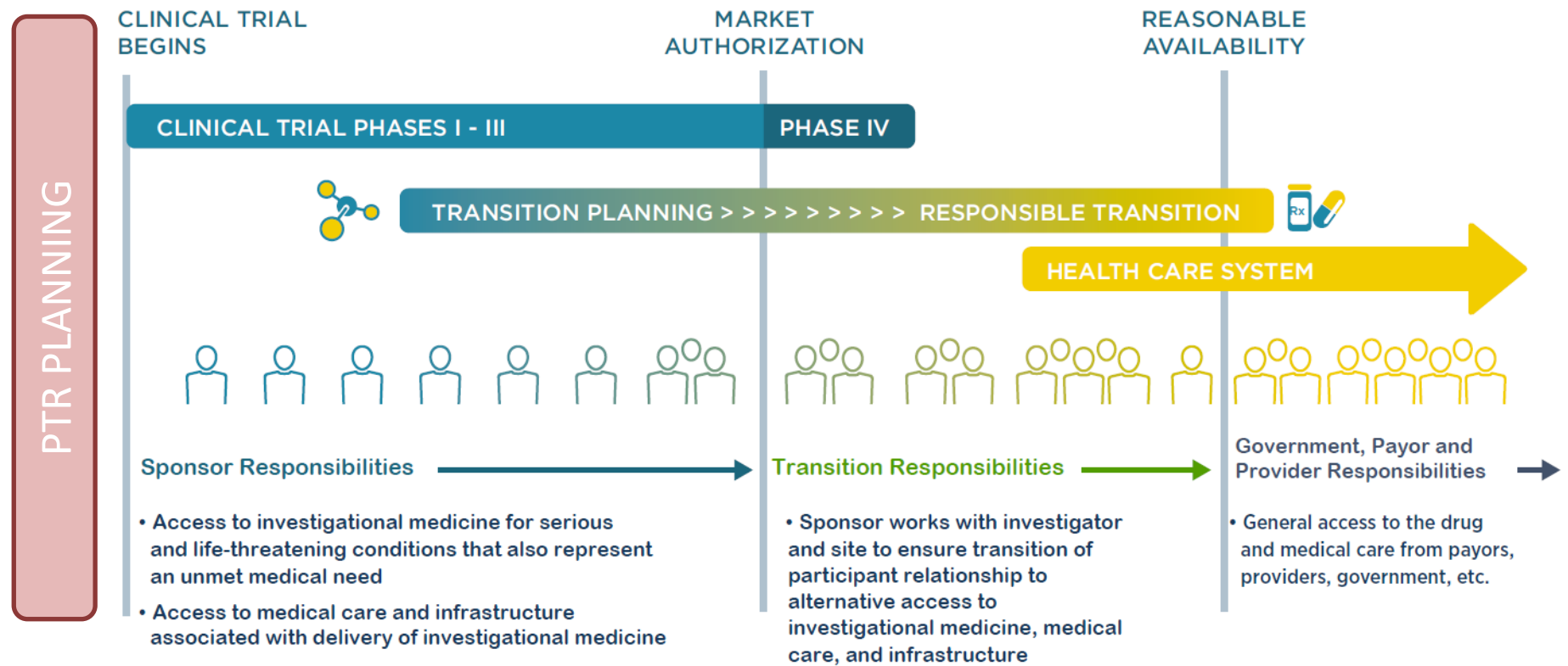
Overall and over time, the responsibilities of the sponsor for providing access to the investigational medicine, related medical care and infrastructure transition from the end of individuals' participation in a clinical trial to market authorization of the product. During the clinical trial, the sponsor (and their designees) are responsible for provision of the investigational medicine. If and by the time the product is approved by the relevant regulatory agency and available on the local market, it is the responsibility of government, payors/insurers, and health care providers to provide access to that product, to necessary medical care to deliver the product, and to related infrastructure. During the transition period from clinical trial to availability in the local health care system, the sponsor should work with the investigator, payors, and government to ensure appropriate transfer of responsibility.

**Figure 2: A spectrum of PTR**

**POST-TRIAL TRANSITION RESPONSIBILITIES:**

**Investigational medicine approval pathway: from clinical trials to general access**

(If investigational medicine is not approved, see Scenario Table I, ID #5)



## Keys to Using this Toolkit



## Section 2: Decision-Making Tools

The tables below present practical checklists for decision-making about post-trial responsibilities with regard to access to investigational medicines, associated medical care and infrastructure. The checklists address the weight of factors such as the benefits, risks, severity of disease and other key elements in the consideration of whether to provide continued access. If the rationale for one or more elements is “weaker,” sponsors, of course, may still choose to provide continued access at their discretion; if the rationale for all (or almost all) the elements is “stronger,” however, a “stronger” recommendation—if not an ethical mandate—for provision of continued access exists.

For further detailed guidance, the responses to the questions in Table 1 track closely to the guidance in this document as to the rationale for provision of continued access (see Scenario Tables). The separate [\*Guidance document\*](#) discusses in detail many of the considerations that are only bulleted or described briefly here.

In this section you will find:

- Table 1: Criteria and Rationales for Continued Access to Investigational Medicine
- Continued Access to Medical Care (considerations for decision-making)
- Continued Access to Infrastructure (considerations for decision-making)

## A. Clinical Trial Planning

Planning for (1) continued access to investigational medicine, (2) continued access to medical care and (3) continued access to infrastructure, as related to delivery of investigational medicine, should be part of each clinical trial planning. Sections 1, 2, 3 below list overall considerations for each. In addition, Figure 1 “Clinical Trial Planning Checklist” in Section B includes specific questions that should be considered at the planning stage.

### 1. Continued Access to Investigational Medicine

**Table 1: Criteria and Rationales for Continued Access to Investigational Medicine**

STAGE 1: PLANNING (Program level)		
Criteria	Answer	Rationale for providing continued access
Condition being studied is serious/life threatening		
	YES	STRONGER
	NO	WEAKER
Suitable approved therapeutic alternatives are available		
	YES	WEAKER
	NO	STRONGER
Suitable approved therapeutic alternatives are available		
	YES	WEAKER
	NO	STRONGER
The investigational medicine addresses an unmet medical need		
	YES	STRONGER
	NO	WEAKER
Provision of investigational medicine will affect the viability of the research		
	YES	WEAKER
	NO	STRONGER

STAGE 2: MONITORING OF AVAILABLE ALTERNATIVES OVER TIME (Program level)		
Criteria		Rationale
Suitable approved therapeutic alternatives becomes available with no or minimal risk of harm to patients		
	YES	WEAKER
	NO	STRONGER

STAGE 3: DECISION POINT 1 (Individual Level)		
Criteria		Rationale
<b>Evidence of benefit <u>for the individual participant</u> outweighs evidence of risk with the use of the investigational medicine – or study has an acceptable safety profile in a prevention trial</b>		
Individual has not shown benefit	YES	NONE
Individual has shown benefit	YES	STRONGER
<b>Participant completed study participation, research procedures, and obligations of the trial?</b>		
	NO	No commitment to provide continued access
	YES	Threshold met for consideration of potential continued access
<b>Risk of death or serious harm if investigational medicine is withdrawn</b>		
	NO	WEAKER
	YES	STRONGER

STAGE 4: DECISION POINT 2 (Program Level)		
Criteria		Rationale
<b>Evidence of benefit outweighs evidence of risk with the use of the investigational medicine <u>at study level</u> – or study has an acceptable safety profile in a prevention trial</b>		
Study population has not shown benefit	YES	NONE
Study population has not shown benefit but Individual has shown benefit	YES	APPROPRIATE (and STRONGER still if individual is part of an identifiable subset of patients for which benefit is shown)
Study population has shown benefit	YES	STRONGER

STAGE 5: TRANSITION		
Criteria		Rationale
<b>Other ways to access the investigational medicine (e.g., availability following regulatory approval)</b>		
	YES	WEAKER
	NO	STRONGER

## 2. Continued Access to Medical Care

- Determine if medical care necessary for the continued administration of the investigational medicine can be provided.
- Define appropriate standard of care contemporaneously with study planning, in consultation with those who work within a country, and justified to the relevant research ethics committees.
- Determine who is responsible for the provision of accompanying medical care after the participant's role in the trial or the trial itself is concluded and inform participants.

If continued access to medical care will be provided, go to Table 4.

## 3. Continued Access to Infrastructure

- Decide for each trial the degree of investment in the local infrastructure based on the specific facts presented.
- Determine if the sponsor needs to continue to provide access to the investigational medicine following the trial. If so, the sponsor should be responsible for the maintenance of infrastructure related to such provision until the continued access is concluded, unless the medical facility has agreed to share maintenance costs.
- During pre-trial planning, define the responsibility and requirements for equipment ownership and maintenance after the trial concludes.

If continued access to infrastructure will be provided, go to Table 5.



## B. Scenarios

### 1. Clinical Trial Planning

#### A. Overview

As stipulated in the Declaration of Helsinki and CIOMS International Ethical Guidelines for Health-related Research Involving Humans sponsors, researchers, and the host country government should make provisions for post-trial access *in advance of any clinical trial*. Further, this information should be disclosed to participants in the informed consent process. Continued access or plans for provision of post-trial access of beneficial investigational interventions, if any, should be mentioned in the informed consent process and document.

If there is insufficient information regarding the safety and efficacy of an investigational agent at the beginning of a study to make a decision regarding whether to offer continued access. The informed consent document should clarify how and when a decision will be made as to the provision of continued access.

If an affirmative decision is made not to provide continued access (e.g. there are appropriate alternative therapies for which approved medicines are available), that decision should be disclosed.

Although not commonly used, one mechanism to address continued access during the informed consent process is through a “pre-trial agreement” developed to inform the research participant about the opportunity and specific conditions for continued access. The ‘pre-trial agreement’ should include information about the accompanying care: who will be responsible for necessary accompanying medical care and how the transition from trial to post-trial care necessary to provide the investigational medicine will happen.

#### B. Pre-trial Planning

The sponsor in collaboration with the investigator(s), site(s) and often government agency(ies) should plan the program for continued access before the trial begins. The plans will impact the final protocol, informed consent, case report forms, data management and statistical plans. The plans will also be shared with ethics committees and potentially other external stakeholders. In general, the questions to consider are independent of the phase of drug development, although the specific answers may change.

#### C. Points to Consider

- |   |
|---|
| <ul style="list-style-type: none"> <li>• What are the inclusion criteria for continued access?</li> </ul> |
|---|

- How will participants be enrolled in a continued access protocol after trial completion?
- Which stakeholders will be involved and what are their responsibilities?
- What is the source of funding for continued access?
- Would investment in local infrastructure to support continued access to investigational medicines be an undue or improper inducement to regulators, ethics committees, or local authorities with respect to approving the trial and/or to the site or participants to join the trial?
- How long will continued access be provided?
- What are the criteria for discontinuation of the post-trial investigational medicine?
- What are post-trial provisions if the investigational medicine does not get approved by the regulatory authority in the country or will not be put forward for approval by the national regulatory authority?

**Figure 3: Clinical Trial Planning Checklist**

1. Is a study extension or separate “rollover” study anticipated/desired after the clinical trial (“core”) study treatment period is over?
  - a. Can a study extension protocol provide additional safety and/or efficacy information that might be important for regulatory decision-making and other purposes?
  - b. If yes, what are eligibility requirements and/or other conditions that must be satisfied for a trial participant to transition from the core study to the extension protocol?
  - c. Determine if the extension trial will be blinded or if conditions for an open-label extension can be met.
  - d. Clarify all information, procedures and data to be collected in the extension phase. Include this information, in aggregate in the protocol, by reference in the informed consent document, in Case Report Forms (CRFs), and in analysis plans.
2. Is the condition being studied a serious, life-threatening disease or a disease associated with chronic symptoms significantly impacting the patient’s life?
  - a. If not, and there are no plans to provide post-trial access to the investigational medicine, core study documents should reflect that intent.
  - b. If there are conditions under which the investigational medicine and/or comparator might be made available to study participants following completion of the core study treatment period or extension, then define:
    - i. Conditions for access, including (see Table 1)
      1. Patient has completed the study protocol

2. Patient exhibiting benefit and the benefit/risk ratio is judged to be favorable for the patient
    3. There are adequate drug supply and resources available so as not to jeopardize completion of the core clinical study program
  - ii. Duration of provision of the investigational medicine or comparator, for example:
    1. Until investigational medicine is approved and commercially available in the country, or
    2. There will be a transition plan communicated at some point in the future
    3. Conditions under which provision of the investigational medicine or comparator will be terminated, for example:
      - a. Patient no longer deriving benefit
      - b. Patient experiencing risk or adverse events
      - c. Alternative approved treatment becomes available
      - d. Investigational medicine not approved in country
      - e. After a predetermined period of time agreed on by sponsors, researchers, and community members (CIOMS 2016).
3. Does the Informed Consent document address the opportunity and specific conditions for continued access to investigational medicine and accompanying medical care after the trial has ended?
    - a. Has the Informed Consent document been developed before the trial starts, approved by IRB/REC and shared with participants before and during the trial?
    - b. Does the Informed Consent document address and define:
      - i. Either: A decision not to provide continued access –or–
      - ii. Conditions under which participant may be continued on beneficial investigational intervention
      - iii. Conditions under which continued access will be dependent upon the safety profile in other participants
      - iv. Conditions under which continued access will be dependent upon efficacy and safety information of overall study
      - v. Conditions under which the investigational intervention will be discontinued (e.g., local alternative therapies available, product not put forward for approval in the jurisdiction)
      - vi. Time limit for continued access.
      - vii. Conditions under which continued access plans may change during the course of the drug development.
  4. Planning costs of post-trial access in the contract between researchers, sponsors and host research site
    - a. Does the contract include an agreement between the host research site, researchers and sponsor on how post-trial access cost would be shared?
    - b. Does the contract stipulate how much clinical researchers or treating physicians would be paid during post-trial access programs and by whom?

- c. Does the contract stipulate what are the costs that the sponsor should bear?
- d. Does the contract stipulate what are the costs that the host research site should bear?

5. Starting of post-trial access program

- a. Is there a clear protocol how to start a post-trial access program?
- b. Who would be in charge of deciding when to start a post-trial access program?

## 2. Continued Access to Investigational Medicine

### A. Overview

The first and most important determination is whether and under what conditions continued access to the investigational medicine will be provided; if it is, then access to appropriate medical care and infrastructure necessary for safe access to the product also need to be considered. If and when the investigational medicine is approved and marketed, responsibility shifts to the government and local healthcare system. Prior to regulatory approval, however, or in situations when the investigational medicine is not approved, a more detailed inquiry will be necessary.

The amount of information known about the investigational medicine (which varies by trial phase) is one critical factor in the determination of who is responsible and for what: in early phases of drug development, whether patients benefit from the drug, what risks are attendant with drug administration, and toxicity of the drug may be unknown or inadequately studied. Both while the investigational medicine is in development and while awaiting approval, the sponsor should investigate whether suitable safe and effective alternatives to the investigational medicine exist, and whether discontinuing the investigational medicine and/or transitioning to a suitable alternative could potentially harm the patient.

In general, where no such alternatives exist for a serious or life-threatening condition and when the patient has shown benefit from the product, provision of continued access is indicated.

If the investigational medicine is not approved by the regulatory agency, the sponsor must respect the local regulatory authority and discontinue provision. On very rare occasions, the sponsor may elect to engage with the government to determine if an exception may be made for the individual patient.

Where suitable alternatives exist, if the risks are significant or the product is shown to be ineffective, no further access to the investigational agent is recommended and responsibility for patient medical care will shift to the healthcare system.

### B. Points to Consider

- What are the relevant national laws and regulations regarding the provision of post-trial access to an investigational medicine?
- How much is known about the safety and efficacy of the investigational medicine, and at what stage is the drug development program?
- How will benefit and risk be defined in the context of this trial?

- What is the potential for harm to the participant if the investigational medicine is discontinued and/or continued access denied?
- What is the expected timeline for approval of the investigational medicine?
- What alternatives to the investigational medicine exist and how do those alternatives compare to the benefits and risks experienced with the investigational medicine?
- What is the impact of providing continued access and will it affect the viability of the research?
- Will the government or local healthcare system bear the responsibility of providing the product if and when that product is approved? If not, is it ethical to conduct the study in that country?

### C. Cases

Example 1: Although the benefit-risk of a drug for pediatric gastrointestinal reflux disease (GERD) was not yet established, the 12-year-old clinical trial participant (patient) had benefited from the investigational treatment in the opinion of the investigator. Further, the patient had tolerated the investigational medicine well and had not previously responded to any available alternative. While GERD was not considered a serious or life-threatening disease, the investigational medicine had been approved for the same indication in adults and the risk profile in adults was negligible. There was no reason to believe that the risk profile in the pediatric indication would differ. Therefore, the sponsor continued to provide access to the product in this case.

Example 2: After the completion of a clinical trial for the antiretroviral drug Indinavir, the sponsor provided post-trial access to the investigational drug based on (1) an evaluation of its safety (low risk profile) and apparent efficacy (as measured by the CD4+ count as a biomarker of disease) and (2) the lack of alternative options for clinical trial participants in a low-resource country. The sponsor worked with the local government to arrange ancillary medical care and access to infrastructure, and executed a written agreement before the trial was initiated. Participants were appropriately informed of the option of continued access at the time of initial informed consent; each participant was re-consented at the time of the provision of continued access to drug and enrolled on a continued access trial in order to collect further safety data. --- see Section 3 for complete case discussion

### D. Resources

Beauchamp TL, Childress JF. *Principles of biomedical ethics*. 6th ed. New York, NY: Oxford University Press; 2009.

Sofaer N. Reciprocity-based reasons for benefiting research participants: most fail, the most plausible is problematic. *Bioethics* 2014;28(9):456-471.

WMA. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310(20):2191-2

CIOMS, 2016. International ethical guidelines for health-related research involving humans. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS).

**Table: 2 Responsibility Grid by Stage and Role**

Stage / When	Role/Responsibility	Task
<b>Stage 1: Planning</b> This occurs before the trial begins at the Program Level. The sponsor should evaluate whether the drug and disease under study meet the criteria (Table 1) for continued access. If the sponsor decides to provide continued access, appropriate resources should be allocated.	IRB/REC Sponsor	Reviews ICF & Protocol, protects patients
<b>Stage 2: Monitoring</b> This occurs as the study is ongoing. The sponsor assesses whether there is still an unmet medical need that requires continued access	IRB/REC Principal Investigator Sponsor	
<b>Stage 3: Decision Point 1</b> This occurs at the Individual Patient Level during the patient's last study visit. At this juncture, the investigator evaluates and communicates to the Sponsor whether the individual's benefit/risk warrants continued access.	Treating physician	Performs benefit/risk for individual patient
<b>Stage 4: Decision Point 2</b> This occurs at the Program Level after database lock, unblinding and data analysis. At this juncture, the sponsor evaluates whether the overall study population benefit/risk is acceptable for the particular study.	Sponsor  Treating physician  Research Ethics Committee Regulatory Authority	Performs benefit/risk assessment for the trial population Performs benefit/risk for individual patient and, if appropriate, requests continued access from the sponsor Approves request Approves request, if required.
<b>Stage 5: Transition</b> This occurs at the Individual Patient Level at the point where the investigational medicine becomes commercially available, there are other satisfactory alternatives for treatment, or the patient no longer requires treatment.	Sponsor Principal Investigator Health care system/government	



**Table 3: Scenarios for Continued Access to Investigational medicine**

ID	STAGE / SCENARIO	RESPONSIBILITIES	RESPONSIBLE PARTY	DURATION	TASKS
1	<b>Stages 1-5</b> General considerations for all stages (Planning, Monitoring, Decision Point 1, Decision Point 2, Transition)	Provide continued access for (1) participants (patients) who complete the study with (2) serious or life-threatening illness who (3) experience clinically important benefit at the end of the study and who (4) may potentially be harmed without continued access to investigational medicine, and 5) no suitable alternative is available.  (If a study is blinded, give the same blinded treatment that patient has been receiving while on trial.)	<b>FOR ALL SCENARIOS</b> (1) Sponsor performs benefit/risk assessment for the trial population (2) Treating physician performs benefit/risk for individual patient and, if appropriate, requests continued access from the sponsor (3) Research Ethics Committee approves request (4) Regulatory Authority, if required, approves request	(1) Until investigational medicine or suitable alternative is available <sup>1</sup> to the patient or (2) Development of the product is discontinued or (3) Until patient no longer derives benefit or experiences harm or (4) Until patient decides to voluntarily discontinue the investigational medicine or (5) After a predetermined period of time agreed on by sponsors, researchers, and community members (CIOMS 2016)	Unless otherwise specified below, the following applies:  (1) Determine which data will be needed to make benefit-risk decisions; and  (2) Consider different outcome scenarios, make appropriate plans for post-trial provision of the investigational medicine in advance of the trial, and address PTA in informed consent documents prospectively (see Table 6. Pre-commercialization Mechanisms in Section 4). Sponsor should know the alternative
2	<b>Stage 3: Decision point 1 (individual level)</b> Early Phase Trials (Typically Phase I/II)	Determine evidence of benefit on a case-by-case basis for those with serious / life-threatening conditions; offer continued access if there is sufficient evidence			

<sup>1</sup> Available refers to the investigational medicine being available on the local health care market

		of favorable benefit-risk balance			treatments in each country.
3	<b>Stage 4: Decision Point 2 (program level)</b> Efficacy Trials – Registration studies (typically Phase III)	<p>Provide continued access for patients with serious or life-threatening illness who experience clinically important benefit at the end of study participation and who may potentially be harmed without access.</p> <p>Once trial results are known, do the trial results support continuing to provide investigational medicine to study participants?</p> <p>If the trial results are not positive, are there any participants for whom providing investigational agent should nevertheless be considered?</p>			<p>(3) Prepare protocol and consent forms to specify plans when study ends</p> <p>(4) Consider national laws and regulations</p> <p>(5) Continue assessment of safety parameters and monitoring. Health authorities should be consulted.</p>
4	<b>Stage 5: Transition</b> Investigational medicine is never approved	Responsibilities to individual patients with serious or life-threatening illness who derived benefits; in rare instances, sponsor may decide to provide		Until suitable alternative therapy is identified and available or clinical supplies are exhausted or individual no	Note: Company cannot be expected to manufacture more drug if it will not be further developed or marketed

	Development pathway abandoned or marketing authorization withdrawn	continued access in these instances if feasible.		longer derives benefit or experiences harm	Regulatory approval is necessary for either continued access program or alternative pathway
5	<b>Stage 5: Transition</b> Investigational medicine not yet approved and potential alternative treatments are available	Determine if alternative is appropriate for any patient with serious or life-threatening illness, considering the risk / benefit of continuation of use of the investigational medicine. If alternative chosen, assist the patient with transition to receiving alternative		Until access <sup>2</sup> to suitable alternative treatment is obtained or investigational medicine is approved	Include in consent form if alternatives to investigational medicine are available and expectations of transition
6	<b>Stage 5: Transition</b> Investigational medicine is approved for investigational indication and becomes commercially available	Sponsor works with investigator to transition patient to medical provider; investigator to ensure no interruption of care		Until patient has access to approved product	If reimbursement is not available for the patient, sponsor may consider provision of the product through patient-assistance program

<sup>2</sup> Access refers to the ability of the patient who participated in the clinical trial to obtain the investigational medicine on his/her own, which may involve adequate reimbursement by health care provider or third party payer.

### 3. Continued Access to Medical Care

#### A. Overview

Building upon many of the considerations in the previous section related to access to the investigational medicine, this section concerns medical care<sup>3</sup> necessary for the administration of the product. From an ethical perspective, the principles of non-maleficence, beneficence, and distributive justice impact this determination somewhat differently than in the case of the investigational medicine. For example, in most situations while the Sponsor is responsible for providing access to the investigational medicine, the local healthcare system is better situated to provide access to medical care. Therefore, this framework recommends that sponsors evaluate the local standard of care prior to implementing the trial, and work with local governments to determine arrangements for post-trial access to medical care during the planning stage. If the standard of care in the country is suitable for the adequate administration of the investigational medicine, the healthcare system should provide access to medical care; if the standard of care is poor, the sponsor may choose, as an option, to cover reimbursement (or purchase insurance) or develop *ex ante* agreements to share responsibility with the local government.

In cases where clinical trials are hosted in contexts with poorly supplied and equipped health care systems, sponsors and researchers should be aware of the increased likelihood of research participants being locally forced or coerced to enroll into clinical trials to gain access to post-trial medical care and infrastructure for the host community (Ledefor 2014, Mastroleo 2016). Appropriate measures of education on local authorities and other relevant host country stakeholders should be put in place to ensure valid informed consent from participants.

#### B. Points to Consider

- Which components of medical care are necessary to administer the investigational medicine safely and to monitor safety?
- What is the local standard of care?

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<sup>3</sup> Here we consider only that medical care essential to the safe provision of the investigational medicine, not other associated medical care that the patient may need for his or her medical condition(s)

### C. Cases

Example 1: A study on methods for improving reproductive health in Africa introduced a higher standard of care during the trial without considering the sustainability or cost of such medical care. After the trial, the sponsor could not continue to provide medical care for trial participants and the local government was not equipped to provide medical care, which led to an ethical issue concerning the well-being of participants. Had the issue of post-trial access to medical care been considered in advance of the trial commencement, the sponsor and host country may have reconsidered the feasibility of the study.

Example 2: An intervention to reduce neonatal mortality focused on premature infants that faced high mortality rates in developing countries. Surviving infants needed intensive medical care and support after the trial, but such provision was outside of the scope of the trial and beyond the capacity of the sponsor. Sponsor arranged for participants to transition to local medical care, thus fulfilling an ethical responsibility to participants.

Example 3: In a 2004 HIV prevention trial, participants demanded life-long provision of anti-retroviral (ARV) therapy if they became infected during the trial. Since they had received ARV during the trial, they would be worse off without the accompanying care than if they had never participated in the trial. In this case, the principle of nonmaleficence directly applies. At the time of the trial, provision of lifelong post-trial access was an anomaly, leading to a debate over who should be provided with post-trial access and whether obligations might last for a patient's entire life.

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**Table 4: Scenarios for Continued Access to Medical Care**

ID	STAGE / SCENARIO	RESPONSIBILITIES	RESPONSIBLE PARTY	DURATION	TASKS
1	<b>Stages 1-5 --</b> - Provision of the investigational medicine is discontinued <sup>4</sup>	None	N/A	N/A	N/A
2	<b>Stages 3-5 --</b> - Provision of the investigational medicine is continued - Investigational medicine is not yet approved by regulatory authorities - Local standard of care is compatible with necessary care for intervention <sup>5</sup>	Care necessary for proper use of the investigational medicine according to the study protocol (not above and beyond standard of care)	Healthcare provider—continuation of medical and ancillary care that had been given during the trial  Sponsor (financial responsibility for care associated with the investigational medicine administered according to protocol) – link the provision of medical care to the continued access of the investigational medicine	Related to the timing of provision for post-trial access to the investigational medicine	Time frame/availability of care should be determined prior to trial with the local government.  Avoid gaps in medical care

<sup>4</sup> For the purposes of this *Framework*, “access to medical care” is limited, by definition, to medical care necessary to the provision of the investigational medicine. Therefore, if the product is no longer provided, the sponsor and investigator involvement in medical care will also cease and the responsibility for standard care and treatment of the patient will revert to the healthcare provider and local health care system. Where provision of the product is continued, further inquiries regarding who is responsible are represented in this chart.

<sup>5</sup> The local standard of care should be decided in relation to WHO “essential care” requirements for standard of care or the local equivalent of WHO “essential care” list—if the local standard of care meets WHO standards, it is sufficient, unless the WHO standard is not adequate for the administration of the investigational drug.

			<p>Sometimes researcher / sponsor provides follow-up care for a certain period of time</p> <p>Link the medical care to the condition being studied by clinical trial, not to other medical conditions that participants may also have</p>		
3	<b>Stages 3-5 --</b> - Provision of the investigational drug is continued - Drug is not yet approved by regulatory authorities - Local standard of care is poor	Medical care necessary for proper use of the investigational medicine according to the study protocol	Healthcare / provider (caregiving responsibility)  Sponsor (financial responsibility for care associated with the investigational medicine)	Related to the timing of provision for post-trial access to the investigational medicine	Sponsor pre-arranges prior to post-trial period for reimbursement of the medical care
4	<b>Stages 3-5 --</b> - Provision of the investigational drug is continued - Drug is approved by regulatory authorities	Medical care necessary for proper use of the investigational medicine according to the study protocol or approved product information	Healthcare System / third party payer	Related to the timing of provision for post-trial access to the investigational medicine	Transition from trial to local care. Transitional plan should be delineated prior to trial.



## 4. Continued Access to Infrastructure

### A. Overview

In the context of clinical trials and most commonly in lower resource settings, sponsors may need to invest in local infrastructure to conduct clinical trials safely. Such infrastructure may include refrigerators to store investigational medicines or diagnostic or testing equipment such as x-ray machines. This investment may be necessary to meet comparable standards for quality and safety at all sites involved in multi-regional clinical trials.

If the sponsor continues to provide access to the investigational medicine following the trial, they will be responsible for the maintenance of infrastructure necessarily related to provision of the investigational medicine, unless the medical facility has agreed to share or assume maintenance responsibilities and costs. If provision of the investigational medicine is discontinued and the medical facility is unable to utilize the infrastructure, the sponsor is responsible for removal of the infrastructure or for making other arrangements determined prior to the trial. If the medical facility is able to utilize the infrastructure, then responsibility for its maintenance should transition to the facility, and the transition plans--including responsibilities and liabilities--codified in an agreement.

In cases where clinical trials are hosted in contexts with poorly supplied and equipped health care systems, sponsors and researchers should be aware of the increased likelihood of research participants being locally forced or coerced to enroll into clinical trials to gain access to post-trial medical care and infrastructure for the host community (Ledefor 2014, Mastroleo 2016). Appropriate measures of education on local authorities and other relevant host country stakeholders should be put in place to ensure valid informed consent from participants.

### B. Points to Consider

- Is a trial sponsor making investments in the local research and healthcare infrastructure that may be used after the trial is completed?
  - How significant is the planned investment?
- Should the sponsor remove the equipment or infrastructure improvement at the end of the trial, even when the cost to remove the equipment would be significant?
- What role should the government play in this determination?
- Who is responsible for maintenance of donated infrastructure and equipment after the post-trial period and access to the investigational medicine is complete or if the product is marketed or some other point in time?
- Is there an increased likelihood of research participants being locally forced to enroll so host community can gain access to post-trial medical infrastructure?

### C. Cases

Example: A refrigerator is necessary for storage of an investigational medicine and is used throughout the trial. After the trial, however, access to the refrigerator is not necessary as alternative treatments are available and continued access will not be provided. The site, however, would appreciate if the sponsor donated the refrigerator. In advance of the trial, the sponsor provides a schedule of depreciation so that the site can purchase the refrigerator at the end of trial for \$1.00. The intention to donate the refrigerator is disclosed to the research ethics committee in advance of approval, so that the oversight body can review the conditions of the trial for undue inducement. An agreement is executed at the end of trial conferring all responsibilities and liabilities to the site.

**Table 5: Scenarios for Continued Access to Infrastructure**

ID	STAGE / SCENARIO	RESPONSIBILITIES	RESPONSIB LE PARTY	DURATION	TASKS
1	<b>Stages 1-5 --</b> Substantial investment in local infrastructure in a low-resource setting	Be transparent about the infrastructure investment and reasons for it  Depreciate the equipment over the life of the trial and factor into compensation that is offered to the sites OR  Reserve decision on whether to leave the equipment until after the trial has been approved OR  No responsibility to donate – NO continued responsibility to maintain after the post-trial access period but if not donated, sponsor responsible for removal	Sponsor	Based on the responsibility (see second column)	Donation may be possible; other factors may be considered.  Refer to World Health Organization <i>Guidelines for Health Care Equipment Donations</i> , March 2000 <sup>6</sup>  Agreements can guarantee that the infrastructure created during the trial will be handed over to governments when the trial is over for the continuing care of those receiving PTA, or agreements for sharing responsibility may be otherwise determined during the planning stage.  RECs, sponsors and researchers should monitor and remove local pressure on

<sup>6</sup> [http://www.who.int/hac/techguidance/pht/1\\_equipment%20donationbulletin82WHO.pdf](http://www.who.int/hac/techguidance/pht/1_equipment%20donationbulletin82WHO.pdf) [accessed 18 November 2015]

					research participants to enroll in clinical trials
2	<b>Stages 3-5 --</b> Provision of the investigational medicine is continued  Medical facility will share the benefit of the infrastructure for other purposes	Maintenance of the healthcare infrastructure	Sponsor/Medical facility	Until provision of the investigational medicine ceases.	Ex ante agreement should provide for a shared maintenance responsibility.
3	<b>Stages 4-5 --</b> Provision of the investigational medicine is discontinued  Medical facility continues to rely on the infrastructure	Maintenance of the healthcare infrastructure	Medical facility	N/A	Ex ante agreement should address the transition process by which medical facility will assume maintenance responsibility.
4	<b>Stages 4-5 --</b> Provision of the investigational medicine is discontinued  Medical facility does not require the infrastructure	Removal of the infrastructure	Sponsor	Until infrastructure is adequately disposed of	Sponsor is responsible for removal of infrastructure. If cooperation of the medical facility is required, ex ante agreement should outline its responsibility in the process.

	or is unable to maintain it.				
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## Keys to Using This Toolkit



## Section 3: Case Studies

In the initial stages of this project, these cases were provided by workgroup members. They are included in this section to assist the reader in identifying issues and illustrating the complexity of real-world issues. As these are real world cases, sometimes information is incomplete or lacks clarity. This reality is instructional and should stimulate thoughts about additional questions that should be asked when making continued access decisions. The questions listed with each case may not be answered directly from the [Guidance Document](#) but should be able to be deliberated by referencing the principles in the Executive Summary.

### Stage 1: Planning

#### A. An Intervention to Reduce Neonatal Mortality

##### **Trial Background**

Developing countries often do not have access to medical advances that improve quality of life and reduce mortality rates as in developed countries. One study seeking measures to equalize this imbalance was a multi-country, randomized controlled trial investigating the effectiveness of a pharmaceutical intervention in reducing neonatal mortality in preterm infants without increasing severe maternal infectious morbidity. The trial involved an investigational medicine that had demonstrated efficacy when administered through hospitals in developed countries, but for which there were few data for countries where at-home births were common and which lacked neonatal intensive care units.

The study focused on evaluating methods in 3 key areas: 1) improving the identification of women at risk of premature delivery; 2) increasing the study medication's availability; and 3) providing training to birth attendants at all primary health care levels regarding the administration of the study medication. Researchers anticipated that, due to the drug's efficacy in other regions, it would likely improve survival rates. Regardless of the drug's effect in more favorable environments, however, preterm infants in developing countries continued to face myriad challenges threatening their survival. Thus, trial implementers faced a difficult ethical question concerning whether and what steps should be taken to ensure participant survival after the trial.

##### **How did trial implementers approach post-trial mortality risks?**

As the drug had demonstrated efficacy in other regions, trial implementers were fairly confident that the study medication would demonstrate efficacy in the trial in developing countries. However, they worried that even if the intervention was successful, many of the trial participants in developing countries would not survive due to the countries' weak medical infrastructure and

other health challenges. From an ethical perspective, it was unclear what responsibilities were owed to participants; from a practical perspective, it was unclear how much of this burden the sponsor/investigators could undertake. Provision of post-trial access to the drug alone would likely be insufficient. However, the conditions in these resource-poor countries indicated that the medical care required by the participants would far exceed the scope of the intervention, particularly after its completion.

An ethical consultation service proposed two primary solutions to address the issue of infant mortality following the conclusion of the trial. The first was to improve community health capacity and integrate the trial into the health network by referring participants to other sources of care. This would enable local actors to continue care when trial implementers' capacity was exceeded. The second consideration was to extend the follow up period of the trial by adding an additional time point. In this way, treatment related to infant survival would remain within the scope of the trial until the risk of mortality was less severe.

**Other questions to consider:**

- Are sponsors/investigators responsible for additional health risks that face trial participants in developing countries after completion of the trial?
- Who is responsible for mortality risk unrelated to an intervention?
- What level of burden should a sponsor/investigator be expected to bear in a high-risk environment?
- How does the age and vulnerability of a population impact benefit/risk analysis of post-trial plans and design of the protocol?

## **Stage 2: Monitoring**

### **B. A Study in Methods for Improving Reproductive Health in Africa (MIRA)**

#### **Trial Background**

This study concerns the Methods for Improving Reproductive Health in Africa (MIRA) study, a Phase 3 trial of diaphragm and lubricant gel for HIV prevention among women in Zimbabwe and South Africa. Recognizing that the cervix is highly vulnerable to HIV infection, the study explored whether covering the cervix during intercourse might decrease the risk of contracting HIV. Participants were randomized either to (1) the intervention group that received a latex diaphragm, lubricant gel, and condoms, or (2) the control group, which received only condoms.

In addition to the core treatment, the trial also provided a variety of accompanying services. These included risk reduction counseling and HIV education, condom provision and counseling,



STI treatment services, cervical cancer diagnosis and treatment (in some settings), partner testing and referrals, and case management. In addition, the trial provided significant infrastructural development, including construction and renovation of clinics, development of state of the art laboratories, and training of technicians.

Over the course of the study, from 2003 – 2006, 151 out of 2,476 participants in the control group contracted HIV. A similar proportion, 158 out of 2,472 participants in the intervention group, also contracted HIV. Thus, the intervention was found to have no impact. Notably however, the sponsor had committed—in advance of the trial and independent of the outcome of the trial—to the provision of a diaphragm to all trial participants at the end of the trial. Additionally, whether the sponsor would continue to provide other services as had been provided during the trial was not clear.

#### **What impact did the trial's outcome have on PTA provision?**

The lack of a positive outcome for the trial led to serious discord on the issue of PTA. All participants had been told that they would receive a diaphragm following completion of the trial. However, the treatment intervention was found to have no benefit; in addition, there were participants who left the trial prior to its completion, meaning that there had been no determination on the efficacy of the treatment at the time they sought PTA. This led to an ethical question regarding distribution of the product without a positive outcome. The sponsor opposed providing PTA under these conditions. After consulting with ethicists and lawyers, the investigators made the diaphragm available but after explaining the trial results, also provided a short quiz that accompanied the consent form, to establish that participants understood that the intervention was not successful.

#### **How did the study's higher standard of care impact the PTA plan?**

As described above, the MIRA study included a standard of care that far surpassed the local standard of care. This raised questions regarding the sustainability of the intervention following completion of the trial. Would or should the sponsor continue to fund treatment for trial participants? Who would maintain and provide the large staff that had been supported by the trial after the trial was over? The allocation of significant resources to this purpose might deprive other sites of necessary care. Should the trial have been implemented with the knowledge that the standard of care could not be maintained following completion of the trial? In light of these types of situations, some recommend adopting a slightly lower standard of care in order to ensure sustainability and a comparison to a more realistic standard of care.

#### **Other questions to consider:**

- How should local standard of care be factored into PTA considerations?
- If a standard of care is not sustainable, is it ethical to implement the trial in that location?

- Under what conditions should treatment be provided if it has not been found beneficial in the intervention?

## **C. Developing a treatment for Chronic Myeloid Leukemia**

### **Trial Background**

When the sponsor began its Phase I trial for Gleevec®, or imatinib mesylate, the drug's high level of efficacy exceeded the sponsor's most optimistic expectations. Gleevec®'s success in treating Chronic Myeloid Leukemia during early trials led the company chairman to make a commitment of lifetime access for study participants. While providing a major boon to study participants, including some whose life expectancy was extended from "months" to potentially "decades," a comprehensive—and flexible—post-trial access (PTA) plan was required in order to fulfill this commitment.

The sponsor initiated Phase II registration studies in 1999, enrolling more than 1,000 participants. Although the PTA plan was not included in the informed consent form (ICF) for the earliest trials, ICFs for later trials notified study participants that they could continue to receive the drug for as long as the investigator determined that it was beneficial for the patient. Many patients, especially in the United States, transitioned to the commercial drug once it became available in 2001, which was a more convenient option for some than returning to the study site for treatment.

Although not considered post-trial responsibility (PTR), following the enrollment of global Phase II registration studies, the sponsor launched its expanded access studies, which enrolled more than 7,000 participants from 34 countries in less than 3 years in order to make this investigational therapy available prior to approval to patients who had not been enrolled in clinical trials. For these patients, it was established that the drug would be provided until it was commercially available in that country. A separate local transition plan was developed for each country based on local regulations, payor and access models. Under these plans, many patients transferred to the roll-over study; some transitioned to the commercial drug under their insurance coverage; and a number received free drugs via a patient assistance program.

### **What were some of the challenges to providing PTR for Gleevec®?**

Given the large numbers of patients being treated, it was a challenge to provide the drug and collect the appropriate amount of data required, without putting prohibitive burdens on the investigators and their staffs, patients, their families and the company. The sponsor was at that time also initiating and conducting other large trials studying earlier chronic phase CML patients, as well as patients with other life-threatening conditions, such as gastrointestinal stromal tumors.

### **What approach to PTR planning was most effective for Gleevec®?**

The sponsor found that proactive planning and anticipation of various scenarios is the best approach for PTR. However, the Gleevec® study demonstrated that clinically impactful study results which change the course of a life-threatening disease may require mid-stream adjustment and flexibility of PTR plans. Thus, sponsors should be prepared to adjust PTR plans during the

course of the development program, considering and adapting data collection and study procedures over time. Another factor critical to PTR planning was the partnership and commitment of multiple stakeholders, (including investigators and patients/patient groups) which enabled the sponsor to consider local regulations and limitations in order to work toward alignment of all stakeholders.

**Other questions to consider:**

- What is the duration of post-trial responsibilities?
- Does commercial availability satisfy obligations?
- Should all participants be treated equally?
- How should special post-trial provision such as patient assistance program be planned for uninsured or underinsured participants?
- Should various cohorts in the trial be differentiated? Should company size factor in to consideration of PTR obligations?

### **Stage 3: Decision Point 1 (at Individual Level)**

#### **D. Individualized Assessment versus Overall Study Results in a Pediatric Clinical Trial**

##### **Trial Background**

This case study demonstrates that an individualized determination of a patient's need for post-trial access (PTA) may impact the PTR plan, even when the risk-benefit for the trial population is not established. In this case, the patient was a 6-months-old enrolled in a clinical trial to evaluate the safety and efficacy of an investigational treatment in children 0 to 11 months old. The disease occurs more commonly in adults and there have been several drugs approved for use in this population, however, none had been approved for the same disease in the infant population. The patient had a history consistent with the disease and had failed medical therapies of the same class that were marketed, but not approved, in this population. Due to the patient's unique situation, he was granted post-trial access to the investigational therapy. Ultimately, the study did not meet its endpoints, and therefore market authorization for an indication in this population was not pursued.

The trial was designed as an open label run-in; those who had a positive response were randomized to placebo or active drug in a withdrawal design. During the 3-week open label period, the patient improved dramatically on the investigational drug. However, the patient's symptoms returned during the 5-week double-blind, placebo controlled, randomized withdrawal phase. Once the patient had completed the trial, the principal investigator who believed that the infant benefited from receiving open label drug during the run-in phase requested the investigational medicine for the patient. Although the informed consent form (ICF) was not

explicit regarding PTR, there was no PTR plan in place, and the drug's efficacy in the trial population was not established, the exigencies of the situation led the sponsor to approve post trial access to the drug.

#### **What considerations led to the adjustment of the PTR plan?**

Several factors led to the sponsor's decision to alter its PTR plan based on the patient's condition. First, although the condition is not life-threatening, it can lead to serious complications; the patient was an infant and thus there was a high level of concern regarding his well-being. Second, although alternative drugs were available, the patient had failed these therapies and so lacked other treatment options. Third, local regulations in this case required the sponsor to make the investigational drug available to study participants if the investigator believed that the subject benefited from the investigational therapy. With the force of law behind the investigator's request, the sponsor had a legal obligation to supply the investigational drug.

#### **Who was responsible for determining the PTR plan?**

In this case, there was a lack of clarity as to whether the sponsor or the investigator was most ideally situated to issue a determination regarding PTR. Having worked closely with patients, the investigator is more familiar with patients' needs and their reaction to the medication. The sponsor, on the other hand, is most familiar with the safety profile of the drug and has an obligation to assess risk/benefit of the drug for the target population.

#### **Other questions to consider:**

- Should sponsors have a consistent approach to PTA? If not, what are the criteria by which PTR should be determined?
- Who is responsible for the PTR plan determination?
- How should PTR be approached if a subset benefited from the drug but the overall trial did not meet the primary endpoint?
- What is the ethical obligation to make a non-commercialized formulation available for a non-life threatening disease?
- How should the potential benefit of investigational drug be balanced against the risks of adverse effects?

## **E. Extending a “Multi-Octave” antiretroviral study**

### **Trial Background**

As HIV/AIDS treatments have become more widely available around the world, a new problem has emerged for people with HIV and AIDS: over time, some people develop resistance to their original antiretroviral regimens, or acquire drug-resistant strains of HIV, and therefore require second- and third-line regimens. In high-income countries, these second-line and third-line regimens are formulated through plans that are tailored to the individual patient; such approaches have been deemed “impracticable” for low and middle-income countries. In order to test an algorithm that could efficiently approximate an individualized treatment plan, the National

Institute of Allergy and Infectious Diseases recently implemented a global, prospective interventional strategy study known as the Multi-Octave trial.

The Multi-Octave trial was a 48-week open label, Phase IV trial with sites in India, Brazil, Kenya, Malawi, Peru, South Africa, Thailand, and Uganda, which involved 500 HIV-1 infected adults failing a second-line regimen containing a protease inhibitor (a type of antiretroviral). At Step 1 of the trial, patients were assigned to one of four treatment cohorts. If virologic failure was detected, the patient would be then assigned into Step 2, a new treatment cohort. Researchers hypothesized that the combined algorithm, biologic testing, genotype resistance testing, and monitoring would enable a 65 percent or greater rate of success for biologic control at 48 weeks.

While the drugs included in the study were commercially available in high-income countries, they were not generally available in the trial countries. At the end of the trial, then, patients might be unable to access the treatment that was keeping them alive. Therefore, the research team decided to expand the study to include a Step 3, that would comprise an additional two years of treatment for participants who were benefiting from a given treatment regimen. For this step, the manufacturers of the three drugs that were not commercially available (darunavir, etravirine, and raltegravir) agreed to provide the drug free of charge. It was believed that after two years, the drugs would be approved, available, and marketed in these countries.

#### **How did NIH guidance on PTA impact the PTA plan?**

The NIH has issued limited guidance on PTA, which says that in the context of provision of antiretroviral (ARV) treatment for HIV ARV trials in developing countries, investigators are expected to address the provision of ARV treatment to trial participants after their completion of the trial. The NIH, however, cannot support or provide services following the completion of a trial. Here, the NIH researchers who worked out this plan acted in a way that was consistent with the NIH regulations, addressing the provision of ARV therapy to trial participants and identifying available sources of ARV treatment.

#### **What are the implications of incorporating PTA into a new study?**

In this case, what is normally referred to as a “post-trial” plan was incorporated into a new study. This approach offered certain benefits, such as enabling NIH researchers to maintain the standard of care beyond mere provision of the drug and comply with the regulation that forbids NIH to support or provide services following the completion of a trial. It also provided important information regarding the longer-term effectiveness of the drug regimens. On the other hand, the incorporation of PTA into a new study raised interesting questions such as whether a new ethical obligation arose to provide PTA after the additional study to fulfill the requirements of a responsible transition.

#### **Other questions to consider:**

- How long should post-trial access be provided?
- If a PTA endpoint depends on commercial availability in the host country, who bears the responsibility for the patient if the drugs are never approved by the host country?

- Beyond access to the drug, what other treatment should be provided as part of the PTA plan?
- If a sponsor is allowed to limit support of health services following the completion of a trial or not at all, how will PTR planning be adapted to fulfill the requirements of responsible transition and to leave no gaps in the care of study participants?

## **Stage 4: Decision Point 2 (at Program Level)**

### **F. Testing an antiretroviral therapy in Brazil**

#### **Trial Background**

At the height of the AIDS crisis in the late 1980s, therapies for HIV/AIDS remained limited. Pharmaceutical companies raced to find an efficacious treatment to address the major public health issue of the era. Indinavir, known as CRIXIVAN<sup>TM</sup>, was one of the first protease inhibitors. The introduction of protease inhibitors ushered in the era of modern HIV therapy, with highly active antiretroviral therapy (HAART). Through the FDA's accelerated drug approval regimen, the sponsor was able to obtain approval for indinavir in less than six years (despite major setbacks, including the failure of two lead compounds, as well as the tragic death of the sponsor's lead HIV biochemist in the bombing of Pan Am flight 103 over Lockerbie, Scotland).

The sponsor conducted late-stage trials for indinavir in the United States, Europe, Australia, and Brazil during the mid-1990s. Although the sponsor had not previously included developing countries in its major clinical trials, Brazil was one of the first countries to prioritize HIV prevention and control, and several centers of research excellence existed. Despite concerns that conducting a clinical trial in a developing country without well-established clinical trial research expertise might pose a risk for efficient clinical trial conduct, a combination of public health burden and local advocacy led the company to conduct the research in Brazil. Following demonstration of the safety and efficacy of indinavir in the trial, the sponsor determined that participants in all trial countries should receive post-trial access (PTA) to the drug.

#### **Why was PTA provided in Brazil?**

The decision to provide post-trial access (PTA) to indinavir was based upon several factors: 1) perception that the sponsor bore a responsibility to the participants, particularly due to the safety and efficacy demonstrated in the trial, the nature of the underlying disease, and the limited alternative therapeutic options in country; and 2) the general public health importance of monitoring the performance of the drug over a longer period of time (as it was expected that the drug would need to be administered chronically).

#### **What was included in Brazil's PTR plan?**

Due to Brazil's status as a developing country, the sponsor designed a unique PTA plan that differed in several key aspects from its PTA plan for the United States, Europe, and Australia. In wealthier countries, it was expected that the drug would become generally available shortly after licensure. In Brazil, the timing of access to indinavir following licensure was less certain. It was consequently decided to make the drug available for up to five years (as needed by the individual



patient), based on the expectation that five years following licensure would be a sufficient period to assure that the national health care system would be able to make the drug available through routine medical care. The sponsor also provided its sites in Brazil with critical infrastructure necessary for the trial such as laboratory equipment. Finally, the results of the Brazil-based clinical trial were published in a Brazilian journal; unfortunately, despite efforts by both investigators and the sponsor, the results of the extension studies were not published. This was a period of rapid progress in HIV therapeutics; by the time of completion of the extension study, journal editors did not consider the findings sufficiently novel to publish.

#### **How does this case relate to international standards for AIDS/HIV PTR?**

The sponsor's PTA plan for Brazil satisfied a majority of the post-trial recommendations that were later outlined by the International AIDS Society's Industry Liaison Forum in 2003. These included: making the treatment available for at least two years; avoiding the use of generic drugs; advancing continuing research during the PTR period; and location of studies preferentially in countries with national treatment programs. The sponsor did not meet the standard of detailing all responsibilities and demarcations for PTR in the pre-study contract with this trial since it did not have a formal PTR policy at the time.

#### **Other questions to consider:**

- Does the status of the country (emerging/developing) matter, or should all countries be treated equivalently?
- What is the responsibility of the host country versus the responsibility of the sponsor?
- Is there an obligation to support the country's medical infrastructure?
- What is the standard of care in the particular region, as related to treatment?
- How can sponsors ensure safety in monitoring patients following completion of the trial?

## **G. Access for control arm patients in childhood cancer study**

### **Trial Background**

A Phase III randomized controlled trial found that adding immunotherapy (specifically Ch.14.18 immunotherapy) to standard therapy significantly improved outcomes in patients with high-risk neuroblastoma when administered within 110 days of stem-cell transplantation. After careful deliberation and consultation, the children's oncology group committee decided to offer this immunotherapy to trial participants who had been in the control group and had not received immunotherapy—regardless of the time that had elapsed since their stem-cell transplantation. This decision was made in the context of a limited supply of antibodies for immunotherapy and with no data related to its efficacy when administered beyond 110 days.

### **What ethical considerations led to the adjustment of the PTR plan?**

Ch.14.18 immunotherapy was the first new agent that prolonged survival among children with high-risk neuroblastoma in more than a decade. Therefore, the committee believed that withholding the active drug from the randomly assigned control arm might be problematic. The

consultative process recognized the lack of evidence of efficacy when administered beyond 110 days, the potential serious adverse effects, and the limited drug supply. Ultimately, the committee decided to offer the drug to the control arm patients, who remained progression free, if specific eligibility criteria were met. Parents were informed that access was part of ongoing research, were asked to provide new authorization for their child, and were alerted in the crossover consent form to the possibility that no benefit would occur.

### **What considerations impact patient decision-making?**

Although the parents of 52 eligible children were offered access to Ch14.18 immunotherapy, only four parents accepted the offer. These four children enrolled at 391 to 550 days after stem-cell infusion. Speculating why most parents chose not to receive Ch14.18 for their children: issues could include concern about the quality of life and the associated toxicities of the treatment; the absence of data for using Ch14.18 immunotherapy late after stem-cell infusion; and given that their children may have experienced 8 to 10 months of intense chemotherapy prior to the offer of Ch14.18 immunotherapy, the additional 5 months or more of therapy may have been overwhelming.

### **Questions to consider:**

- How should PTR plans be designed to comply with responsible transition requirements for participants assigned to the control arm(s)?
- Do investigators have reciprocity-based obligations to prior and current research participants no matter what arm were they assigned to?
- Before starting a trial, should investigators be obliged to ensure that an adequate supply of the investigational medicine exists for all participants in the trial, and for how long?
- Does the extremely limited supply of an investigational medicine affect this obligation?
- How do researchers reconcile potential obligations to control-arm participants (using the drug within a timeframe for which there is no proven efficacy) with the likelihood that using the investigational medicine for this group may decrease availability of the investigational medicine for future patients?

### **Reference:**

Unguru, Y., Joffe, S., Fernandez, C. V., & Yu, A. L. (2013). Ethical issues for control-arm patients after revelation of benefits of experimental therapy: a framework modeled in neuroblastoma. *Journal of Clinical Oncology*, 31(5), 641-646.  
<http://doi.org/10.1200/JCO.2012.47.1227>



## Stage 5: Transition

### H. HIV Pediatric Study in Thailand

#### Trial Background

The PIANO study (Paediatric study of Intelence As an NNTRI Option) was an Investigational New Drug (IND) study of etravirine (ETR) that was initiated in 2009 in sixteen countries including Thailand. At the time of the study, ETR had not been approved to use in patients <18 years but was approved for use in adults only. The PIANO study was a Phase II study to evaluate the safety, tolerability and antiviral activity of ETR in antiretroviral experienced HIV-1 infected children and adolescents over a 48-week period. This study included children age 6-17 years who had experienced antiretroviral treatment (ART) with current viremia (HIV plasma viral load  $\geq 500$  copies/mL). The ETR dosing was according to the sponsor's treatment guideline. Children who were enrolled in the PIANO study received ETR from the sponsor plus a background regimen determined by genotyping results prior to start the study entry. The sponsor agreed to support the provision of all background regimen antiretrovirals (ARVs). However, information of PTR providing of ETR after the 48-week trial was not included in the original informed consent form (ICF) for study participants, although the sponsor agreed to provide PTR after the study end. This study occurred against a backdrop of no national regulatory guidance regarding PTR in Thailand.

In summary, the study drug (ETR) had good efficacy and was safe for use in children. Therefore, after the study completed their 48-week follow-up, all patients were offered the possibility of a roll-over to the long-term follow up study to continue monitoring of efficacy and safety of ETR. In this long-term follow up study, the sponsor notified investigators that the patient could continue to receive the study drug (ETR) according to the standard dosing guideline until the patient no longer benefited from the study drug or if ETR became available through the Thai Public Health System, or the study participant reached 18 years of age. In addition, backbone anti-retroviral treatments were reimbursed for 2 years. Information of providing the study drug (ETR), duration and conditions to discontinue ETR were included in the informed consent form at that time. Recently, the sponsor launched a new (PTR) study for continuing access to the study drug for children over the age of 18. Information of the PTR plan was included in the ICF. This plan indicated that participants could continue to receive the drug as long as they benefited from the treatment, and provided that they resided in countries in which the drug was not accessible, either because the drug was not commercially available, not reimbursable, or not available through a government program. The PTA included Etravirine and Darunavir, but did not include other therapies in the background regimen.

#### How did the lack of national PTA regulations impact the Etravirine PTR plan?

Thailand has no rule, regulation, guideline, or specific statement from the Ministry of Public Health, the Ethics Committee (EC), or other health authorities regarding PTR. It is also not mandated to include information on PTA in the ICF. The EC does generally include a comment regarding PTR in the protocol review. However, this is not mandatory and may depend on the EC's view. For the Etravirine study, because the provision of PTR and its inclusion in the ICF were not mandated, the sponsor had more freedom in determining its own PTR plan. Its experience in implementing the

study, as well as feedback from investigators and patients, led to a somewhat more robust PTR plan as the study progressed.

### **How did the weak national health infrastructure impact the Etravirine PTR plan?**

While the sponsor initially indicated that PTR would be provided until the drug became commercially available, this type of provision lacks effectiveness in a country with a relatively impoverished population and insufficient coverage from the National Health System. Therefore, investigators encouraged the sponsor to adjust the PTR plan such that PTR was provided until the drug was available through a government program. The background regimen, which the sponsor did not provide, also posed a significant problem for participants, as the background medicines were not covered by the National Health System.

### **Other questions to consider:**

- Should there be a PTA requirement for the background regimen in addition to the study drug? Whose obligation is this?
- Should inclusion of a PTR plan in the informed consent form be mandatory?
- In what regard should the sponsor's share of post-trial responsibilities increase in a developing country?
- How might PTA obligations interfere with healthcare development in the country?

## **I. Strategy Clinical Trial: cART**

### **Trial Background**

Strategy clinical trials are trials that test treatments outside the current country guidelines. The Effective Combination Antiretroviral Therapy (cART) for HIV (i.e., earlier HIV treatment regardless of the CD4 cell count) is one example of this type of trial. In the HPTN 052 study, participating couples were randomly assigned to an experimental group in which infected participants immediately began receiving cART or to a control group in which participants delayed taking antiretroviral treatment (ART) until either their CD4 counts fell below 250 cells/mm<sup>3</sup> or they were diagnosed with AIDS as defined by WHO guidelines (CD4+T cell count less than 200 cells/mm<sup>3</sup> at the time they began enrolling in 2005) (NIADID 2015).

If an individual participant benefits from such a study, the trial would require providing continued access to the investigational medicine as well as access to medical care to deliver that product, per the countries' policies. However, countries' guidelines often change only incrementally. The resource status of countries can further influence the continued access to medical care of the commercially available regimen.

### **Do changes in country guidelines affect the PTR plan?**

When the HPTN 052 study began enrolling participants in 2005, the country guidelines were consistent with WHO 2003 guidelines that proscribed therapy for patients with CD4 counts less than 200 cells/mm<sup>3</sup>. Over the course of the clinical trial, WHO modified its HIV guidelines twice to direct initiation of treatment to patients with CD4 counts less than 350 cells/mm<sup>3</sup> irrespective of clinical symptoms; countries, however, were reluctant to adopt the second revision mainly due to lack of drug supply (NIADID 2015). Notably, in these cases physicians and health care

providers were required to follow the National Guidelines. In the HPTN 052 study, the investigator maintained the study design with a slight modification. The study team explained the new WHO Guidelines and any corresponding changes in national guidelines to participants, and reminded them that they were free to leave or to start ART based on the local standard of care.

#### **Regulatory Landscape: What were the responsibilities after participants completed the trial?**

After the completion of the trial, sponsors/investigators referred all of the infected participants in the trial to local medical care for ongoing cART treatment (NIADID 2015).<sup>7</sup> A strategy for continued access was necessary for access to cART of the same or equivalent drug/products as those provided through the trial.

Responsibilities did not change for the (i) access to the investigational cART, (ii) the access to accompanying medical care, or medical care related to the investigational cART:

- For participants who ended the trial after Phase II for reasons not attributable to the participant, sponsors/investigators had an ethical obligation to refer them to local health care providers;
- For infected participants who completed the trial, sponsors/investigators had a responsibility to provide access to the investigational cART equivalent or refer them to the local health care provider.

#### **Other questions to consider:**

- How do changes in the international standard of care affect PTR plans?
- How do differences in the national and international standard of care recommendations affect PTR responsibilities of sponsors and researchers?
- Should participants be informed of changes in national and international recommendations of standard of care?

#### **Reference:**

National Institute of Allergy and Infectious Diseases (NIADID) (2015). Questions and Answers: The HPTN 052 Study. Available at: <http://www.niaid.nih.gov/news/Qa/pages/hptn052qa.aspx>, [accessed 30 October 2015]. Accessed August 30, 2016.

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<sup>7</sup> The modified protocol for a control group is that: start ART when CD4 count fell between 200 and 250 cells/mm<sup>3</sup>; entry criteria: modified from 300-500 cells/mm<sup>3</sup> to 350-550 cells/mm<sup>3</sup>.

## Keys to Using This Toolkit



## Section 4: Resources

This section includes resources for post-trial mechanisms and post-trial responsibilities such as country regulations.

### A. Post-Trial Mechanisms

Post-trial mechanisms refer to specific practices in order to comply with post-trial responsibilities. The same responsibility might be met with different methods in different settings, and different PTR mechanisms may need to be used and coordinated in order to secure access to individual research participants. PTR mechanisms can be divided into pre- and post-commercialization because of the difference in the regulations of licensed or unlicensed medical products. For instance, mechanisms to provide continued access with a beneficial investigational medicine before its licensure (pre-commercialization mechanisms) may include open-label trial extensions, rollover studies, separate protocols, or protocol amendments, as described in the table below. In some instances, particularly following late stage clinical trials, there may be mechanisms to provide continued access outside of a clinical trial protocol. Post-commercialization mechanism may include appropriate referral to the public health system, reimbursements, paying for private insurances when available, etc.

**Table 6: Pre-commercialization mechanisms**

Pre-commercialization Mechanism	Description
Built-in study extension	The original study protocol includes an option for continued access to the same treatment assigned during the study if the investigational medicine is beneficial to the study participant.
Open-label extension	All parties involved know which participants have been assigned to which intervention. Blinding is no longer needed. <sup>8</sup>
Protocol amendment	The protocol of the original study is amended to allow for continued access to a treatment that is beneficial for the study participant.

<sup>8</sup> <https://clinicaltrials.gov/ct2/about-studies/glossary#O>

Roll-over study	Patients from one study “roll over” to a second, related study. This can be after a fixed period of time or after another event (e.g., beneficial treatment response). <sup>9</sup>
Separate protocol /extension study	A new study protocol provides an opportunity for patients to enroll for continued access to a treatment that they benefited from in a prior study.

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<sup>9</sup> <http://i-base.info/ttfa/8-clinical-trials-and-research/8-14-glossary-of-other-terms/>

## B. Selected Country Regulations (current as of July 2015)

This resource provides a landscape view of different global regulations related to continued access to investigational medicines. It is not meant to be exhaustive nor a reference for current requirements. Anyone contemplating continued access should review current regulations in the respective country.

**Table 7: Selected country regulations**

Country	Organization	Rule	Location	Language	Content
Argentina	National Administration of Drugs, Foods and Medical Devices (ANMAT)	Provision 6677/2010	<a href="http://infoleg.mecon.gov.ar/infolegInternet/anexos/170000-174999/174557/norma.htm">http://infoleg.mecon.gov.ar/infolegInternet/anexos/170000-174999/174557/norma.htm</a> (Original language)  <a href="http://www.anmat.gov.ar/Comunicados/Disposiciones/Disposicion_6677-10_en.pdf">http://www.anmat.gov.ar/Comunicados/Disposiciones/Disposicion_6677-10_en.pdf</a> (English)	Spanish (English also available)	<p>SECTION B: DOCUMENTATION REQUIREMENTS FOR THE AUTHORIZATION OF CLINICAL PHARMACOLOGY STUDIES</p> <p>[4.] PROTOCOL</p> <p>[4.11.] Ethical Aspects</p> <p>[(f)] [plan of] access for participants to the intervention identified as beneficial in the trial or to an appropriate alternative or benefit upon completion of the trial;</p> <p>SECTION C: GUIDELINE FOR GOOD CLINICAL PRACTICE FOR PHARMACOLOGY STUDIES.</p> <p>[6.] PROTECTION OF STUDY PARTICIPANTS</p> <p>[6.4.] An investigator who is a doctor of medicine or a dentist, as appropriate, shall be responsible for all the participants' health care related decisions throughout the study.</p> <p>[6.8.] Participants requiring to continue their treatment after the study completion shall have access to the intervention that turned out to be beneficial or to an alternative intervention or another proper benefit, which shall be approved by the REC for the time it decides or until such access is ensured by any other means.</p>

National Administration of Drugs, Foods and Medical Devices (ANMAT)	FAQ of Provision 6677/2010	<a href="http://www.anmat.gov.ar/medicamentos/6677-10_Preguntas_y_Respuestas_Junio%202011.pdf">http://www.anmat.gov.ar/medicamentos/6677-10_Preguntas_y_Respuestas_Junio%202011.pdf</a>	Spanish	<p>[Question regarding paragraph C.6.8 above] What are the regulatory mechanisms for importing post-study medication?</p> <p>[Answer] The criterion for the decision to continue with the study treatment is the individual benefit. That is, the participant should continue with treatment that was beneficial for that case, according to the individual medical evaluation. At the end of the study, when it is required to continue to import a drug not yet licensed in the country for an indication and /or in that population, in a similar way as laid down in the protocol and according to the plan established or approved by the REC [research ethics committee] the possible mechanisms for the import authorization of the ANMAT are:</p> <p>(a) An extension study, which may be submitted with the original protocol;</p> <p>(b) single import authorization for compassionate use (Disp 840/95.); or</p> <p>(b) [sic.] import authorization for compassionate use post EFCA [post-Clinical Pharmacology Studies] (resolution under development)</p>
National Administration of Drugs, Foods and Medical Devices (ANMAT)	ANMAT-MED-UCO-001-00  Project of provision (Superseded by provision 12.792/2016)	Version 1.0  <a href="http://es.scribd.com/doc/254273983/Proyecto-ANMAT-2012-v1-0-Regimen-de-Acceso-Posinvestigacion">http://es.scribd.com/doc/254273983/Proyecto-ANMAT-2012-v1-0-Regimen-de-Acceso-Posinvestigacion</a>	Spanish	<p>ARTICLE 3 - In the application ACCESS FOR SUBJECT TO TREATMENT UNDER INVESTIGATION, the sponsor must submit:</p> <p>a) Letter of application indicating the involved health centers and the patients that will continue with therapy under investigation;</p> <p>b) General form of the informed consent for the patient;</p> <p>c) Copy of the disposition of authorization of EFCA [clinical pharmacology study] and certificates of approval of the corresponding site;</p>



					<p>d) Opinion of the REC [research ethics committee] corresponding to the site where the plan of access to treatment is approved;</p> <p>e) Approval of the responsible medical director of the site and researcher acceptance letter;</p> <p>f) Details of the products and quantities to be authorized for import by the sponsor</p> <p>ARTICLE 5 - Establish that the sponsor is subject to the obligation to inform to this ANMAT [National Administration of Drugs, Foods and Medical Devices] all suspected unexpected serious adverse reactions (SUSARs) related to the investigational medicine.</p>
	National Administration of Drugs, Foods and Medical Devices (ANMAT)	Disposition 12792/2016, Application procedure for import of medication / treatment and materials for post-study access	<a href="http://www.anmat.gov.ar/boletin_anmat/BO/Disposicion_12792-2016.pdf">http://www.anmat.gov.ar/boletin_anmat/BO/Disposicion_12792-2016.pdf</a>	Spanish	<p>That the intervention of the ethics committee, envisaged in Provision No. 6677/10, referred to in numeral 6.8 above, is intended to evaluate if it is appropriate the continuation of the treatment of the clinical study, once it is completed, identified as beneficial to the particular patient, and to ensure that the interests of each of the subjects are duly safeguarded, since it is an act of medical care and has no registration purpose.</p> <p>ARTICLE 1. The present provision establishes the APPLICATION PROCEDURE FOR IMPORT OF MEDICATION / TREATMENT / MATERIALS FOR POST-STUDY ACCESS to the persons participating in a clinical pharmacology study authorized by this National Administration.</p> <p>ARTICLE 2. Excluded from this provision are CLINICAL EXTENSION STUDIES AUTHORIZED BY THIS ADMINISTRATION, which will be governed by the</p>

					<p>Provision ANMAT 6677/ 2010, and in the terms of the respective authorization.</p> <p><b>ARTICLE 3. In the APPLICATION FOR IMPORT OF MEDICATION / TREATMENT and MATERIALS FOR POST-STUDY ACCESS</b>, prior to the completion of the study, the sponsor must submit:</p> <p>a) Note indicating the health centers involved and the list of potential patients to continue the research therapy, preserving the confidentiality regarding the identity of the persons; in due time, it will be submitted the final list of the patients actually included, with the same precautions;</p> <p>b) General informed consent formulary for the patient approved by the research ethics committee (REC) of the research site;</p> <p>c) Copy of the provision of authorization of the Clinical Study and proof of approval of the corresponding site;</p> <p>d) Opinion of the REC corresponding to the site in which the plan for access to medication / treatment is approved, who will follow up the plan;</p> <p>e) Authorization of the medical director responsible for the site and letter of acceptance of the investigator.</p> <p>f) Detail of the products, including the batch number and expiration date and quantities to be authorized to the sponsor for their importation, as well as the materials. These products</p>
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					<p>and materials should not differ from those used in the clinical study approved by this Administration.</p> <p>g) Statement from the sponsor that ensures that the provision of the medication / treatment and materials in question will be at no cost to the participant, the health care establishment or its health coverage.</p> <p>h) Authorization of the designated place for storage of the product to be imported.</p> <p>ARTICLE 4. This Administration, through the Department of Evaluation and Registration of Medicines (DERM), will intervene verifying the documentation submitted and will authorize or reject the application for IMPORT OF MEDICATION / TREATMENT and MATERIALS FOR POST-STUDY ACCESS, in the site(s) in charge of the respective investigator, stating that it will be effective for twelve months from the date of approval of the procedure.</p> <p>ARTICLE 5. The importation of the products indicated in the subsection f of article 3 will be substantiated before the Department of Foreign Trade of INAME.</p> <p>ARTICLE 6. The sponsor is obliged to inform ANMAT of any adverse drug reactions serious and unexpected related to the Medication / Treatment, imported according to the procedure established by this provision. The communication will be made by separate procedure, referring to the authorization file of the Clinical Study and to which the post-study provision was authorized</p>
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	Ministry of Health	Provision 1480/2011	<a href="http://www.infoleg.gov.ar/infolegInternet/verNorma.do;jsessionid=650B877AF7D1E6B7C272DE595DF81C53?id=187206">http://www.infoleg.gov.ar/infolegInternet/verNorma.do;jsessionid=650B877AF7D1E6B7C272DE595DF81C53?id=187206</a>	Spanish	<p>SECTION A: ETHICAL ASPECTS. A9. SPECIAL CONSIDERATIONS FOR CLINICAL TRIALS. P19. When finalizing the investigation, all participants should share the benefits that have arisen from it, for example, continue to receive the intervention that has been identified as the most beneficial for them. If it is not possible to ensure that intervention, for a justified reason, it must be guaranteed access to an appropriate intervention or other adequate alternative benefit, approved by the REC [research ethics committee] and for the period of time the REC determines or until access is guaranteed by other means</p> <p>In particular, in clinical trials sponsored by a pharmaceutical company that have demonstrated that an experimental product is beneficial, the sponsor should continue its provision to participants until their access is guaranteed by other means. The requirement of this requirement should be determined on the basis of certain relevant considerations, such as the severity of the medical condition in question and the expected effect of withdrawing or modifying treatment, such as leaving a sequel or causing the death of the patient. When it is not possible to fully comply [with this requirement], it may be agreed to provide an alternative intervention or other appropriate benefit, approved by the REC and for a period determined by the REC.</p>
	Ministry of Health	Circular No. 9/2009 HIV Programs		Spanish	<p>1- Every laboratory sponsoring a research study MUST [sic] provide ALL the medication (study Drug plus accompanying Drugs) until the end of the study.</p> <p>2- Once the study is completed [the sponsoring laboratory] must provide ALL the drugs that are not available through the usual suppliers (in this case, the drugs that are NOT included</p>

					in the Vademecum of the AIDS Office) until they are incorporated and distributed by the usual supplier.
	Argentine National Congress <sup>10</sup>	Law 26.994 Argentina Civil and Commercial Code Article 58, subsection (j)	<a href="http://www.infoleg.gob.ar/infolegInternet/anexos/235000-239999/235975/texact.htm">http://www.infoleg.gob.ar/infolegInternet/anexos/235000-239999/235975/texact.htm</a>	Spanish	Article 58. Research in humans. Medical research involving humans through interventions such as treatment, prevention methods, diagnostic or predictive tests, whose efficacy and safety are not proven scientifically, can only be realized if it complies with the following requirements: [...] j) to ensure research participants the availability and accessibility to treatments that research has shown beneficial.
Brazil	Health Surveillance Agency (Anvisa)	RDC 38/2013	<a href="http://www.sbppc.org.br/site/images/publicacoes/dou%20-%20resolu%E7%E3o%20rdc%2038_%20de%2012%20de%20agosto%20de%202013.pdf">http://www.sbppc.org.br/site/images/publicacoes/dou%20-%20resolu%E7%E3o%20rdc%2038_%20de%2012%20de%20agosto%20de%202013.pdf</a>	Portuguese	Chapter V – Post-trial provision of drugs Art. 15 – The provision of treatment after the trial is concluded will be available free of cost to research subjects, for as long as it is beneficial, according to medical criteria. Art. 18 – It is the responsibility of the sponsors: (...) (I) the provision of free and comprehensive treatment with the drug that is object of expanded access and post-trial access programs; (...) (V) the provision of financial resources for the comprehensive care for the side effects and harm derived from predicted and unpredicted risks related to the use of drugs that are object of expanded access or post-trial access
	Health Surveillance Agency (Anvisa)	Law 6.360, September 1976	<a href="http://www.anvisa.gov.br/legis/consolidada/lei_6360_76.pdf">http://www.anvisa.gov.br/legis/consolidada/lei_6360_76.pdf</a>	Portuguese	Article 12 – None of the products mentioned in this Law, including imported ones, can be industrialized, exposed for sale or delivered to the consumer before it is registered with the Ministry of Health,

<sup>10</sup> [http://en.wikipedia.org/wiki/Argentine\\_National\\_Congress](http://en.wikipedia.org/wiki/Argentine_National_Congress)

					except for – Article 24 – New drugs for experimental use only do not need to be registered with the National Health Surveillance Agency and may be imported with the explicit authorization of the Ministry of Health.
	National Health Council	Resolution 196/1996 (Not current; replaced by 466/2012)	<a href="http://conselho.saude.gov.br/resolucoes/1996/Reso196.doc">http://conselho.saude.gov.br/resolucoes/1996/Reso196.doc</a>	Portuguese	(III.3m): “ensure that research carried out in communities, wherever possible, will translate into benefits of which effects will continue to be felt after its completion”; (III.3n) “ensure the return of benefits gained through researches to individuals and the communities in which they are carried out”; (III.3p) “to ensure the research subjects will receive the benefits resulting from the project, either in terms of social return, access to procedures, products or investigation agents”; (V.3) “as soon as the superiority of one method undergoing investigation over another is established, the project should be suspended, and all subjects must be offered the benefits of the best regimen”; (VI.3h) “present estimates of reimbursements to research subjects; the amount cannot be such that it may interfere with the autonomy of the individual’s or the person in charge of this decision on whether or not participate in the research”.
	National Health Council	Resolution 251/1997	<a href="http://conselho.saude.gov.br/resolucoes/reso_97.htm">http://conselho.saude.gov.br/resolucoes/reso_97.htm</a>	Portuguese	“IV. 1 - access to the medicine being tested must be assured by the sponsor or, if there is no sponsor, by the institution, researcher, or promoter in the event that its superiority over the conventional treatment is proven.”
	National Health Council	Resolution 404/2008	<a href="http://conselho.saude.gov.br/resolucoes">http://conselho.saude.gov.br/resolucoes</a>	Portuguese	“Considering the responsibility of the CNS to protect the integrity of research subjects and the several existing national and international guidelines, all participating patients must have guaranteed access to the best methods identified by the

			/reso_08.htm		study, preserving the 2000 version of the Declaration of Helsinki”
	National Health Council	Resolution 466/2012	<a href="http://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf">http://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf</a>	Portuguese	<p>“III.3 – Biomedical research studies of experimental methods involving human subjects, (...) should (...): d)</p> <p>Ensure all participants at the conclusion of the study free access by the sponsor, and for an indeterminate period, to the best prophylactic, diagnostic and therapeutic methods the efficacy of which have been demonstrated.</p> <p>d.1) Access will also be ensured during the interval between the end of an individual participation and the conclusion of the study, which may occur through expanded access programs, according to the medical assessment of the physician assisting the participant.”</p>
Chile	Chilean Congress	Ley 20850/2015 (Ricarte Soto Law), June 2015	<a href="http://www.leychile.cl/Navegar?idNorma=1078148&amp;idParte=">http://www.leychile.cl/Navegar?idNorma=1078148&amp;idParte=</a>	Spanish	<p>Article 17</p> <p>(...) clinical trial subjects will have the right to continue receiving free of cost the treatment administered according to the clinical protocol from the holder of the "special provisional authorization for research purpose" or, where appropriate, from the holder of the registration, even when the trial is concluded and while the therapeutic utility remains.</p> <p>Article 111 C.-</p> <p>Clinical trial subjects, once concluded the study, will have the right to continue receiving the treatment free of cost from the holder of the "the special provisional authorization for research purpose" and, afterwards, from the holder of the sanitary registration of the referred treatment for as long as its therapeutic necessity remains, according to the respective clinical protocol.</p>

					This obligation applies to the holder of the sanitary registration even when it has not been the holder of "the special provisional authorization for research purpose" or if the registry has been purchased afterwards.
Costa Rica	Costa Rican Congress	Law for the Regulation of Biomedical Research, (Law 9234), Article 28, April 2014	<a href="http://www.pgrweb.go.cr/scij/Busqueda/Normativa/Normas/nrm_texto_completo.aspx?param1=NRTC&amp;nValor1=1&amp;nValor2=77070&amp;nValor3=96424&amp;strTipM=TC">http://www.pgrweb.go.cr/scij/Busqueda/Normativa/Normas/nrm_texto_completo.aspx?param1=NRTC&amp;nValor1=1&amp;nValor2=77070&amp;nValor3=96424&amp;strTipM=TC</a>	Spanish	<p>Article 28 – “The right to enjoy the benefits that result from a trial.</p> <p>The participants in a clinical trial shall have the right to enjoy, free of cost and for as long as they require them, the preventive, therapeutic and diagnostic treatments generated by the trial if it is demonstrated that they are beneficial to health whenever the prescription of these methods or treatments are endorsed by the professionals responsible for the patient’s treatment and follow-up, and according to what is expressed in this act.”</p> <p>Article 53 – “The duties of sponsors (...)</p> <p>k) To provide the participant, free of cost and after the conclusion of the clinical trial, the drug, device or procedure that was the object of a trial, except if</p> <ul style="list-style-type: none"> <li>i) the drug, device or procedure stops being effective or required for the participant, which should be established by the doctor treating the patient through a reasoned declaration (...)</li> <li>ii) the development of such drug, device or procedure is suspended.</li> <li>iii) the researcher certifies that it is not indispensable to preserve the participant’s health and there are therapeutic alternatives.</li> <li>iv) the patient does not sign the informed consent required the continuity of the treatment.”</li> </ul>
Israel	Ministry of Health	Ministry of Health Directive	<a href="http://www.health.gov.il/Laws/Pages">http://www.health.gov.il/Laws/Pages</a>	Hebrew	<b>17.1</b> “If it transpires after completion of a clinical trial, and is recommended by the Principal Investigator that the wellbeing of the patient participating in the trial requires continued



			/Legislation Page.aspx	<p>treatment with the investigational medicine and no other alternative treatment is appropriate for him/her, the patient shall continue to receive the investigational medicine, free of charge, in accordance with a written structured follow-up protocol, even after completion of the clinical trial, for a period not exceeding 3 years, except in one of the following instances:</p> <ul style="list-style-type: none"> <li>a. The Investigational medicine has been approved for marketing in the State of Israel for the indication and is available from the HMO with which the patient is insured. [1]</li> <li>b. Development of the product was discontinued or the clinical trials of the product were not successful.</li> <li>c. Administration of the Investigational medicine for such a prolonged period of time may jeopardize the patient's health due to insufficient information about the long-term safety of the product.</li> <li>d. When the Investigational medicine is not a medicinal product, such as a cosmetic product / food / food supplement / medicinal herb.</li> </ul> <p><b>17.2</b> The decision on continued provision of the Investigational medicine is made by the Institutional Ethics Committee, which may reconsider its decision periodically. The Principal Investigator and the Sponsor have the right to appeal this decision to the Director General of the Ministry of Health or his designee, appointed for this purpose.</p> <p><b>17.3</b> Continued provision of Investigational medicine after completion of the clinical trial is subject to the following conditions:</p> <p><b>17.3.1</b> Continued treatment shall be governed by a structured follow-up protocol to be written by the Principal Investigator and approved by the Sponsor and the Institutional Ethics Committee.</p>
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					<p><b>17.3.2</b> Continued treatment shall be provided to the participant, after approval by the Director of the medical institution, as is customary with clinical trial applications.</p> <p><b>17.3.3</b> The Principal Investigator is responsible for the ongoing monitoring of the patient's health condition and for reporting to the Ethics Committee on any adverse events occurring during the follow-up treatment, as generally accepted in clinical trials.</p> <p><b>17.3.4</b> The Principal Investigator shall report to the Ethics Committee at least once a year on the progress of the patient's treatment.</p> <p><b>17.3.5</b> The Medical Institution, in which continued treatment is being provided, shall take out appropriate insurance to cover the liability of the Medical Institution and the Principal Investigator towards the patient, in the settings of continued provision of the investigational medicine after completion of the clinical trial."</p>
Portugal	National Authority of Medicines and Health Products (INFARMED)	Law 46/2004	<a href="http://www.fcsaude.ubi.pt/comissaoetica/docs/Lei_2004_46.pdf">http://www.fcsaude.ubi.pt/comissaoetica/docs/Lei_2004_46.pdf</a>	Portuguese	<p>Article 39(2) of Law 46/2004 on Clinical Trials states: "After the end of the trial and until its introduction onto the market, the investigational medicinal product shall be made available free of charge by the sponsor to the trial subject, if the investigator considers that continuation of its use by the trial subject is essential and there are no therapeutic alternatives."</p> <p>Article 2 of Law 46/2004 defines "investigational medicinal product" as: "a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form."</p>

Uruguay	Ministry of Public Health	Decreto 379/008	<a href="http://archivos.presidencia.gub.uy/web/decretos/2008/08/C515_26%2006%202008_00001.PDF">http://archivos.presidencia.gub.uy/web/decretos/2008/08/C515_26%2006%202008_00001.PDF</a>	Spanish	Art. 24 "[Once] the investigation has been completed, all patients participating in the study should be assured of access to benefits demonstrated in the investigation" --- <i>This regulation is not in force because the National Research Ethics Committee, which would regulate PTA, has not yet been created</i>
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