MRCT Center Post-Trial Responsibilities

Continued Access to Investigational Medicines Guidance Document

Framework

MULTI-REGIONAL CLINICAL TRIALS

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

Version 1.2

22 November 2017

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

Post-Trial Responsibilities Framework: Continued Access to Investigational Medicines Guidance Document

Table of Contents

Table of Figures

Key Tables

1. WRITERS AND REVIEWERS OF PTR GUIDANCE DOCUMENT AND TOOLKIT

Primary Authors

Carmen Aldinger	Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center)
Barbara E. Bierer	MRCT Center/ Brigham and Women's Hospital / Harvard Medical School
Rebecca Li	MRCT Center/ Brigham and Women's Hospital / Harvard Medical School
Luann Van Campen	Eli Lilly and Company

Additional Authors

Mark Barnes	MRCT Center/ Ropes & Gray LLP
Eileen Bedell	Takeda Pharmaceuticals
Amanda Brown-Inz	MRCT Center
Robin Gibbs	Takeda Pharmaceuticals
Deborah Henderson	Merck
Christopher Kabacinski	MRCT Center
Laurie Letvak	Novartis
Susan Manoff	Merck
Ignacio Mastroleo	CONICET – FLACSO Bioethics Program, Argentina
Ellie Okada	Boston Cancer Policy Institute
Usharani Pingali	Nizam's Institute of Medical Sciences, Hyderabad, India
Wasana Prasitsuebsai	HIV-NAT (The HIV Netherlands Australia Thailand Research Collaboration), TRCARC (Thai Red Cross AIDS Research Centre), Thailand

Hans Spiegel	Henry M. Jackson Foundation for the Advancement of Military Medicine
Daniel Wang	Queen Mary, University of London, United Kingdom
Susan Briggs Watson	Eli Lilly and Company
Marc Wilenzik	International Aids Vaccine Initiative

Reviewers

Mary Ellen Allen	Genentech
Rafael Dal Re	Ciudad Universitaria de Cantoblanco, Spain
Ricardo Eccard da Silva	ANVISA, Brazil
Elizabeth Frank	Dana-Farber Cancer Institute
Christine Grady	National Institutes of Health
Ariella Kelman	Genentech/Roche Group
Otmar Kloiber	World Medical Association
Bernard Lo	Greenwall Foundation
Amy Paul	Johns Hopkins University
Juliana Rossi	Eli Lilly and Company
Jessica Scott	GlaxoSmithKline
Sheldon Sloan	Johnson and Johnson
Walter Straus	Merck
Mitchell Warren	AVAC

Disclaimer: All author and reviewer contributions and comments were considered but not all were necessarily incorporated. All authors and reviewers and their respective institutions have not necessarily endorsed this framework.

Post-Trial Responsibilities Workgroup

Carmen Aldinger	MRCT Center
Mark Barnes	MRCT Center/ Ropes & Gray LLP
Eileen Bedell	Takeda Pharmaceuticals
Barbara E. Bierer	MRCT Center/ Brigham and Women's Hospital / Harvard Medical School
Amanda Brown-Inz	MRCT Center / Harvard Law School
Rhea Coler	IDRI/ Bill and Melinda Gates Foundation
Sonia Dainesi	Recepta Biopharma S.A., formerly: UCB Biopharma S.A., Brazil
Ricardo Eccard da Silva	ANVISA, Brazil
Pamela Gavin	National Organization for Rare Disorders
Robin Gibbs	Takeda Pharmaceuticals
Kate Heffernan	Verrill Dana LLP
Deborah Henderson	Merck
Joan Herbert	MMV, Bill and Melinda Gates Foundation
Patrick Kelly	Takeda Pharmaceuticals
Ariella Kelman	Genentech/ Roche Group
Laurie Letvak	Novartis
Rebecca Li	MRCT Center/ Brigham and Women's Hospital / Harvard Medical School
Susan Manoff	Merck
Ignacio Mastroleo	FLACSO Bioethics Program, Argentina
Lindsay McNair	WIRB-Copernicus Group
Ramadhani Abdallah Noor	Harvard T.H. Chan School of Public Health
Ellie Okada	Boston Cancer Policy Institute
Wellington Oyibo	University of Lagos, Nigeria
Usharani Pingali	Nizam's Institute of Medical Sciences, Hyderabad, India

Wasana Prasitsuebsai	HIV-NAT (The HIV Netherlands Australia Thailand Research Collaboration), TRCARC (Thai Red Cross AIDS Research Centre), Thailand
Juliana Rossi	Eli Lilly and Company, Brazil
Beth Roxland	Johnson & Johnson
Jessica Scott	GlaxoSmithKline
Seema Shah	National Institutes of Health (NIH)
Lana Skirboll	Sanofi
Sheldon Sloan	Johnson and Johnson
Hans Spiegel	Henry M. Jackson Foundation for the Advancement of Military Medicine
Walter Straus	Merck
Jeremy Sugarman	Johns Hopkins Berman Institute of Bioethics
Jocelyn Ulrich	PhRMA
Luann Van Campen	Eli Lilly and Company
Daniel Wang	Queen Mary / University of London, United Kingdom
Jayne Ware	Merck
Mitchell Warren	AVAC
Marc Wilenzick	International Aids Vaccine Initiative

2. EXECUTIVE SUMMARY

The MRCT Center Post-Trial Responsibilities: Continued Access to an Investigational Medicine Framework outlines a case-based, principled, stakeholder approach to evaluate and guide ethical responsibilities to provide continued access to an investigational medicine at the conclusion of a patient's participation in a clinical trial. The Post-trial Responsibilities (PTR) Framework includes this *Guidance Document* as well as the accompanying *Toolkit*. A 41-member international multi-stakeholder Workgroup convened by the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard University (MRCT Center) developed this Guidance and Toolkit.

Background

A number of international organizations have discussed the responsibilities stakeholders have to provide continued access to investigational medicines. The World Medical Association, for example, addressed post-trial access to medicines in Paragraph 34 of the Declaration of Helsinki (World Medical Association, 1964; Amended 2013):

> *"In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process."*

The Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), states in its *International Ethical Guidelines for Biomedical Research Involving Human Subjects:*

> *"Before requesting an individual's consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand …*

> *[W]hether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them…" (CIOMS, 2002).*

These paragraphs and other international guidance documents converge on several consensus points:

- Post-trial access (hereafter referred to as "continued access" in this Framework [for terminology clarification – see definitions]) is a shared responsibility of sponsors, researchers, and host country governments;
- The plan for continued access should be determined before the trial begins, and before any individual gives their informed consent;
- The protocol should delineate continued access plans; and
- The plan should be transparent to potential participants and explained during the informed consent process.

However, there is no guidance on how to fulfill these responsibilities (i.e., linking specific responsibilities with specific stakeholders, conditions, and duration). To fill this gap, the MRCT Center convened a working group in September of 2014 to develop a framework to guide stakeholders with identified responsibilities. This resultant Framework sets forth applicable principles, approaches, recommendations and ethical rationales for PTR regarding continued access to investigational medicines for research participants.

Project Scope

Although there are a number of important responsibilities associated with the end of an individual's participation in a clinical trial, the Workgroup agreed to the following scope for this project:

- Continued access to the intervention (either investigational medicines or comparator) at the conclusion of study participation

- Continued access to necessary medical care for appropriate provision of the investigational medicine (or comparator)

- Continued access to health care infrastructure required for appropriate provision of the investigational medicine (or comparator)

The Workgroup limited its consideration to interventional studies involving clinical treatment of participants, and excluded consideration of studies with healthy participants as well as non-therapeutic studies (e.g., mechanistic studies). Further, the Workgroup did not address responsibilities to the broader host community or country or to the scientific community at large. This framework is intended to be applicable to all sponsors of clinical trials of investigational medicines, including for-profit or not-for profit organizations, government agencies and academic institutions. It is also intended to apply to sponsors and sponsor-investigators, as described further below.

Overview of the Framework

The Framework provides both narrative background and guidance as well as a practical toolkit to guide planning, discussions and decisions:

1. Guidance Document (this document)

    a. Background

        i. Introduction
        ii. Terminology and Definitions
        iii. Existing Reference Guidance
        iv. Ethical Principles
        v. Stakeholder Roles

    b. MRCT Guidance

        i. Paradigm: Stages, Criteria and Stakeholder Considerations
        ii. General Guidance
        iii. Specific Guidance
        iv. Special Considerations

2. Toolkit (companion document)
    a. Decision-making tools
    b. Case studies
    c. Resources

Paradigm for the Framework: Stages, Criteria and Stakeholder Responsibilities for Continued Access

Decision Stages of Continued Access

For purposes of description, as described below, we have divided the critical decision-making in clinical trials with respect to PTR into five theoretical "stages," in which the sponsor is responsible for some parts and the participant/investigator others. Some decisions are made principally by the sponsor, depending on what is known about the medicine, the drug development program and the disease/condition under study; we term this the "Study Program Level." At some decisional points, the response of the individual participant to the investigational medicine is evaluated; we term this the "Individual Participant Level." These stages are generally, but not strictly, arrayed in time across the course of a clinical trial (see also Section 4.2.1).

Stage 1: Planning

At the Study Program Level, the sponsor is responsible for planning before the trial begins. The sponsor should evaluate whether the drug and disease/condition under study may potentially meet criteria (see below) for continued access. If so, the sponsor should develop a plan, in collaboration with relevant stakeholders, to determine the circumstances and conditions for continued access including establishing criteria for the transition of a patient to another mechanism of access. In multinational clinical trials, the sponsor should plan continued access based on national legislation and local health care capabilities of the clinical sites, and involving the cognizant research ethics committees and regulatory agencies of each country as appropriate.

Stage 2: Monitoring of available alternatives

At the Study Program Level, the sponsor is responsible for ongoing monitoring throughout the course of the clinical study and drug development program to assess whether an unmet medical need persists that requires continued access to the investigational medicine. In other words, during the course of the clinical trial, other interventions may become available that modify or eliminate the ethical justification to provide continued access. This monitoring responsibility is differentiated from monitoring of adverse events.

Stage 3: Decision Point 1

At the Individual Participant Level, the investigator is responsible for the first operative decision. At the participant's last patient visit, the investigator evaluates and communicates (to the patient and sponsor) whether the individual's benefit/risk assessment warrants continued access to the intervention(s) received during the trial (investigational medicine or comparator, and associated medical care, as discussed below) in accordance with Study Program planning.

In some trial designs, where it is not possible to know if the participant has had benefit at the last visit (e.g. in asymptomatic condition where the endpoint is prevention, or in trials in which the endpoint is progression-free survival etc.), there would be no rationale to continue therapy after completion of the trial unless the results are known.

Stage 4: Decision Point 2

At the Study Program Level, the sponsor is responsible for a second operative decision. After database lock and data analysis, the sponsor evaluates whether the overall study population benefit/risk assessment warrants ongoing continued access to the investigational medicine (or comparator medicine). In certain instances, the benefit/risk assessment will be so positive as to warrant consideration of providing access to everyone on study. In others, safety concerns or lack of efficacy may warrant reconsideration of continued provision; each should be communicated to the

investigators, and this will likely trigger further discussion of individual participant treatment decisions with the sponsor. Other decisions may be made, as described in detail below.

Stage 5: Transition

At the Individual Participant Level, the investigator is responsible for a third operative decision as to whether and when participants should be transitioned from the investigational medicine (or comparator). Events such as the commercial availability of the investigational medicine, other satisfactory alternatives for treatment (see Stage 2), the participant no longer requiring treatment, the medicine's lack of efficacy, or the occurrence of adverse events may trigger a transition decision.

Notably, the decisions made at the Study Program level are (generally) the responsibility of the sponsor of the study; the decisions made at the Individual Participant level are (generally) the responsibility of the investigator caring for the participant.

Continued Access Criteria

The sponsor and the investigator should weigh a number of interdependent criteria to inform decisions about the provision of continued access at both a Study Program and Individual Participant level (see Section 4.2.2). These criteria include the following:

a. Study Program Level (Sponsor)

   i. The disease under study is serious or life-threatening and/or the research participant could be adversely impacted if the medicine were to be discontinued;
   ii. The investigational medicine addresses an unmet medical need in that there are no suitable therapeutic alternatives available to participants;
   iii. There is no alternative access to the investigational medicine;
   iv. The provision of continued access to the investigational medicine will not affect the viability of the research or the ability to complete the trial or other trials being conducted to develop the new medicine; and

v. After data lock and analysis of the results, the overall study population benefit/risk assessment is favorable.

b. Individual Participant Level (Investigator)

i. The eligible participant has completed the clinical trial protocol;[1] and
ii. There is demonstrable evidence of benefit exceeding risk for an individual participant as determined by the investigator.

Stakeholder Responsibilities

Stakeholder post-trial responsibilities (PTR) change during the drug development program. The responsibilities at the outset of drug development (e.g. Phase I trials, when little is known about the safety or efficacy of the medicine) differ greatly than those after registration and approval by the appropriate regulatory authority. Figure 1 shows the evolution of stakeholder PTR over time (see Section 4.2.4).

Fig. 1: Post-Trial Responsibilities along investigational medicine approval pathway: from clinical trials to general access

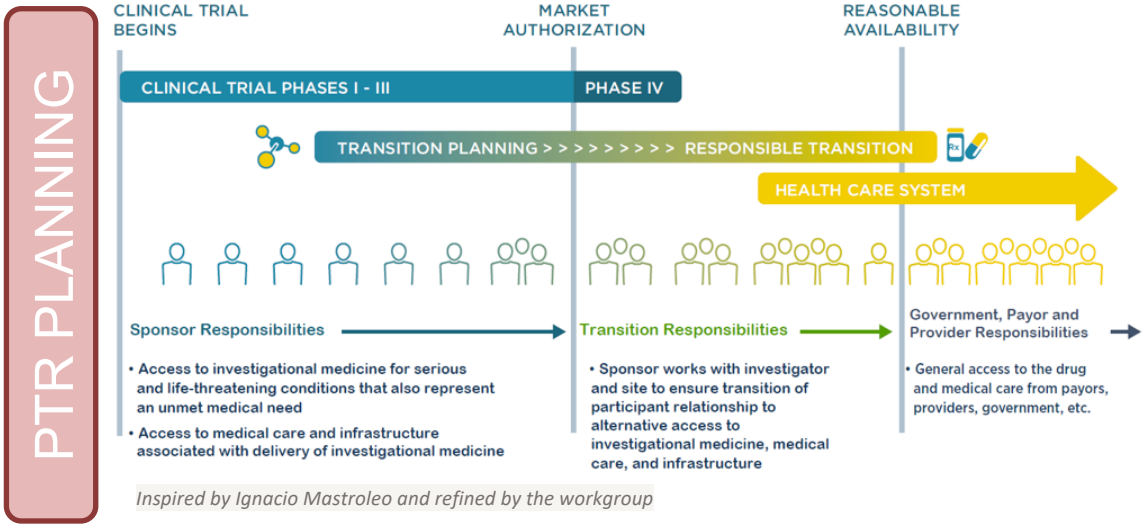


Figure 1 shows selected responsibilities for providing continued access. Prior to this, the "Continued Access Criteria" (see page 9), need to be applied to inform the decision of whether to provide continued access.

[1] If the participant voluntarily withdraws during the study, continued access should not be provided.

Summary of the Guidance Document

The following is a summary of the key points from this guidance document:

Ethical Principles Employed (see Section 3.3)

- General ethical considerations in biomedical research in concert with PTR duties
- Non-maleficence
- Autonomy and Respect for Persons
- Justice (Distributive and Justice as Reciprocity)
- Beneficence

Principles Applied to Guidance on Continued Access to Investigational Medicines

1) Post-trial responsibilities to a research participant (patient) at the end of participation in a clinical trial are **shared among all stakeholders**: sponsor, investigator, site, health care provider, health care system and the participant. (See Section 4.2.4)

2) Provision of continued access is a **bounded and not a limitless responsibility** of any one stakeholder. (See Section 4.1)

3) **Responsibilities are generally equivalent** whether the sponsor is a for-profit, not-for-profit or governmental agency, and whether the trial is conducted in a well- or low-resourced setting. (See Section 4.3.1)

4) **Provision of continued access must be fair** and not inadvertently advantage some and harm others. (See Section 3.3)

5) The plan to offer or not to offer continued access to an investigational medicine should be **determined before a trial begins and appropriately communicated** to investigators, ethics committees and participants. (See Section 4.3.1)

6) If there is **evidence of benefit exceeding risk**, and importantly in settings of unmet medical need, continued access to a beneficial treatment should be considered for a participant.

7) Decisions regarding the provision of continued access to an investigational medicine or comparator to a participant are made on a **case-by-case basis**, influenced by the patient's clinical condition, the benefit/risk assessment and response to the intervention, and what is known about the investigational medicine at the time of the decision. (See Section 4.2.2 and Section 4.3.2)

8) Generally, **informed consent for continued access** should be solicited prior to provision of the medicine. (see Section 4.3.1)

9) If continued access to an investigational medicine is offered, **medical care and infrastructure** specifically necessary for the appropriate provision of the investigational medicine must also be provided. (See Section 4.3.3 and Section 4.3.4)

10) Continued access to an investigational medicine should always be provided under mechanisms that **satisfy local regulatory requirements** for investigational medicines. (see Section 4.3.1 and Section 4.4.1)

11) The sponsor is responsible for **continuously assessing whether there is an ongoing unmet medical need** for the investigational medicine during the clinical trial and drug development program. (see Section 4.2.1)

12) For the health and safety of an individual participant, **responsible transition** from the investigational medicine to other appropriate care may be, and is often, necessary.

3. BACKGROUND

3.1 Introduction

3.1.1 History, Scope, and Purpose of the Framework

History of the Project

In September 2014, the MRCT Center and the Petrie Flom Center for Bioethics at Harvard Law School co-hosted a conference entitled "Post-Trial Responsibilities: Ethics and Implementation." Proceedings of that conference are available (MRCT Center, 2014). That conference, and a review of the literature, revealed a number of different definitions and interpretations of PTR, a lack of clarity and specificity in guidance documents, and uncertainty regarding by who, to whom, when, why and for how long continued access to investigational medicines (or comparator) should be fulfilled. The lack of clarity has, in turn, led to varying approaches to PTR.

Subsequently, in February 2015, the MRCT Center assembled the Post Trial Responsibilities Workgroup, co-chaired by Barbara E. Bierer, M.D. (Brigham and Women's Hospital/MRCT Center) and Luann Van Camped, Ph.D., MA-Bioethics (Eli Lilly and Company).

The PTR Workgroup comprised 41 members from 11 countries and included academics, practitioners, industry representatives, government representatives, and patient advocates. Participants are listed in the Appendix.

Scope of the Project

Consensus View

There was consensus that the topic of PTR should encompass multiple stakeholder responsibilities, and that individual research participants comprise the primary group to whom responsibilities are due, as they assume the risk of the research. Therefore, the Workgroup focused on delineating responsibilities to individual research participants when they have completed clinical trial participation or at the conclusion of a clinical trial itself, rather than to the broader host community or country or to the scientific community at large.

There was also consensus that the scope of the Framework should focus primarily on access to investigational medicines (and/or the comparator in a blinded trial.) Because investigational devices have unique challenges, they will be addressed more thoroughly in a follow-on MRCT Center multi-stakeholder workgroup.

Rationale for Scope

There are a number of potential benefits of clinical trial participation. We define *primary* potential benefits as those that should be or are outcomes derived *directly* from the assessment of the investigational medicine.

Potential primary clinical trial benefits may include:

1) Potential therapeutic benefit for research participants,
2) Scientific knowledge generated by the research, and
3) Potential access to new medicines being evaluated in the clinical trial via
    a) Participation in the trial itself
    b) Continued access to an investigational medicine or comparator for research participants at the end of their participation or close of the trial and/or
    c) Patient access to a commercially available medicine, if and when approved by regulatory authorities (as prior participants occasionally obtain preferred access upon regulatory approval).

Additionally, the conduct of a clinical trial may result in potential benefits that are *not directly* derived from the investigational medicine, but rather relate to the clinical trial process itself. These can be considered '*collateral*' potential benefits.

Potential collateral clinical trial benefits include:

1) Access to medical care necessary for the safe delivery of the investigational medicine or as a consequence of the trial itself
2) Access to health care infrastructure

The consensus of the Workgroup was to address PTR related to the ongoing provision of *investigational* medicines to research participants; this *Framework*, therefore, addresses roles and responsibilities for:

- Continued access to investigational medicine (primary benefit), and
- Access to medical care necessary to provide the investigational medicine[2] safely and effectively (collateral benefit), and
- Access to health care infrastructure necessary to use the investigational medicine appropriately (collateral benefit).

Responsibilities Out of Scope for This Framework

Other responsibilities associated with the end of an individual's participation in a clinical trial, although important and worthy of deliberation, were deemed out of scope for this current project:[3]

- Access to research results (in aggregate)[4]
- Access to relevant individual health care information, such as individual research results or incidental findings.[5]
- Access to benefits for the broader host community or country or to the scientific community at large.
- Access to ancillary medical care and infrastructure, that is beyond that required for the delivery of the investigational medicine (or comparator) itself.
- Access to appropriate compensation and treatment for subjects who are harmed as a result of participating in research

[2] Ancillary medical care and infrastructure that is *not* required for the delivery of the investigational medicine is not further considered here.
[3] Also out of scope for this project was the topic of off-trial expanded access, sometimes referred to as "compassionate use," to an investigational medicine for individuals who could not participate in a trial but who seek access for their own treatment purposes.
[4] The MRCT Center has completed significant prior work on the return of summary, aggregate results to research participants. See (MRCT Center, 2017a) and (MRCT Center, 2017b).
[5] An Independent MRCT Center Workgroup is currently working on a separate guidance document and toolkit. See "Return of Individual Results to Participants: Principles" (MRCT Center, 2017c)

Purpose of the Project

The aim of the Workgroup was to provide guidance on PTR that is both ethically sound and practically applicable.

The Workgroup objective was to develop a *Framework* for post-trial responsibilities that would include both narrative background and guidance and a practical toolkit to guide PTR planning, discussions and decisions:

1. *Guidance* document (this document)
2. *Toolkit* (companion document)
    a. Decision-making tools
    b. Case studies
    c. Resources

3.1.2 Approach and Process

The *Framework* is intended for a wide audience that includes investigators, sponsors (for profit and non-profit organizations, academic institutions, other), trade organizations, governments, regulators, payors, institutional review boards (IRBs)/research ethics committees (RECs), and patients and patient advocacy groups. In particular, the document aims to assist in determining appropriate approaches to PTR for research participants within the context of a particular trial.

Approach

The *Framework* integrates both "case-based" (descriptive) and "principles-based" (normative) stakeholder approaches to the ethical consideration of PTR.

Process

First, because terminology varies with regard to PTR, it was necessary to agree upon certain definitions and terminology, as well as to delineate key stakeholders and their traditional role in biomedical research and healthcare.

Second, historical cases were solicited from members of the Workgroup in order to identify the major PTR issues and thus determine the scope of the framework. These cases were used to produce a master list of questions regarding PTR. Additional cases were reviewed until no further significant questions were raised.

Third, the group identified and elucidated ethics principles relating to PTR, as well as how these principles relate to the traditional roles of stakeholders engaged in clinical trials. These principles and roles were then used to address the master list of questions to develop the MRCT Center PTR *Framework*. Workgroup discussions additionally illuminated a number of practical considerations that informed 'points to consider.'

Fourth, the group produced a series of recommendations that were applied to the case studies.

We welcome comments and suggestions, new case examples and collaborative discussion (to MRCT@bwh.harvard.edu).

3.2 Existing Reference Guide

3.2.1 Declaration of Helsinki

The World Medical Association (WMA) addressed the benefit of post-trial access to an investigational product in Paragraph 34 of the Declaration of Helsinki (DoH) (World Medical Association, 1964; Amended 2013):

> "*In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. . This information must also be disclosed to participants during the informed consent process*."

Note that this paragraph does not specifically address whether the "intervention" is the investigational medicine or the comparator, and therefore, the "intervention" could be either. The DoH is addressed primarily to physicians; other stakeholders, however, who are involved in human subjects research are encouraged to adopt its principles (World Medical Association, 1964; Amended 2013). Although the DoH was first adopted in 1964, an ethical principle referring to post-trial responsibilities was first introduced in 2000 and later amended. This history is relevant since many ethics guidelines, documents and legislation refer to different versions of the DoH and may not be appropriately updated to the 2013 version (e.g., U.S. FDA regulations) (Goodyear et al., 2009) and (United States Food and Drug Administration, 2015a).

Embedded in the DoH (WMA, 2013) Paragraph 34 are a number of considerations that must be read in the context of other directives espoused by the DoH itself:

- Shared responsibility. Post-trial access is viewed as the responsibility of sponsors, researchers, and host country governments; the DoH does not point to one responsible party but views the responsibility as a shared endeavor (WMA, 2013, paragraph 34).
- Planning. The plan for continued access, for the investigational medicine/comparator, health care and infrastructure required, should be determined[6] before the clinical trial begins, and thus before any individual gives their informed consent, in order to comply with the DoH principle that the potential participant be informed of post-trial access plans in advance of "freely-given informed consent" (WMA, 2013, paragraph 26[7] and 34).
- Informed consent. The plan for post-trial access should be transparent to potential participants and explained during the informed consent process (WMA, 2013, paragraphs 26 and 34).
- Documentation. The protocol must delineate post-trial access plans (WMA, 2013, paragraph 22).[8]

[6] As discussed further below, sometimes the plan for continued access cannot be determined in its entirety before the trial begins, as specifics may only be known once certain information is available as a consequence of the trial.
[7] DoH Paragraph 26 states in part, "In medical research involving competent human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-trial access and any other relevant aspects of the study" (World Medical Association, 1964; Amended 2013).
[8] DoH Paragraph 22 states, "…the protocol must also describe appropriate arrangements for post-trial provisions" (World Medical Association, 1964; Amended 2013).

- Justice. Individuals included in the research should stand to benefit from interventions that result from the research. If vulnerable individuals are included in the research, they should also stand to benefit from interventions that results from the research. (WMA 2012, paragraph 20).

Notably, the DoH does not explicitly reference either access to medical care and/or to infrastructure, either or both of which may be necessary for the safe delivery of the investigational product or the comparator. However, the term "intervention identified as beneficial" might be reasonably interpreted as referring to an appropriate health care package that includes medical care and/or infrastructure required for delivering the investigational product.

3.2.2 The Council for International Organizations of Medical Sciences (CIOMS)

The Council for International Organizations of Medical Sciences (CIOMS) issued *International Ethical Guidelines for Biomedical Research Involving Human Subjects* in 2002. These guidelines are applicable to the interpretation of the DoH Paragraph 34. CIOMS (2002) stated in the commentary of Guideline 10 (which addresses research in low-resource populations and communities) that:

> *"[…] if an investigational drug has been shown to be beneficial, the sponsor should continue to provide it to the subjects after the conclusion of the study, and pending its approval by a drug regulatory authority."* (Council for International Organizations of Medical Societies (CIOMS), 2002)

In 2016, CIOMS released a revised version of its Ethical Guidelines for Biomedical Research. The proposed Guideline 6 relates to "caring for participants' health needs" (CIOMS, 2016). Among other suggestions, the draft guideline states that researchers and sponsors must make plans for:

- *transitioning participants who continue to need care or preventive measures after the research to appropriate health services;*
- *providing continued access to study interventions that have demonstrated significant benefit; and*

- *consulting with other relevant stakeholders, if any, to determine everyone's responsibilities and the conditions under which participants will receive continued access to a study intervention, such as an investigational drug, that has demonstrated significant benefit in the study.*

  When access is provided after the research to investigational interventions that have demonstrated significant benefit, the provision may end as soon as the study intervention is made available through the local public health-care system or after a predetermined period of time that the sponsors, researchers and community members have agreed before the start of a trial. Information on care for participants' health needs during and after the research must be included in the informed consent process (CIOMS, 2016).

Thus, the proposed revision to CIOMS tracks to and conforms with the Declaration of Helsinki. A few salient differences exist: (1) CIOMS introduces the concept that the provision of the study intervention may be for a pre-determined limited period of time, (2) post-trial access provided by the sponsor may terminate (even for former individual participants) when the product is available through the local health care system or after a predetermined period of time agreed to before the start of a trial, (3) community members are appropriately involved in the decision as to when to terminate access, and (4) the expectation to transition medical care is explicitly enumerated.

3.2.3 Additional Sources of Guidance

Governments and international non-profit organizations have issued additional influential guidance materials on PTR. Thus, any specific recommendations made in this *Guidance* must be interpreted in light of local directives. Some of these materials are summarized in Table 1, but careful study of local laws, regulations and guidance is necessary.

Table 1: Guidance materials on PTR[9]

Year	Issuing Authority	Target	Nature of Requirement
2001	U.S. National Bioethics Advisory Committee	Researchers and sponsors	Good faith efforts to "secure" post-trial access to beneficial interventions (National Bioethics Advisory Commission, 2001, Rec 4.1)
2002	CIOMS	Sponsors	For research in low-resource communities, "Continue to provide" access to beneficial intervention pending regulatory approval (Council for International Organizations of Medical Societies (CIOMS), 2002, p. 52)
2005	UNESCO	"States" and other stakeholders	Benefit sharing requirement includes the "provision of new diagnostic and therapeutic modalities or products stemming from research;" (e.g. investigational medicine) and "support for health services" (accompanying medical care and infrastructure).[10] (UNESCO, 2005).

[9] Table 1 is adapted from Seema Shah's presentation "Post-trial Obligations: Policy Approaches Around the Globe," at a *Conference on Post-Trial Responsibilities: Ethics and Implementation*, Harvard Law School, Cambridge, MA, September 18, 2014.

[10] Specifically, UNESCO "Article 15 provides for 'Sharing of benefits' as: 1. Benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community, in particular with developing countries. In giving effect to this principle, benefits may take any of the following forms: (a) special and sustainable assistance to, and acknowledgement of, the persons and groups that have taken part in the research; (b) access to quality health care; (c) provision of new diagnostic and therapeutic modalities or products stemming from research; (d) support for health services; (e) access to scientific and technological knowledge; (f) capacity-building facilities for research purposes; (g) other forms of benefit consistent with the principles set out in this Declaration. 2. Benefits should not constitute improper inducements to participate in research (UNESCO, 2005).

2005	Nuffield Council on Bioethics	Stakeholders	"Begin negotiations about post-trial treatment at an early stage." Requiring researchers/sponsors to fund treatment "may be unrealistic and lead to sponsors curtailing other research." (Nuffield Council on Bioethics, 2005, § 4.19)
2012	UNAIDS Ethical considerations in biomedical HIV prevention trials	Stakeholders	Participants who are infected during a prevention trial should "be provided access to treatment regimens from among those internationally recognized as optimal." Agreement on mechanisms to do so should be sought in advance of trial (UNAIDS, 2012, Guidance Point 14) [11]
2011	US Presidential Commission for the Study of Bioethical Issues	Researchers; Federal government	"[R]recommends 14 changes to current practices to better protect research subjects, and called on the federal government to improve its tracking of research programs supported with taxpayer dollars." (Presidential Commission for Study of Bioethical Issues, 2011)
2013	WMA Declaration of Helsinki	Stakeholders (Sponsors, researchers, host-country governments)	"[M]ake provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial" (World Medical Association, 1964; Amended 2013).

[11] "Prior to initiation of a trial, all research stakeholders should come to agreement through participatory processes on mechanisms to provide and sustain such HIV-related care and treatment." (UNAIDS, 2012).

3.2.4 Summary

Although directionally helpful, all of the materials described above leave key questions unanswered. First, neither the DoH nor CIOMS defines how one determines whether an intervention (DoH) or drug (CIOMS) is "beneficial" and under what circumstances responsibilities emerge. Second, they do not address how safety (risk) of an investigational medicine should be evaluated and factored into the determination of whether to provide continued access. Finally, sponsors, investigators, host countries, and other relevant stakeholders are uncertain about the specific responsibility(ies) of each stakeholder to comply with PTR requirements and how long those responsibilities last.

This MRCT Center *Framework* builds upon the existing international guidance documents and is consistent in spirit with these documents. It is not intended to challenge or replace the existing guidelines. Rather, it was developed to identify the considerations and circumstances that are relevant to determine if and when there is an ethical duty to provide continued access to research participants. The *Framework* complements existing international guidance by interpreting that guidance in light of practical experience, feasibility, and the overarching considerations of applied research ethics.

3.3 Ethical Principles

Drawing upon the existing literature, we consider that no ethical principle, if read separately and without reference to other materials or facts, can provide a satisfactory justification for either an unrestricted duty to provide continued access to the study medicine or for the complete absence thereof. However, if the bioethical principles are analyzed together as interwoven and interdependent concepts, it is possible to identify circumstances in which there are compelling reasons to fulfill the responsibility to provide the medicine, as well as reasons that this duty is not boundless or unlimited. These principles should be considered in each case-by-case evaluation.

3.3.1 General Ethical Considerations in Biomedical Research in Concert with PTR

Although the MRCT guidance takes PTR duties as its main subject, it is important to consider them in the wider perspective of research ethics. In this wider perspective, PTR duties are one ethical issue among many in otherwise well-designed clinical trials that follow all other special ethical principles for research with human beings. For example, the ethical framework for biomedical research developed by Emanuel, Wendler, and Grady (2008) includes (1) collaborative partnership, (2) social value, (3) scientific validity, (4) fair participant selection, (5) favorable risk-benefit ratio, (6) independent review, (7) informed consent, and (8) respect for participants. PTR belongs and is included in the eighth principle, respect for persons. That said, PTR cannot compensate for the failure of meeting the other basic responsibilities in a clinical trial, including robust study design and other underlying basic ethical principles.

3.3.2 Non-Maleficence

The principle of non-maleficence dictates that research participants should not be intentionally harmed and that adequate care should be provided in order to minimize the risks of research. Participants' rights and immediate health should also always have precedence over the interest of science.

With regard to PTR, there is a duty to provide an investigational intervention based on the non-maleficence principle when participants may be harmed by the trial in the sense that they are, or may be, worse off after the trial than they would have been had they not participated the trial. More specifically, non-maleficence would support continued access if withdrawal of an investigational medicine at the end of a trial would cause known participant harm. Note that in this context, whether withdrawal of an investigational medicine would cause participant harm is important. In some situations, it may be difficult to differentiate between harm caused by cessation of the intervention and harm caused by disease progression. In the latter case, the non-maleficence principle is not operative.

The principle of non-maleficence also directs that provision of continued access would not be recommended when the expected benefits do not outweigh the risks, as discussed further below.

3.3.3 Autonomy

Autonomy in the context of a clinical trial implies that participation by individuals capable of giving consent as research participants must be voluntary. Individuals cannot be coerced, improperly induced or deceived to participate in a trial. Therefore, consent is only valid when it is free, express and informed, and given prior to any research intervention or activity. To make an informed decision, participants must be provided with relevant information including, according to the Declaration of Helsinki, information about "post-study provisions" (World Medical Association, 1964; Amended 2013). This information allows individuals to decide whether to participate in a trial – and to adjust their expectations – with the knowledge of what will happen to care and treatment when the trial is concluded. This prior knowledge is especially important in countries where patients see participation in trials as the preferred alternative to inadequate care (Cash et al., 2006). Therefore, research participants need to be informed at the start of a trial whether there will be continued access to an investigational medicine and under what conditions this may occur.

Some individuals and IRBs/RECs have been concerned that the possible provision of continued access will be interpreted as undue inducement—that the potential for such benefit undermines the participant's ability to make a rational choice as to whether to volunteer in a trial. We reject that argument. An IRB/REC should only approve a protocol in which the benefits of participation (not continued access, but of the trial itself) exist in proportion to the risks of the research. If the risks and benefits of the research are appropriately balanced (e.g. clinical equipoise exists), then continued access cannot be an undue inducement. Related points to consider may be found in Section 4.3.2.

A variant of the concept of respect for persons (autonomy, informed consent, voluntariness) is the concept of treating the individual with respect, that is consideration and deference to individual choice and agency. It implies listening to and responding to the needs of each participant. It implies treating each participant appropriately, particularly as it relates to terminating relationships (e.g. at the end of participation on trial) and responsible transition to healthcare providers and alternative care.

3.3.4 Justice

Distributive Justice

PTR will have distributive consequences. In settings of scarce resources, the duty to continue to provide the experimental investigational medicine may disadvantage others in their access to care. For instance, if sponsors are required to provide continued access to the investigational medicine (e.g., in Brazil (Wang, 2013)), and if that product is not licensed, resources will be used to benefit research participants with treatments that are not available to others in similar conditions. PTR responsibilities may also affect availability and accessibility of new technologies to other patients, as when the costs of PTR result in delay or abandonment of promising research or are recouped by sponsors via higher prices in the market. If the government is required to provide continued access, as for instance to an approved product for a different indication, scarce resources may be shifted from other public health needs to the provision of the experimental treatment (Merritt & Grady, 2006). Similarly, medical care or health care infrastructure components dedicated exclusively to trial participants may divert public resources away from the general public.

Thus, the duty to provide continued access to the investigational medicine creates a disequilibrium in the distribution of health care resources in favor of research participants—who will receive treatment first, free of cost, and accompanied by the attendant medical and health care—prior to, or even instead of, the general public—even if patients who have not participated in the trial could also benefit from the investigational medicine. This is not inherently unjust but requires justification.

Another argument from the principle of distributive justice is that the location (e.g., setting) of the research may increase or decrease the level of obligation for PTR. Some propose that there is a stronger responsibility to those who are economically less advantaged and are less likely to have access to alternative treatments. The MRCT Center Workgroup rejects that notion on the grounds that if a responsibility exists, it should be fulfilled, regardless of setting. The setting (e.g., well resourced, developed countries with well-insured populations versus low and middle income countries where access to health care may be more challenging) may impact who assumes the responsibility for execution but the responsibility exists nonetheless. Details are discussed in Section 4.3.4.

Justice as Reciprocity

Granting health care priority to certain individuals based on their special or unique contribution to a cooperative system is a sound ethical reason to prioritize scarce resources although it is not the only one. For example, granting treatment priority (e.g., preferential vaccine administration) to health workers who bear more risks than other stakeholders because of their role is considered ethically sound. Hence, it can be argued that research participants deserve preferential treatment because they have participated in the drug development process: research participants were exposed to the risks and inconveniences inherent in clinical trials for the benefit of not only future patients and sponsors (in the form of potential profits) but also of society as scientific knowledge advances. Following this reasoning, it can be argued that research participants deserve to receive continued access to a beneficial investigational medicine in return for their contributions. Withdrawal of the treatment (whether the experimental treatment or the comparator,) after trial closure could be viewed as a form of exploitation of the participant – particularly when there are no alternative treatments.

However, the principle of reciprocity does not automatically create an unlimited duty to provide continued access to medicines (Grady, 2005). First, it can be argued that the duties generated by the principle of reciprocity could be fulfilled in other ways, that is, by the provision of other types of benefits not directly related to the investigational medicine. Further, assuming participants were properly informed and agreed to the research knowing there would be no or limited PTR, some would argue that no further obligations exist. Finally, when it is possible that participants receive direct therapeutic benefits from research, it can be assumed that many accept the risk of participating in exchange for the possibility of beneficial treatment during the trial that would not be accessible outside of a research context.

The reciprocity principle justifies continued access for individuals assigned to control groups based on their contribution to the overall project. Since some clinical trials need both control and experimental groups in order to obtain scientifically valid data, the contribution in terms of data points from individuals randomized to control groups is equally valuable and necessary for the final outcome to the contributions for individuals of the experimental group. Consequently, beneficial intervention should be offered to control group participants if the conditions for continued access are met, since its contribution to the overall research project is the same as the participants assigned to the experimental group. Thus, in blinded trials, the participant who

has benefitted from an intervention should continue on their assigned treatment arm. In blinded trials, provision of the intervention to which the participant was assigned during the trial is generally recommended, until the results of the trial are known.

In many instances, at the end of a clinical trial in which an investigational medicine has been shown to be beneficial, participants in the control arm may appropriately be offered access to the investigational medicine via open label extension, assuming other considerations are met (unmet medical need, no alternative therapy, etc.); in some instances, however, timing is critical: the investigational medicine may be timed to administration of another treatment (e.g. concurrent with standard oncology treatment or proximal to surgery) or immediately after diagnosis, (conditions that are no longer true for control arm patients at the end of trial) (Unguru et al., 2013). Indeed, there may be some unanticipated risks when giving an investigational medicine at a time that has not been previously studied. These considerations should be addressed in advance of the clinical trial and in the informed consent document.

Non-inferiority trials (including many biosimilars trials) present a special case in which continued access to the investigational medicine rarely, if ever applies. The specified endpoint of a non-inferiority trial is the demonstration that the investigational medicine is not unacceptably worse than the standard of care or comparator arm, when the comparator treatment has been established to have a significant clinical effect. Therefore, at the end of trial, participants should be placed on the comparator arm, in which safety and efficacy are already known.

3.3.5 Beneficence

In a research trial, sponsors and researchers have a duty to make efforts to secure participants' well-being by maximizing the possible benefits to them and minimizing risk of harm (UNESCO, 2005). A physician-investigator has a duty to provide medical care as it relates to the trial. However, there is no general obligation for sponsors or researchers to provide medical care outside the context of a clinical trial as this duty lies with health care providers and payors. A duty for the sponsor or investigator, unlike the treating physician or health care provider, to provide care after the trial is exceptional and thus requires justification.

However, there are circumstances when the beneficence principle drives certain sponsor and researcher post-trial responsibilities (see Section 4.2.2).[12]

3.4 Stakeholder Rules

Of all stakeholders involved in continued access to investigational medicines, an investigator/physician is the only one who has a direct relationship with a research participant.[13] Nevertheless, many stakeholders have ethical responsibilities with respect to research participants, and therefore there are stakeholders who should be involved in providing continued access to investigational medicines. Before delineating specific continued access responsibilities, it is necessary to appreciate the traditional primary roles of key stakeholders in the clinical trial and drug commercialization enterprise.

Table 2. Primary roles of stakeholders[14]

Stakeholder	Traditional Role
Sponsor (may be an individual, company, institution or organization including a pharmaceutical company, governmental agency, academic institution, or private organization)	In the US, holds the investigational new drug (IND) application (United States Food and Drug Administration, 2016). Takes responsibility for the initiation, management and/or financing of a clinical trial (Ravinetto et al., 2015). Does not interact with research participants directly unless the sponsor is a sponsor-investigator (see below) or the participant gives express permission as part of the informed consent process.

[12] The duty described here is analogous to that described by Peter Singer, 'Famine, Affluence and Morality', *Philosophy and Public Affairs* who argued that if a person is walking past a shallow pond and sees a child drowning, that person has a moral duty to pull the child out. There is no risk to the savior's life or health and the nuisance of getting wet and muddy is outweighed by the importance of saving a life.
[13] In the limited case of sponsor-investigators, the investigator/physician will also play the role of sponsor.
[14] Most terms and references in this table refer to U.S. regulations. We invite readers to comment (to MRCT@bwh.harvard.edu.)

Sponsor-Investigator[15]	Initiates and conducts an investigation. In the US, holds the investigational new drug (IND) application (United States Food and Drug Administration, 2016). Directs the administration or dispersal of the investigational medicine (United States Food and Drug Administration, 2015b, 21 C.F.R. § 312).
For-profit sponsor (typically biopharmaceutical or device company) or their designee (e.g. contract research organization)	Discovers, develops, manufactures, and commercializes products for the benefit of populations of patients (Klopfenstein, Van Campen, & Garnett, 2015). The clinical trial is a key component of this role, as it serves as the conduit process through which a company establishes the safety and efficacy of an investigational medicine. Responsible for submitting marketing application for regulatory approval (United States Food and Drug Administration, 2016). Assumes certain post-market obligations (such as safety surveillance).
Non-profit sponsor	Discovers and develops products for the benefit of populations of patients in a manner that comports with their organizational mission or mandate. Does not typically commercialize product. Generally commits a specific amount of funding to a project, and may not be able to alter this amount significantly during or after study implementation (Padian, 2014).

[15] The sponsor-investigator has similar responsibilities to the participant as a sponsor, but insofar as they are (often) not the manufacturer of the investigational product, special considerations apply. The sponsor-investigator is advised to (1) address post-trial access to investigational medicines in advance of the trial, (2) arrange with the manufacturer whether medicines will be provided, and under what conditions, and (3) describe what is known about continued access in the study protocol and informed consent document and process (see Section 4.3.1).

Investigator/physician[16] (For most trials, there is a *Principal (Lead) Investigator* responsible for the overall conduct of the trial and a *Study Investigator(s)* at each site responsible for research participants and study conduct at that site, sometimes reporting to the Principal (Lead) Investigator)	Ensures a clinical trial is deemed ethical by obtaining review from a qualified IRB. Implements the approved trial protocol by following its prescribed direction. Provides for the well-being of each research participant, including: a) identifying, recruiting and consenting prospective participants, b) monitoring and providing medical care for each participant relating to and throughout the clinical trial, c) following good clinical practices, d) generating data with integrity, and e) representing the interests of research participants to sponsors and other stakeholders before, during and after the trial (United States Food and Drug Administration, 2009) and (National Bioethics Advisory Commission, 2001). Is a health care professional (usually a physician in an interventional biomedical trial) who leads the clinical research team and, along with members of the research team, regularly monitors each study participant's health and continually assesses whether or not it is in the participant's best interests to remain in the study (National Institutes of Health, 2015). At the end of the study participation or trial, the study investigator assesses whether or not it is in the participant's best interests to receive the investigational medicine, if available. After trial participation ends, the participant's treating physician or healthcare practitioner (who may be the study investigator) assumes the care of the participant.

[16] On occasion, the investigator/physician role may be assumed by a nurse practitioner or other licensed professional. Throughout the document, we use the term investigator/physician to encompass all licensed professionals who have direct interaction with the participant and/or are responsible for direct care in the study.

Research participant	Consents to participate in a clinical trial after providing voluntary informed consent based on a description of both potential benefits and risks of participation, among other information (Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center), 2014). Adheres to the clinical trial protocol for the purpose of contributing to the generation of generalizable knowledge. Understands that post-trial continued access to medicine is dependent upon completion of the trial and under what conditions, if known, access will be provided, including that the benefit/risk assessment for the participant is deemed favorable by the investigator/physician.
National Regulatory Authority (NRA)	Assesses, licenses, controls, surveys and monitors products (World Health Organization, 2015). Protects public health by ensuring the safety and efficacy of drugs, biological products and medical devices Advances public health by helping to accelerate innovations that make medicines safer, more effective, and more widely available, and by helping the public receive accurate, science-based evidence and the information they require. Formulates and articulates regulatory rules, standards, and guidance for assessment, pharmacovigilance, licensure, control, and surveillance of investigational medicines (World Health Organization, 2015).
National Health Care Authority (HCA)	Oversees all issues related to public health and makes decisions about the allocation of healthcare resources. In some countries, the HCA may also be a payor and/or healthcare provider.
Payor (private or government)	Ensures that clients receive "coverage [and reimbursement] that provides for the payments of benefits as a result of sickness or injury," including products that have been approved for market distribution (Claxton & Lundy, 2008).

Health care provider	Provides health services and health care to patients (The Free Medical Dictionary by Farlex, 2016)
Research ethics committee (REC)/ Institutional Review Board (IRB)/Ethics Review Board (ERB)	Reviews individual protocols to ensure they comply with research ethics principles (World Health Organization, 2011). Safeguards participants' well-being and interests. Reviews and approves all clinical trial materials (informed consent, protocol, investigator brochure, etc.). May review case-by-case post-trial arrangements.

4. MRCT CENTER GUIDANCE FOR CONTINUED ACCESS TO INVESTIGATIONAL MEDICINES

4.1 Paradigm—Stages, Criteria, and Stakeholder Responsibilities

The Workgroup consensus was that responsibilities to provide continued access to an investigational medicine is not an unbounded, limitless responsibility, for the following reasons:

- Resources (including financial, human, product, infrastructure) to provide such access are never limitless;
- Those who hold resources must be good stewards of those resources and take into consideration whether providing continued access to some may inadvertently disadvantage or harm others; and
- Different stakeholders serve different roles and, therefore, should and will assume different responsibilities (see Section 3.4);
- Some stakeholders (particularly health care providers) have direct fiduciary responsibilities to determine what is in the best interest of an individual research participant.

As such, it was thus necessary to create a workable paradigm from which to develop both general and specific guidance. Foundational to this paradigm is an acknowledgement that although PTR implies post-trial activity, stakeholders need to conceptualize and consider continued access throughout the stages of a clinical trial – pre-trial, during-trial, and post-trial. In order to accomplish this, it was necessary to establish justifiable criteria consistent with the ethics principles discussed in Section 3.3, and to delineate which stakeholders have responsibilities, when these responsibilities should be initiated, and when they can be transitioned to another stakeholder. Judgment will invariably be necessary, and cooperation among stakeholders is essential. Finally, in this MRCT Center *Framework*, we utilize the concept of the 'strength' of the responsibility to provide continued access and that strength is stronger or weaker depending upon the variables considered (see Table 1 and 2 in the *Toolkit*).

4.1 General Guidance

4.2.1 Stages of Continued Access to an Investigational Medicine

As described above, five theoretical decision points during a clinical trial when continued access will be considered, either at a Study Program Level (i.e., relative to the medicine, drug development program, and disease/condition under study) and/or Individual Participant Level (i.e., relative to the benefit/risk assessment of the individual participant). These stages are generally, but not strictly, arrayed across the time-course of a clinical trial.

Stage 1: Study Planning

At the Study Program Level, the sponsor is responsible for planning before the trial begins. The sponsor should evaluate whether it is possible, in principle, that research participants will meet the criteria for continued access given the drug and disease/condition under study. If so, the sponsor should develop a plan in discussion with relevant stakeholders, including establishing criteria for when a patient should be transitioned to another mechanism of access or to other alternatives. In multinational clinical trials, national legislation and local health care capabilities should be considered.

Stage 2: Monitoring of available alternatives

At the Study Program Level, the sponsor is responsible for ongoing monitoring throughout the course of the clinical study and drug development program to assess whether there is still an unmet medical need that requires continued access to the investigational medicine. Other alternatives may become available that modify or eliminate the ethical justification to provide continued access.

Stage 3: Decision Point 1

At the Individual Participant level, the investigator is responsible for the first operative decision. At the participant's last patient visit, the investigator evaluates and communicates (to the patient and sponsor) whether the individual's benefit/risk assessment warrants continued

access to the intervention(s) received during the trial (investigational medicine or comparator, and associated medical care) in accordance with Study Program planning.

In some trial designs, where it is not possible to know if the participant has had benefit at the last visit (e.g., in asymptomatic condition where the endpoint is prevention, or in trials in which the endpoint is progression-free survival), there would be no rationale to continue therapy after completion of the trial unless the results are known (see Decision Point 2).

Stage 4: Decision Point 2

At the Study Program Level, the sponsor is responsible for a second operative decision. After database lock and data analysis, the sponsor evaluates whether the overall study population benefit/risk assessment warrants ongoing continued access to the intervention or, in some cases, offering all participants access to the intervention. In others, safety concerns or lack of efficacy may warrant reconsideration of the initial decision to provide continued access.

Stage 5: Transition

At the Individual Participant level, the investigator is responsible for a third operative decision as to whether and when participants should be transitioned off the intervention. Events such as the commercial availability of the investigational medicine, other satisfactory alternatives for treatment (see Stage 2), or the participant no longer requires treatment may trigger a transition decision. These possibilities, and the timing thereof, should be outlined in the informed consent to the trial, in collaboration with the sponsor.

Notably, the decisions made at the Study Program level are (generally) the responsibility of the sponsor of the study; the decisions made at the Individual Participant level are (generally) the responsibility of the investigator caring for the participant.

4.2.2 Criteria for Continued Access to an Investigational Medicine

Criteria

The criteria listed below should be weighed by the sponsor and the investigator to inform decisions about the provision of continued access at both a Study Program (Box 1) and an Individual Participant level (Box 2).

Box 1: Study Program Level (related to the medicine and disease/condition under study)
• Impact of discontinuation: The disease/condition under study is serious or life threatening and the research participant could be adversely impacted if the medicine were to be discontinued. • Medical need: The investigational medicine addresses an unmet medical need in that there are no suitable therapeutic alternatives available to participants. • Access: There is no alternative access to the investigational medicine.[17] • Research viability: The provision of continued access to the investigational medicine will not affect the viability of the research or the ability to complete the trial or other trials. • Benefit/risk assessment (population): After data lock and analysis of the results, the overall study population benefit/risk assessment is known.

Box 2: Individual Level (related to the individual research participant)
• Trial participation: The eligible participant has completed the clinical trial protocol. • Benefit/risk assessment (individual): There is demonstrable evidence of benefit exceeding risk for an individual participant as determined by the investigator.

[17] Sometimes the investigational medicine will be marketed for a different indication.

Justification for Criteria

As mentioned previously, the criteria are interdependent and therefore, the justifications for the criteria may relate to either or both the Study Program Level and the Individual Participant Level.

Risk of death or serious harm if treatment is withdrawn

Based on the principles of beneficence and non-maleficence the higher the benefit expected from the use of the beneficial intervention, or the bigger the harm if the treatment is discontinued (e.g. risk for new adverse events or rendering participants less responsive to future treatment), the stronger the ethical duty to continue providing the treatment after the trial.

Therefore, in general, a case for offering continued access will be stronger for participants with serious or life-threatening conditions if they are appearing to benefit from the intervention, as opposed to non-serious conditions[18] (e.g., a cosmetic treatment). Considering that sponsors are not responsible in principle for providing health care outside the research context, other criteria have to be considered to assess the harm caused by the non-provision of the drug after the trial, such as whether there are other ways for the patient to access this treatment (e.g. the intervention is commercially available) and if there are other suitable treatment options for the participant. That duty to provide continued access is further strengthened if there is sufficient efficacy and safety data to make a reasonable assessment of potential benefits and risks for the study population and the benefit/risk balance is favorable.

Patients with serious or life-threatening conditions may be more willing to accept risks associated with an investigational medicine. In addition, continued access to investigational medicines is generally offered under a protocol with associated monitoring of safety and efficacy in participants. Therefore, in patients with serious or life-threatening diseases, the benefit/risk balance of continued access is likely more favorable than for those with less serious diseases or conditions.

Benefit and risk determination

[18] Of course, for conditions that are self-limited, even if serious, there may be no medical need for continued access after participant completion of the trial.

In many cases, an improved health status of a participant in a clinical trial can provide *prima facie* evidence of the benefit of that investigational medicine for that individual. However, a positive result demonstrated in an individual participant[19] does not necessarily mean that there is evidence of benefit at the study population level. Moreover, benefit must be balanced by a consideration of safety (risk) at both the individual and population level.

Therefore, whether to provide continued access to investigational medicine will depend upon whether there is evidence of benefit for the individual and/or population. A stronger case for providing continued access can be made when there is evidence of benefit at both the individual and the population level – presuming, of course, that safety (risk) does not counterbalance benefit. But often the decision as to whether to provide continued access is made before the study is complete, when benefit has not yet been determined. Similarly, if evidence emerges that an intervention is unsafe at the population level, or the individual fails to demonstrate continued benefit, access to the intervention may be discontinued.

Because a clinical trial is conducted in a well-designed (often randomized) protocol, it is the sponsor's responsibility to decide whether an intervention has a favorable risk/benefit profile from a population point of view. This judgment is further confirmed by other stakeholders. However, the investigator/physician is responsible for the benefit/risk[20] assessment of the individual participant. A decision as to whether there is a compelling duty to provide continued access will involve a balance between the benefits and risks to individual participants and those to the patient population, informed by the certainty, robustness and durability of the evidence upon which such determinations are made. When there is discordance between the individual and the study population, additional points should be considered (see Section 4.3.2).

Suitable therapeutic alternatives

Based on the principles of beneficence and non-maleficence, the decision whether to provide continued access is stronger if the intervention addresses an unmet need and weaker if other

[19] Further, one must consider that for any given individual, a placebo effect may be observed.
[20] While the Declaration of Helsinki and CIOMS mention "beneficial" treatments, in our opinion, benefit must always be balanced by risk and safety assessments. Therefore, we address benefit/risk assessments in this Framework as illustrative of the necessary balance.

suitable, approved therapeutic options exist. Investigational medicines always carry the potential of new risks or harms not yet identified. Therefore, transition to an approved product should always be considered at the end of an individual's trial participation. If there are no suitable therapeutic alternatives, then the duty to provide continued access becomes stronger. As discussed above, during the course of a clinical trial a suitable therapeutic alternative may become available, even if not available at the outset of the trial (e.g. a competitor therapy is approved or regulatory approval occurs). The sponsor is responsible for monitoring regulatory activity in addition to the individual trial and to alert the IRB/REC, data monitoring committee if appropriate, and the investigator(s) of any change. The investigator will then need to review each participant's situation on a case-by-case basis.

Other ways to access treatment

If the investigational medicine is available through means other than continued access, such as when the drug is granted market approval, then the patient should be directed to those means of access. This provides an appropriate termination point so that patients can be transitioned and continue to receive the drug through the regular care offered by health care providers to all patients. It is important to note that availability does not necessarily mean accessibility. Due to priority-setting, resource or contract reasons, health care providers may not be under the obligation to provide an approved treatment. Therefore, at the planning stages sponsors should consider whether, following market approval, participants will likely have access to the treatment through their regular health care providers.

Adverse effects to the research viability

The principle of beneficence can be applied not only to individuals but also to the greater community for the common good. The purpose of clinical research during medicines development primarily is to provide a medicine with favorable benefit to risk profile a population of patients suffering from a disease or condition. In the course of participation in clinical research, it is possible for individual patients also to benefit. The challenge with clinical research, and by extension PTR, is how to balance the needs of the individual with the needs of the population of patients. Decisions regarding the provision of continued access to

investigational medicines must be weighed with both in mind – seeking the best interest of individuals, while not adversely affecting the research mission to provide answers to relevant questions regarding unmet or incompletely met medical need. If providing continued access could adversely affect the viability of current or planned clinical research (e.g. insufficient product will be available to complete the trial in a timely fashion), then the responsibility becomes weaker. Incomplete (or never-started) trials will not support the common good. Nevertheless, even in these situations, the merits of individual cases should be assessed.

Eligible population

Based on the principles of reciprocity, justice (fairness) and non-maleficence, only research participants who complete study participation, research procedures, and obligations of the trial should be eligible for continued access after their time on study ends. Of course, exceptions may be made on a case-by-case basis, including instances where the participant completes the trial but cannot reasonably undergo a research procedure (e.g., implanted metal object preventing a required research MRI study, withdrawn prematurely by the investigator.) But generally, individuals who withdraw from the study before completion should not be eligible for continued access for several reasons. In the absence of clarity concerning ineligibility for access to the study medicine, there may be a temptation to withdraw from the study in order to receive the investigational medicine—without undergoing research procedures, appropriate data collection, or assessment of the outcomes of the study. In addition to other problems, this would bias the aggregate results of the study. Further, if the participant has withdrawn from the study, it is likely for cogent reasons: intolerance to drug, inability to execute research procedures, etc.; these reasons remain operative during continued access.

The involvement of vulnerable populations (pregnant women, neonates, children, prisoners, individuals with impaired decision-making ability)[21] in continued access to beneficial interventions warrants special consideration. The Workgroup was unable to identify situations in which vulnerable populations of participants would be treated differently—that is, either

[21] Pace et al. (2003) argue for the consideration of uninsured or underinsured individual participants (hereinafter "uninsured participants") as vulnerable. Uninsured participants with the same condition and health status may lack other ways to access treatment when their research participation is concluded. Sponsors and investigators should consider how to transition uninsured participants at study conclusion.

offered or denied continued access—than other participants. That said, because continued access to beneficial interventions is almost always offered under an IRB/REC-reviewed and approved study protocol, or mechanism, vulnerable participants should be afforded special protections during the informed consent process, to ensure consent is voluntary and understood.

4.2.3 Criteria for Providing Medical Care and Infrastructure

The provision of medical care and infrastructure is linked to the safest possible provision of the investigational medicine. Providing medical care or infrastructure outside of this activity could be perceived as a transfer of value and thus viewed as so-called "undue inducement" to participate in the clinical trial either for patients, physicians, institutions, or government or healthcare authorities. For instance, if a sponsor offers to build a much-needed community road but the road is not needed for performance of the clinical trial or offers to provide medical care unrelated to the disease under study, it could be regarded as "deal making" in order to recruit and retain research participants.[22]

Therefore, the MRCT Workgroup restricted its consideration to the benefits of medical care and infrastructure to those necessary to provide continued access to the investigational medicine. As such, decisions about the duration of access to medical care and infrastructure will be directly related to the duration of providing continued access to an investigational medicine.

4.2.4 Stakeholder Roles and Responsibilities

We envision that the spectrum of PTR is not static but dynamic and shifts based on specific roles, timing, and other factors. These factors may include: stage of product development, whether the benefit/risk profile of the investigational medicine is well characterized, stage of the clinical trial, whether the disease or condition is serious and/or life threatening, and whether there is an unmet medical need. This dynamic model of PTR is illustrated in Figure 1.

[22] More subtle examples are more difficult: is the provision of medical care for the disease itself an "undue inducement" in communities with inadequate health care or for the uninsured? The IRB/REC will need to consider these situations, under what conditions individuals will be enrolled, and what post-trial responsibilities exist.

One may debate the point of transition of responsibility from one party to another, but the premise of our work is that the responsibility is shared among the sponsor, investigator and clinical trial team, government, payors, health care providers, and participants. The more the responsibility relates directly to the investigational medicine, the greater the share of responsibilities the sponsor and investigator owe — particularly in early phases of development (e.g., before product approval). The more the responsibility relates directly to medical care and access to infrastructure, the greater the responsibilities will transition to government, payors, and health care providers.

In appreciating this relationship and shared responsibility, we offer a perspective on PTR that takes into account the plurality of circumstances and research participants in order to provide guidance on *if*, *when*, *to whom*, *by whom, for how long* and *why* PTR may need to be fulfilled.

With regard to continued access, both specific responsibilities and the responsible party(ies) may shift depending on the phase of trial, specifics of the drug development path, the underlying and current illness(es), and the local environment.

4.3 Specific Guidance

4.3.1 Planning Stage of a Clinical Trial

In principle, continued access to investigational medicines should be considered during the planning of a clinical trial. Because provision of continued access can impact the supply of investigational medicine and may require local support to implement (e.g., approval of health ministries, cooperation of local officials, other health services), sponsors should consider continued access issues early in the clinical development process and develop criteria under which the investigational medicine will be made available for continued access, based on evolving data and/or patient response. Sponsors also need to consider how continued access will be carried through once an individual participant has begun on treatment and how changing conditions during the trial, if any, will be managed.

Especially in resource-poor settings, health care facilities, equipment, storage, maintenance, and the required professional staff may not meet the necessary standards for the continued safe provision of investigational medicine and monitoring thereof. Training, transfer of technology and know-how, and other needs (e.g., refrigeration for medication storage) may be

necessary to continue provision of an investigational intervention. In such cases, when, how, and to whom such responsibility is allocated should be considered. Depending on the circumstances, the plan for continued access should include equipment/maintenance/training, medical care, and the specifics of providing investigational medicine to (former) research participants. Naturally, that plan may be modified after the trial concludes and more is known; nevertheless, a plan outlining continued access is best formulated as part of the conceptualization and drafting of a clinical trial plan and protocol (see Section 4.3.4).

The responsibilities and expected roles of relevant stakeholders should be well defined, as should regulatory considerations. Generally, sponsors/investigators should have a pre-existing plan of action for continued access, and should include that plan in the materials made available to the IRB/REC to review and approve.

It is important to negotiate and finalize a plan for continued access with study sponsors, investigators and regulatory agencies prior to study initiation in order to clarify roles and responsibilities. Often, however, relevant information is not known at the beginning of a study and adjustments to these expectations will need to be made. Further, many regulators do not have regulations or guidance documents with regard to continued access and do not have substantial experience in negotiating these issues. At a minimum, discussion in advance of trial commencement sets the stage for later engagement.

The following information should be considered (Box 3):

Box 3: Considerations for Planning Continued Access

1. Stakeholders involved in the pre-trial agreement and respective roles and responsibilities

- Sponsors
- Regulatory agency and/or representative of host country government, as appropriate
- Cognizant IRBs/RECs
- Investigators/treating physician

2. Information to be included generally (even if the information can only be outlined in general terms)

- Inclusion and exclusion criteria for continued access
- Methods of enrolling after the trial completion or participant completes the protocol
- Methods for monitoring participants after the trial
- Source of funding
- Who is responsible for the provision of accompanying medical care
- Duration of access/transition plan
- Criteria for post-trial drug discontinuation
- How, and when, the patient will be transitioned from continued access to other access venues
- Possibility that the investigational medicine may not be put forward for approval or approved within a jurisdiction, and subsequent effect on those participants on or eligible for continued access
- Options if not participating in continued access or if there is no benefit to investigational treatment
- Informed consent process regarding (1) continued access and (2) alternatives for health care if no continued access will be provided or if participant is not eligible
- Safety information to be collected during the continued access program
- Plans for participants assigned to control or comparator arms regarding post-trial access to those medicines and
- Potential to be offered investigational medicine in trial demonstrates safety and efficacy

We recommend plans be described in written documents. Some sponsors choose to document the continued access plans in a pre-trial agreement, and some only in the protocol and informed consent in which case the IRB/REC would review. Regardless of the form of documentation, the elements to be considered remain the same.

The IRB/REC will review the information provided and determine whether discussion of post-trial provision of medicines at informed consent will contribute to therapeutic misconception.[23] This concern prompts an argument for describing uncertainties around post-trial access to medicines at the time of consent and a commitment to reevaluation at a later time in the trial.

Some sponsors (e.g., sponsor-investigators, governmental agencies, not-for profit sponsors) are not the manufacturers of the investigational medicine; this discordance introduces special considerations insofar as the ethical responsibilities to participants remain. Those sponsor-investigators will need to negotiate with the drug manufacturer(s) whether and under what conditions the investigational medicine will be made available, and communicate the plan in the study protocol and the informed consent.

Pre-Trial Agreement

A 'pre-trial agreement' is an option for helping explain and negotiate PTR plans; alternatively, a protocol and informed consent form will serve the same purpose. The elements listed above, including the roles and responsibilities of the various stakeholders; and the specifics of PTR access, funding, criteria for continued and termination of access, etc. should all be thought through and explained in a pre-trial agreement. The process of writing a comprehensive document is often helpful in ensuring that every element is considered.

Protocol

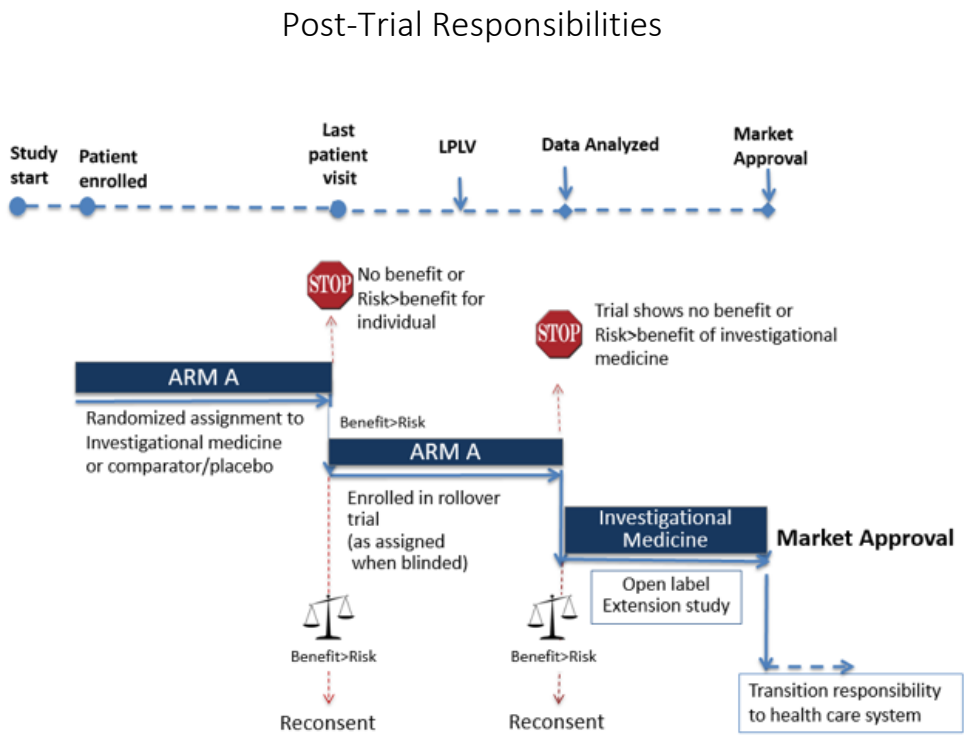
At the planning stage of the study, the sponsor is responsible for establishing guidelines that address continued access to the investigational medicine as well as to the comparator arm, which is of particular importance in a blinded study. Continued access should always be provided in a defined program: continued access will generally be provided, subject to local regulations and ethics approvals, under a study protocol (e.g., long-term safety data collection)

[23] Defined by Appelbaum *et al.* as "To maintain a therapeutic misconception is to deny the possibility that there may be major disadvantages to participating in clinical research that stem from the nature of the research process itself." (Applebaum, 1987)

as a built-in study extension, a separate extension study, or a roll-over study with an accompanying informed consent process (see Section 4 A in *Toolkit*).

Figure 2 illustrates options for continued access when the investigational medicine has been beneficial to individual participants. This figure is a simplified version that does not cover all scenarios. Each trial will need a defined "transition period" based on its specific study design. For all diseases and especially for chronic diseases, the protocol should include whether continued access to the investigational medicine will be provided and for how long.

Figure 2: Options for continued access when product has been beneficial to the individual participant



During a blinded trial, at the patient's last visit and if the treatment is determined to be necessary and beneficial and other conditions are met, continue as per randomized trial assignment (either investigational medicine or comparator/ placebo). If the individual has not benefitted, or the risk is greater than the benefit, the patient is off trial and is given standard of care. At end of trial when the results are known, participant may be given option to transition to the investigational product if the benefit/ risk assessment is positive (by open label extension or other mechanism) and taken off the investigational medicine if the trial shows no benefit or the risk (e.g., safety) is greater than the benefit. If the investigational medicine is approved by the regulatory authorities, the participant should be transitioned to the health care system by a pre-determined date. If no reimbursement exists, other avenues may be pursued, such as patient assistance programs or other support. Note that the termination of an individual's participation may occur long before the last patient last visit (LPLV) and no information will be available as to the benefit, if any, of the investigational medicine.

Informed Consent Document and Process

The sponsor and investigator must consider what and how much information regarding continued access to beneficial interventions (investigational medicine or comparator) should be shared with participants. In principle, abridged continued access plans should be included in the informed consent process (CIOMS, 2002) and, at a minimum, the plans for continued access of a beneficial investigational intervention should be mentioned. If no continued access is planned for whatever reason, that should clearly be stated in the informed consent document.

The informed consent form should define to the extent possible whether and under what conditions the participant may receive an investigational intervention that has been shown to be beneficial at completion of their participation on the study; how benefit will be determined; whether access for the individual will be dependent upon the safety profile in other participants; whether, when, and under what conditions the availability to the investigational intervention will be discontinued (e.g., if local alternative therapies are available or become available, if the product is not put forward for marketing approval in the jurisdiction, if there is a time limit for continued access, etc.). Often at the beginning of a trial there is insufficient information regarding the safety and efficacy of an investigational agent to make a decision regarding whether to offer continued access: the safety profile may be unknown, risks unforeseen, and benefit not evident. Nevertheless, the informed consent document should mention that the circumstances under which it could be made available and what information will be determinative.

Under almost all circumstances, even if the plans for continued access were detailed in the informed consent document of the trial, an investigational medicine given as continued access after the primary trial will generally be made available on a subsequent protocol (e.g., extension trial, roll-over trial etc.) or other defined program; informed consent for continued access should be solicited and granted prior to provision of the drug.

The duration for which an investigational medicine will be made available should be considered during clinical trial planning, and described, to the extent possible, in the protocol and the informed consent form. This disclosure allows for the IRB/REC to perform an ethical review of post-trial access plans and appropriate expectations to be established with investigators and participants. All relevant stakeholders—including the participants—should be informed that

subsequent data or knowledge gained during a trial of the investigational medicine could result in changes to the proposed continued access plans.

4.3.2 Access to the Investigational Medicine

Overarching Responsibility: Assess Benefit and Risk

In order to decide whether there is evidence of benefit, a benefit/risk assessment must be performed for the individual participant by the investigator (and, occasionally, the treating physician) and for the trial population by the sponsor. As mentioned, there may be instances when the individual has benefited but the trial population has not. The investigator and sponsor should work collaboratively to determine whether to provide continued access for each benefiting participant. If, however, a trial or overall data suggest that the benefit/risk is unfavorable, access may need to be discontinued even if an individual participant may have derived benefit. If the investigational medicine is supplied, its availability should be compliant with local laws and regulatory and ethical requirements.

There is always the possibility that post-trial treatment with an investigational medicine can lead to new risks or harms not yet identified. Even if an investigational medicine is initially beneficial, such benefit may be temporary or new risks (e.g., adverse events not evident during the trial) may occur. That said, participants with serious or life-threatening conditions are often willing to accept unknown risks associated with an apparently beneficial treatment. Access to investigational medicines is generally offered under a protocol with associated monitoring of safety and sometimes efficacy in participants. Collectively, these measures mitigate ethical concerns related to non-maleficence.

Points to consider for specific scenarios and issues for contemplation are elaborated in the MRCT Center *PTR Toolkit*.

Responsibilities Over the Time Course of a Clinical Trial

Responsibilities for and decisions by the sponsor and/or the investigator/physician are arrayed over the time course of a trial, and these decisions will change based on the facts at the time. Prevailing responsibilities in the context of specific scenarios are addressed below. Each of these scenarios will be discussed:

Responsibilities of Investigators

i. Responsibilities when a patient has completed study participation, and the study is ongoing
ii. Responsibilities when a patient has completed study participation, the study has ended and the investigational medicine is pending regulatory approval
iii. Additional investigator responsibilities

Responsibilities of Sponsors After the Trial Results are Analyzed and Known

i. Responsibilities at the end of study participation when there are other potential treatment options
ii. Responsibilities when the investigational medicine does not obtain regulatory approval
iii. Responsibilities when the investigational medicine is approved for the indication and becomes commercially available
iv. Additional sponsor requirements

Responsibilities of research participants

Figure 3: Interplay between individual and study population in the determination of risk and benefit

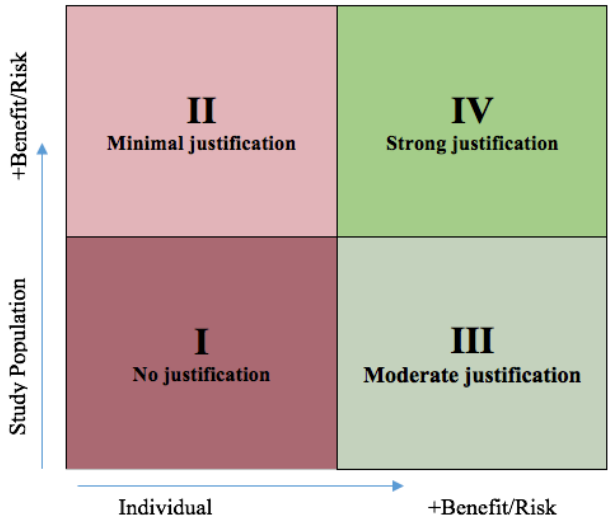


Figure 3 shows the interplay between individual and study population in the determination of risk and benefit. On the one hand, when an individual participant has not benefited (or the risk—e.g., adverse event profile—outweighs the benefit), it is impossible to justify the provision of continued access (Shaded Area I) and difficult to justify even if the benefit/risk assessment of the study population is positive (Shaded Area II). On the other hand, if the individual has benefited (and the risk does not outweigh the benefit), the provision of continued access should be considered if other conditions (see Section 4.2.1) are favorable (Shaded Area III). The rationale for the provision of continued access is even stronger if the benefit/risk assessment of the study population is positive (see Shaded Area IV).

4.3.2.1 Responsibilities of Investigators

Responsibilities when a Patient Has Completed Study Participation and the Study is Ongoing

Sponsors, investigators and the treating physician all share responsibility for assessing the benefit/risk of the investigational intervention during the time period after a patient on study has ended study participation but the study is still ongoing. The investigator is responsible, with the participant, for assessing whether the participant has derived benefit and would therefore be a candidate for continued access to the assigned treatment arm. The treating physician is responsible for continued care of the patient, and, with the participant, for informing the

investigator of adverse events and of any change in the beneficial response. The sponsor is responsible for the decision to and the provision of the investigational medicine and for informing the investigator of any safety signals that arise (that the investigator must then communicate to the health care provider or participant).

Responsibilities When a Patient Has Completed Study Participation, the Study Has Ended and the Investigational Medicine is Pending Regulatory Approval

The responsibilities of sponsor, investigator, healthcare provider and participant extend through the analysis of the data, determination of benefit/risk of the study population, and through regulatory submission. The responsibilities of Section 4.3.2 apply, and additionally, if the study itself demonstrates that the investigational medicine is superior to the comparator arm, consideration should be given as to whether all past participants on the trial, now unblinded, and on continued access should be offered the transition to the investigational medicine. The conditions of transition should be communicated to all sites and investigators and to the regulatory authorities for their review. The responsibility of the sponsor is not of indefinite duration but changes after the regulatory authority has rendered an opinion.

Additional Investigator Responsibilities

The investigator is responsible for the benefit/risk assessment of the medicine for the individual participant and, if appropriate, transitioning the participant to a continued access protocol. If the participant will not continue to be on any study, the investigator is responsible for transitioning the participant to a healthcare provider and responsibly terminating the relationship, as appropriate. This responsibility arises primarily from the professional relationship established between the investigator and the research participant. This relationship is direct (as opposed to the generally indirect relationship between the participant and the sponsor) and creates a fiduciary relationship that should be responsibly terminated.[24] A responsible termination should include activities such as linking the participant with a local

[24] Unless the investigator is also the treating physician and no termination is envisioned.

health care provider, transferring information necessary for an effective transition of care, and providing access to medication to cover the transition period (see Figure 2).

The investigator's responsibility also arises by virtue of the investigator's specialized knowledge of the research participant and the disease or condition under study. This knowledge and training puts the investigator in the unique position of being able to judge whether the research participant is benefiting from the investigational medicine and whether the participant is likely to continue to benefit if treatment is continued after the research has ended. Investigators may need to collaborate with local health care providers and other physicians to make these determinations, especially in cases of participants with multiple co-morbidities. Investigators also have the responsibility to monitor individuals during continued access to evaluate continued benefit and assess adverse events and risks as they may arise and to communicate to the patient's care provider.

Box 4: Investigator Responsibilities for Assessment of Continued Access to Investigational Medicine at Patient Last Visit
The investigator should: • Communicate what to anticipate after last study visit • Determine whether acceptable benefit/risk has been observed from assigned study arm and whether continued access would be recommended; • Advise regarding monitoring for adverse events, both rare and common, severe and serious, if appropriate • Inform, if questions, or adverse events, whom to contact (and contact information) • Remind the participant, if appropriate, that they may be contacted in the future if any adverse events are uncovered that might impact their health.

- Provide information regarding where to access any benefits or care as a consequence of participation, if any

- Determine whether and where to access product, if appropriate; how to enroll in follow-on

Contact the treating physician to discuss the clinical condition of the participant and arrange responsible transition to clinical follow-up and care

4.3.2.2 Responsibilities of Sponsors After the Trial Results are Analyzed and Known

Responsibilities at the End of Study Participation When There are Other Potential Treatment Options

As seen in Section 4.2.2, if the participant has a disorder with an unmet medical need and other requirements are fulfilled, there is a responsibility to consider continued access. However, if an alternative treatment is or becomes available, then the duty to provide access to the investigational agent is weaker and the patient should be transitioned to the alternative treatment. Here an alternative treatment is defined as a product that (1) has been approved by the local regulatory authority for the indication under study, and (2) is reasonably accessible in that country.

The informed consent form should clearly state whether suitable treatment alternatives to the product under study are available and, if new treatments become available during the trial, the cognizant IRB/REC should be informed. The IRB/REC will review the change and determine whether the informed consent should be updated and whether and, if so, how current participants should be informed. If an alternative treatment is reasonably accessible, then the investigator/physician should determine if the alternative is appropriate for a participant, and if so, assist the patient with transition to the suitable alternative. The sponsor is not responsible for providing alternative treatments to clinical trial participants once their study participation has ended. If no suitable alternative is available (or if switching to an alternative available treatment would have a significant risk of harm), the sponsor has responsibility for providing access to the intervention if the other conditions are met.

Responsibilities When the Investigational Medicine Does Not Obtain Regulatory Approval

The core principles and the responsibilities of the sponsors and investigators apply in the setting in which a product is not approved by the sovereign regulatory authority. Non-approval of an investigational medicine can be due to a multitude of reasons and factors, each of which require additional consideration based on the circumstance:

Development pathway abandoned

If drug development is abandoned, the degree of responsibility and the advisability of continued access will vary depending on the reason for discontinuation – safety versus regulatory or commercial reasons. If drug development is abandoned due to the appearance of safety issues, the sponsor should not provide continued access to that investigational medicine except under very rare circumstances. Indeed, continued access may expose former participants to significant risk of harm.[25] If the reason is due to business or strategic reasons,[26] sponsor post-trial responsibilities may persist. In this circumstance, sponsors are not compelled to manufacture additional quantities of investigational medicine if that product will *never* be marketed or pursued.

Rejection of the regulatory submission (or marketing authorization rejection)

When a marketing application of an investigational medicine is rejected in a region/country for the indication under study,[27] administration of the investigational medicine should be responsibly discontinued. Sponsors have an obligation to respect local regulatory authority decisions. Again, specific rare exceptions may be made, but only with regulatory approval and oversight.

[25] In any scenario, rare exceptions may need to be considered. However, in each, continued access should only be provided with regulatory approval and oversight and investigator involvement.
[26] As for instance, if the market potential is significantly smaller than originally calculated, the cost of goods is higher than predicted, a competitor product is introduced, or the benefit is far less than anticipated.
[27] Sometimes the dossier will be resubmitted by the sponsor. In this case, transitions of care should await the final determination by the regulatory agency.

Responsibilities When the Investigational Medicine is Approved for the Indication and Becomes Commercially Available

In a given country, when an investigational medicine (1) receives regulatory approval for the indication under study, and (2) is commercially available in that country, the sponsor's responsibility for providing the product to former participants attenuates and, after a reasonable amount of time to ensure transition, ends.[28] This duty generally transitions to the government, health care system, payor, or provider. Treating physicians should determine if the newly-licensed product is appropriate for their patients (former participants) and prescribe the product appropriately. When reimbursement is not available, or (former) participants are otherwise unable to access the product, the treating physician or investigator may apply to the sponsor to obtain the product, most typically through a patient assistance program. The sponsor may elect to facilitate provision of the product.

Additional Sponsor Requirements

It is not a sponsor's role to provide medical care to individual participants; in the setting of drug development, the objective of clinical research is to gain scientific knowledge that will benefit society and future patients. The responsibility of the sponsor with regard to continued access to an investigational medicine, supported by applicable ethical principles, require careful consideration of the factors outlined above (see Section 4.2.2).

4.3.2.3 Responsibilities of Research Participants

Research participant responsibilities regarding continued access to an investigational medicine arise from any agreements made during the processes of recruitment, enrollment, informed consent, or study participation. Although research participants are free to withdraw from research at any time, while enrolled and participating, they are responsible for adherence to

[28] In some countries, the regulatory authorities may dictate alternative arrangements. Brazil, for instance, currently requires the sponsor to provide the investigational medicine to (former) participants in some settings even after regulatory approval.

study procedures. Research participants have a responsibility to be truthful regarding compliance with study procedures and medications, their symptomatic response or lack of response to an investigational medicine, and any adverse effects they experience while being exposed to the investigational medicine. This responsibility aids the investigator in making sound decisions regarding continued access.

If a research participant electively withdraws from a study prior to completion, there is no obligation to provide continued access or to make the investigational medicine available by other means. The informed consent document should be clear about this eventuality. Nevertheless, the investigator maintains the responsibility to terminate the participant appropriately as described above (Box 1).

4.3.2.4 How Long do the Responsibilities Last?

There is no *prima facie* requirement to provide continued access or to provide continued access indefinitely; each decision in each case is based on an assessment of the absence or presence of relevant factors. Continued access should last as long as the reasons that justify the existence of this duty persist and the participant wishes and consents to continue treatment (see Box 2).

Box 5: Factors that affect the decision to discontinue continued access
(1) Participant is asymptomatic and/or it is not possible to assess individual benefit; (2) Participant declines further treatment; (3) The investigational medicine treatment plan is limited to a specific number of treatment cycles or a time-limited administration regimen and whose continued or prolonged administration may not be beneficial, and may even be harmful, to the participant; (4) The drug becomes commercially available in the host country, and there are now other ways for the former participant to access the treatment (e.g., through the public healthcare system);

(5) The final results of a trial lead to the conclusion that a treatment that had once been considered beneficial is less safe or less efficacious than preliminary results indicated;

(6) The treating physician believes that the risk/benefit ratio is no longer favorable to continued treatment because the drug stops benefiting the participant or the participant experiences adverse events or cannot tolerate the product;

(7) The cost of a prolonged continued access program (which involves, for instance, an ongoing study, the manufacture of drug, and the appropriate resources to collect and manage participant data) becomes sufficiently high as to impact the viability of research or continued product development;

(8) The investigational medicine supply is exhausted.

As the status of an individual participant changes, the data about an investigational medicine changes, or alternatives to continued access become available, the need for continued access should be periodically reevaluated. Ongoing data acquisition and knowledge gained during and after a trial of the investigational medicine often result in changes to the proposed continued access plans.

4.3.2.5 How Should Phase of Product Development be Addressed?

For All Phases of Development

The ability to judge the efficacy, safety and benefit/risk of an intervention increases as clinical development progresses from Phase I, II and through Phase III trials. It is important for the sponsor to consider what data will be needed and when relevant data will be available to make the benefit/risk decisions that will inform access of a given product, with the involvement of appropriate regulatory, legal authorities and IRBs/RECs. In addition, the sponsor will wish to consider what data the investigator should provide about the participant in the request for continued access, and what data to collect from participants that receive the intervention.

There are a number of additional pragmatic issues that affect a sponsor's ability to supply investigational medicines after completion of a study. One is sufficient supply of the investigational drug. This is especially common in early phases of development, before

manufacturing scale-up, but can occur at any stage, including phase III trials when the target patient population is very large. Sponsors will need to consider, model and predict the circumstances of the trial and consult with the other stakeholders, including patient groups, investigators, IRB/RECs, regulators and others in order to make decisions in difficult cases.

Early Phase Trials

Phase I trials include "first-in-human" and dose-finding safety trials, conducted in healthy volunteers and in some cases, in patients with the condition or disease for which the intervention is being investigated. It is nearly impossible to imagine a situation in which a healthy volunteer in an early phase study would be a candidate for continued access. When the number of total participants treated is small, it is difficult to assess the relative benefit/risk of the investigational medicine without additional clinical data. However, early Phase I studies involving patients (e.g., in oncology trials) that have not generally been designed to assess efficacy may nevertheless demonstrate a beneficial effect in an individual patient.[29] If there is clear evidence that the investigational medicine is having a positive impact on the participants' symptoms, function or disease burden, and other relevant requirements are met, the investigator should engage the sponsor to consider providing continued access to the investigational medicine. Notably, Phase I trials are often initiated before final toxicology data are available, and health authorities in host countries will need to be consulted before making any decision. In these rare instances of clear benefit, if the investigational medicine is provided through a continued access program, careful monitoring and safety assessments should be sustained.

Efficacy Trials

Phase II and III (registration trial) often have efficacy data as a component of outcome. There are then two discrete time points when decisions regarding provision of drug need to be made. The first, as discussed earlier, is when the participant completes their personal part of the

[29] With the more recent development of molecularly targeted therapies, it has not been unusual to see significant efficacy even in Phase I. In some cases, these early trials have been expanded to support registration.

study. As mentioned, for a blinded trial, it is important to maintain the blind (and double blind) privilege[30] until all of the trial results are known; a participant would naturally continue to receive the assigned, beneficial[31] intervention (investigational medicine or comparator arm). The second decision point occurs when the trial results are known. If the investigational medicine achieves its endpoint, consideration should be given as to whether some or all participants should receive the product, made available with regulatory and IRB/REC oversight. And if the investigational medicine does not achieve its endpoint, then transitioning participants off the intervention should begin. These decisions will be individualized based on the specific medical condition, investigational medicine and potential alternative therapies.

Phase IV or Post-Marketing Studies

For studies of a marketed drug in which study drug is provided, the protocol and informed consent document should specify the plans for drug when the study ends. If the study is within the approved labeling, it is appropriate to transition the participants to their health care provider so that they may access the drug or device via the usual mechanisms available in the country. However, the sponsor should include in its plans all steps needed to avoid gaps in drug availability. When the study use is outside currently approved indications, factors such as those discussed in the above sections regarding efficacy and benefit/risk need to be considered. It can be appropriate to make the drug available for a specified time.

4.3.3 Access to Accompanying Medical Care

The provision of an investigational medicine alone can be futile or even dangerous for participants when accompanying medical care is necessary but not available. For instance, an antiretroviral therapy will be ineffective and probably harmful for the patient if administered

[30] In most blind and double-blind efficacy trials, a data monitoring committee will have access to unblinded data and will be able to assess safety and efficacy.
[31] If no benefit was discernible, or if the trial was one in which no individual benefit was discernible, no continued access to the intervention would be offered. Of course, the informed consent document would explain the situation.

without adequate infrastructure, personnel, clinical and laboratory monitoring, treatment for side effects, access to derivatives and background regimen or therapy (Ciaranello et al., 2009). Therefore, the availability of medical care necessary for the continued administration of the investigational medicine will be an important factor to consider when planning for continued access. We do not consider here other medical care or social supports that could be provided to participants, only those necessary for the safe provision of investigational medicines (or comparators). The duration of medical care should be concordant with the provision of continued access to the investigational product.

4.3.3.1 Distributed Responsibilities

There is a range of possibilities in terms of who is responsible for providing the accompanying care for the administration of the investigational medicine and for how long. While a sponsor may be the best-suited (and only) party to provide the investigational medicine to the participant, that is not true of the accompanying care.[32] The sponsor's duty will vary depending on the type, quality and coverage of health care in the host country and, therefore, the sponsor's role must be considered along with those of public and private health care providers.

It is important to underscore the importance of participants being informed that there is no guarantee of continuing care by sponsors for conditions unrelated to the study intervention in most jurisdictions.[33] In the event that continued access is provided, participants should be informed about the arrangements for the provision of accompanying medical care after the trial is concluded.

[32] There are arguably circumstances in which sponsors and researchers can be considered to have duties to host communities, but this will not be covered in the present document.
[33] Exceptions occur. In Brazil, for instance, it is sponsor's responsibility to provide the financial resources of care for complications and/or injury arising from the use of the investigational medicine even after the study has concluded (Casa Civil da Presidencia da Repbulica, 2016).

Sponsors and Investigators

There is no duty of sponsors or investigators to elevate the local standard of care outside of the clinical trial setting or continued access program, but adequate supportive care must be provided or secured by sponsors for provision of the investigational medicine. The sponsor should evaluate the standard of care and the infrastructure available prior to study initiation. If the sponsor can assure that the local standard of care (Macklin, 2008) is adequate and available to participants for the proper administration of the investigational medicine outside of the trial context, then the sponsors may proceed with continued access. However, if appropriate care cannot be assured, then sponsors must consider how and what medical care should be provided and by whom, either supplanting or supplementing local health care resources. In either event, this should be anticipated, discussed and clarified with the local health authorities prior to the initiation of continued access (and, as stated, prior to study initiation). Ideally, a written agreement will delineate the shared accountability and canonize the decisions, responsibilities and source(s) of financial support.

Issues regarding accompanying health care are more readily resolved in countries where there is universal coverage and the standards of care are high. While the health care systems cannot provide the investigational medicine, they can provide the standard of care received by other patients. If the standard of care is compatible with what is necessary for the adequate administration of the tested intervention, then there is no duty for sponsors to substitute the public provision of health care.

The most challenging situations, however, arise when there is the duty to provide continued access but the additional care necessary for the proper administration of the investigational treatment is not accessible for research participants outside the context of the trial. This situation would frustrate the purpose of the continued access provision—and would be in breach of ethical principles notwithstanding sponsors' willingness to provide access. There are, however, alternatives for sponsors, even when local medical care is precarious.

In countries where the local (public) standard of care is poor but private providers with higher standards exist, sponsors and others, including private providers, can provide reimbursement for the accompanying treatment as a component of the follow-on continued access trial (e.g. extension trial). In countries where the appropriate care is simply nonexistent, sponsors can consider (a) maintaining the clinical trial site and personnel for continued access or (b)

transitioning the infrastructure and capabilities to local governments for the continuing medical care of those receiving continued access when the trial is over. These arrangements should be considered and documented before study initiation. Alternatively, the sponsor, government and others (e.g. community representatives) can decide not to initiate or place the trial in that community at all.

Government

Governments cannot be expected to provide continued access to investigational medicines prior to health authority approval. Moreover, in a context of scarce resources, a fair allocation of health care resources should not prioritize experimental treatments[34] as opposed to treatments that are already registered and approved at the regulatory agencies (Otterson & Norheim, 2014). Moreover, in most jurisdictions there are legal barriers for the provision of investigational medicines by the public health system.

The fact that governments are not obligated to provide investigational medicines does not relieve them of responsibilities to care for their populations, including individuals who have chosen to participate in a clinical study. Research participants are entitled to receive the same level of care from governments as others in the same condition who did not participate in a study.

If participant safety cannot be assured for continued access secondary to the level of care in the country, then whether and how the responsibilities will be divided should be negotiated by and among communities, local authorities, and sponsors. In any negotiation, and particularly if public resources will be used to prioritize research participants over other community members, it is important that communities are heard and that the discussions are inclusive, transparent and based on sound reasons and fair principles of justice (Daniels, 2007). Costs can

[34] There are exceptions to this statement, in cases where the investigational medicine is easier to administer (e.g., one daily oral dose versus intravenous therapy; short-course, single-dose antibiotic regimen versus multiple daily doses over weeks), curative versus therapeutic (e.g., Hepatitis C treatment), better tolerated and thus improve compliance, cheaper, etc. The government must of course consider what is best for the health and safety of its population and can choose to assume any responsibility.

be divided; sponsors can accept to continue providing background therapy after the trial; governments can commit to raising their standards; or support from charities or international organizations can be sought. If a solution cannot be found, the trial should not be sited there. Governments may consider incentive programs such as reducing or eliminating import taxes for continued access programs that can pose a significant burden in certain countries.

Healthcare Providers

Private health providers are not required to provide continued access. Indeed, in many jurisdictions there are legal barriers for the provision of experimental treatments by private health care providers.

However, if the trial participants are insured or have other sources of third party reimbursement for medical care, they have a right to appropriate reimbursement for or provision of medically necessary care. Thus, if the background therapy and the clinical and diagnostic exams are covered by insurance, third party payors or health systems, investigators can make arrangements for the additional care required for the investigational medicine to be provided and reimbursed. These arrangements are usually finalized in advance of administration of the experimental therapy.

4.3.3.2 Reimbursement

In general, it is the responsibility of the national health systems, third party payors or governments to provide, or provide reimbursement for, medical care related to the background regimen (local standard of care) if the investigational medicine is designed to deliver intended benefits in combination with them.

A problem may arise when the capacity of providers/ governments constrains the provision of support or reimbursement. For example, a government may limit the period of reimbursement

for background regimen to two years after the completion of a clinical.[35] If there is a known limit to reimbursement, participants should be informed, typically during the informed consent process. Sponsors and investigators should identify the source of payment or reimbursement for background regimens before commencing the trial, either as part of the trial or in the form of a sponsor-directed special assistance program, through other sources such as international organizations or national consortia, or in collaboration with international organizations and advocacy organizations.

The provision of ancillary care, that is, the diagnosis and treatment of unrelated co-morbidities that are identified during screening or that develop during a clinical trial are not the responsibility of the sponsor or investigator (Lumberas et al., 2010), (Dal-Ré et al., 2014), and (Wolf et al., 2008). The investigator should refer the patient to a health care provider, and care should be provided through the national health system, third-party payors or other appropriate and customary methods in the local environment.

4.3.4 Access to Required Infrastructure

For the safe provision of an investigational medicine, it is often necessary to make investments in local infrastructure.[36] This includes, in all settings, training of the local staff, quality improvement activities to ensure data quality, and financial resources to support the trial activities. In addition, capital investment is sometimes necessary to provide medical equipment necessary for research procedures, laboratory equipment for data or biospecimen acquisition, and equipment to maintain the physical and chemical properties of the medicine (e.g., cold storage facilities and cold chain transport from distribution location to local site). Many of these issues will be considered for the primary clinical trial; few are different for continued access to the medicine. Nevertheless, we recommend that these considerations be thought

[35] The argument is made that providing reimbursement may be an undue inducement to participants to enroll in a trial. We reject this argument (see above). In addition, some payors and governments restrict coverage because funds are allocated to other public health and health care priorities.

[36] In resource-limited settings, if there is no agreement before study start between the sponsor and the cognizant government authority regarding improvement and investment in infrastructure and local standard of care, the study should not be conducted in the region.

through and planned in advance, and decisions made as to what, when and how to negotiate proper arrangements for the trial and post-trial access.

Box 6: Points to consider associated with investments in the local infrastructure (whether proposed or to be proposed by a trial sponsor) include
• Whether, as a matter of ethical obligation, a trial sponsor should be making investments in the local research and healthcare infrastructure that will be used or allowed to be used, after the trial is completed? • Whether a proposed investment in the local infrastructure would be an undue or improper inducement to potential trial participants? • Whether a proposed investment in the local infrastructure would be an undue or improper inducement to investigators, research clinics and hospitals, regulators, ethics committees, or local authorities, with respect to conducting or approving the proposed trial?

4.3.4.1 What are the Responsibilities?

While post-trial responsibilities to communities were considered out of scope in this Framework, we discuss access to infrastructure as the provision of continued access and ancillary medical care is often not possible without it.[37] By infrastructure, we specifically

[37] In the context of clinical trials, especially those conducted in low resource settings, benefits can include investment in the local health care infrastructure in addition to (or in some cases, in lieu of) other post-trial commitments that sponsors may make to the trial participants. For example, sponsors often provide equipment necessary for the clinical trial to the participating sites and, from time to time, may provide equipment necessary for the clinical trial to the participants; this may be as basic as a refrigerator to store the investigational drug, or it may involve more sophisticated diagnostic or testing equipment such as x-ray machines, trial-specific testing equipment, and so on.

address here fixed capital equipment, not professional training or human capabilities.[38] The short-term beneficiary of access to infrastructure is the research participant; the long-term beneficiary is often the community or local health authority. We discuss the issues attendant on access to and transfer of infrastructure, and the ethical considerations that should be considered.

Trial sponsors seeking to include sites from the developing world often work closely with regulators and local authorities to ensure that appropriate research and clinical infrastructure is in place. Often a sponsor will want something in place that exceeds the minimum amount of infrastructure, either so that all of the participating sites, regardless of the country or region, meet comparable standards for quality and compliance or so that all of the sites offer an appropriate and equivalent standard of care (or even the best standard of care, globally). This often cannot be done in low resource settings without an investment in the research or care infrastructure. Thus, one of the benefits to low resource countries from participating in the process for clinical research is the potential to build its health research infrastructure, separate from and in addition to providing their citizens with access to promising therapies and training and opportunities for their physicians and scientists to participate in the research process. Continued access to investigational medicines may provide a mechanism for continued support of necessary infrastructure, and these decisions should be affirmative and advertent, discussed and negotiated openly.

4.3.4.2 Who is Responsible?

If the sponsor provides access to the investigational medicine following the trial, the sponsor, usually in concert with the local entity and government, should be responsible for the maintenance of infrastructure related to such provision until the provision is concluded. The contributions of the medical facility to its share of maintenance costs should be pre-established and understood. If provision of the investigational medicine is discontinued and the medical facility is unable to utilize the infrastructure, the sponsor should be responsible for removal of the infrastructure or other arrangements, ideally determined prior to trial initiation. If the

[38] Appropriate development and training of staff is required to conduct research in clinical sites, concordant with the expectations of GCP.

medical facility is able to utilize the infrastructure, then responsibility for its maintenance should transition to the facility.

Equipment remaining on-site after the trial, especially when there is no continued access to the investigational medicine, becomes the responsibility of the owner or controller of the trial site or the community. Issues of equipment maintenance, potentially including the need for monitoring and re-calibration by a trained technician, and equipment removal, must be considered. It is important to include these considerations in pre-trial planning. Sponsors need to define the responsibility and requirements for equipment upfront.

4.3.4.3 Duration of Responsibilities

For many, if not most, trials in low resource settings, there will be an investment in the local research infrastructure. In this context, it is possible that the trial sponsor could remove those resources at the end of the trial, even if the cost to remove the equipment or other infrastructure is itself significant. The sponsor can also decide to donate or depreciate (over the life of the trial) the equipment and transfer the responsibility of maintenance to the local community. The sponsor's responsibility ends after it either removes or donates the equipment. Donations, however, should be properly executed and documented as discussed below.

4.3.4.4 How will Specific Conditions be Addressed?

Trial sponsors may need to invest in the training of local medical professionals, in the sites, and in health care infrastructure in order to perform a clinical trial safely and under GCP standards. The potential for sizeable investment exists and the appearance of any undue influence must be recognized, managed, and eliminated.

Under the U.S. Foreign Corrupt Practices Act and other anti-corruption laws, offering something of value such as equipment or other investments that benefit local health care providers or government administrators (by virtue of their employment by or participation in government health care systems) could be construed, in some circumstances, as an attempt to influence the

actions of the official or other person. In this context, it may be perceived that the value of the equipment or investment could be so substantial that the recipient or local decision maker would be influenced to approve or participate in the activity (in this case, the trial). While this is rarely true in clinical research, it informs the necessity for proper consideration and documentation of any planned investment or donation.

While any proposed investment in local infrastructure may be substantial, the value of the equipment or other investment depreciates over the course of the trial, and that schedule can be factored into the compensation that is offered to the participating sites for their work on the trial. When that is done, the potential for a donation of the equipment to be seen as an improper inducement is minimized. Alternatively, in lieu of factoring in the value of the depreciated investment, the sponsor may choose to reserve making a decision on whether to leave or remove the equipment or other investment until after the trial has been approved or agreed to. In this way, if the sponsor chooses to donate the equipment or other investment, it is unlikely to have influenced the decision of the investigator or his or her site to participate, of the regulator or ethics committee to make a favorable decision, of the community leadership to support the trial, or of the local patients to enroll.

A third option for trial sponsors to mitigate concerns about a local investment is to be transparent about that investment. A generous investment in a local hospital's infrastructure, associated with its participation in a specific clinical trial, is less likely to be seen as improper or unduly influential if the trial sponsor is open about what it is contributing and the reasons therefore.

Such investments will vary based on the locale and the trial, and on the sponsor and its capacity to fund infrastructure. For example, government sponsors, such as the U.S. National Institutes of Health, fund research with taxpayer monies and therefore have less discretion to fund investments that would be used after the trial is concluded. Non-government organizations (NGOs) and nonprofit sponsors would have similar limitations in that they often rely on third party grants. Emerging biotech companies may be limited in the capital available to them. Even large, multi-national pharmaceutical companies may have financial limitations for their development programs, Therefore, and considering the need to reconcile PTR and the viability of a research, each program and the degree of investment in the local infrastructure must be decided on the specific facts presented. However, although there are practical differences

between Sponsors, the underlying ethical obligations to study participants should not differ based on the identity of the sponsor or their organization.

4.4 Special Considerations

4.4.1 National Laws and Regulations

Decisions regarding post-trial responsibilities must comply with laws and regulations in the relevant countries and other jurisdictions for each trial. As highlighted in the Background Section, countries across the globe have adopted a wide variety of regulatory approaches to address the issue of post-trial access. Prior to implementation of the trial, therefore, sponsors must ensure that the given country agrees with the plan for providing access to the investigational medicine, access to ancillary medical care, and access to infrastructure. Regulatory regimes on continued access may range from binding laws and regulations in countries such as Argentina and Brazil (Diretoria Colegiada da Agencia Nacional de Vigilancia Sanitaria (Anvisa), 2013), to guidelines and other guidance materials in a larger group of countries including Nepal, South Africa, and Uganda that suggest but do not mandate PTR (South Africa Department of Health, 2006). Many of these non-binding documents emphasize the need for including a continued access plan in the study protocol (South Africa Department of Health, 2006). Some use language such as "should make an effort" or "should make reasonable efforts" (Canada Panel on Research Ethics, 2010), while others offer merely that post-trial arrangements "must be described" (Indian Council of Medical Research, 2006). Some countries, including the United States and Thailand, have not issued regulations regarding continued access (Shah, 2014). Therefore, it may nevertheless be necessary to consult with the relevant government agencies before determining that there are indeed no regulatory limitations to the implementation of continued access in that country, as information regarding regulations may be difficult to locate, and extant regulations may have been recently updated.

Whether or not regulations or guidelines are legally binding, relevant documents may also provide useful guidance in crafting a continued access plan that will meet the approval of a country's regulatory agency. Documents promulgated by various countries reflect a range of priorities in issuing continued access regulations. For instance, these documents adopt different approaches in assigning responsibility among the relevant actors: while most countries mention sponsors, Argentina, Israel, Portugal, Japan, Brazil and Nepal also specifically

reference the role of investigators (Portugal National Authority of Medicines and Health Products (INFARMED), 2004); only Argentina additionally explicitly references the transfer of continued access responsibilities to the government (Argentina National Administration of Drugs, 2013). Countries also vary in terms of the scope of a continued access target population: while in general, trial participants comprise the target population, some countries also include the communities in which research is implemented (Indian Council of Medical Research, 2006). Another area of variance is the type of continued access provision stipulated, which ranges from the "best methods" approach in Japan and Brazil (Diretoria Colegiada da Agencia Nacional de Vigilancia Sanitaria (Anvisa), 2013), to therapies identified as "beneficial" in the study and possibly an "appropriate alternative," (Argentina National Administration of Drugs, 2010) to more vague language in countries such as South Africa and Nigeria (Ministry of Health Department of Health Planning and Research: National Health Research Ethics Committee of Nigeria, 2007). If a country has seen fit to delineate the responsibility of a given stakeholder or the type of care that may be expected, a continued access plan should incorporate these factors in order to ensure effective implementation by all stakeholders.

4.4.2 Research Participants' Access to Post-Trial Research Data

Informing participants about the results of the clinical trial in which they have participated is increasingly being regarded as component of good research practice. Specific guidance in order to promote understanding and transparency has been provided elsewhere:

See http://mrctcenter.org/projects/return-of-results-to-participants/ and http://mrctcenter.org/framework-data-sharing.

A current MRCT Center Workgroup is addressing providing individual research results; please see http://mrctcenter.org/projects/return-of-individual-results. Additionally, see Lumberas et al., 2010; Dal-Ré et al., 2014; and Wolf et al., 2008.

APPENDIX A: Post-Trial Terminology and Definitions

Access: Access refers to the ability, right or permission of an individual to use an object or asset, and implies the removal of barriers to allow such use.

Ancillary care*:* Ancillary care refers to "health care that research participants need but that is not necessary to ensure the safety or scientific validity of the research, to redress injuries caused by research participation, or to fulfill morally optional promises." (see Richardson 2004.)

Availability: Availability refers to the presence of an object in an intended place and time, while access refers to the use of such object by an individual.

> **Relationship between access and availability:** Since the presence of an object is a necessary condition for use of that object, barriers to availability are important barriers to accessibility. However, ensuring availability does not necessarily imply granting access for all relevant individuals. Consequently an investigational medicine might be available in a place, but other barriers (e.g. ability to pay) may preclude an individual participant from having access to it.

Background regimen or background therapy. "Background regimen" or "background therapy" are terms used to denote required additional medications or treatments that are necessary for the effective use of the investigational medicine. Typically, background therapy will be considered in the potential future labeling of the product. For instance, an anti-infective (e.g. anti-HIV) agent may only be considered as a component of combination therapy; an anti-diabetic agent may only be tested in combination with a baseline drug (e.g. Metformin). Background therapy, in this context, does not include medications or other treatments for the participant unrelated to the investigational medicine or indication being tested.

Continued access: Continued access refers to the sponsor's provision of continuity of investigational medicine (or comparator), and the needed medical care and health care infrastructure required to appropriately use the investigational medicine, to individual participants at the completion of their participation in a clinical trial or at the conclusion of a clinical trial. Typically, continued access to an investigational medicine will be provided as part of an ongoing or new clinical trial protocol (see below). In some instances, particularly in late stage clinical development or after a product is approved, there may be established mechanisms to provide continued access outside of a clinical trial protocol.

Expanded access to an investigational medicine: Continued access should not be confused with 'expanded access.' Expanded access, also called "compassionate use," provides a pathway for patients to gain access to investigational drugs, biologics and medical devices for serious diseases or conditions and is directed to individuals who *cannot* participate in a clinical trial, while continued access refers to individuals *who did* participate in a clinical trial.[39]

Investigational medicine: An investigational product that is a drug, biologic or biosimilar. Investigational medicines have not been approved by the cognizant national regulatory agency and that are used or tested as a reference in a clinical trial. This definition includes a product with a marketing authorization that is used for an unapproved indication or in a way that is different from its approved form.

Investigational product: An investigational product refers to a preventative (vaccine),[40] a therapeutic (drug or biologic), device[41], diagnostic, or palliative used in a clinical trial. An investigational medicine may be an unlicensed product or a licensed product when used or assembled (formulated or packaged) differently from the approved form or when used for an unapproved indication or when used to gain further information about the authorized form (National Institute of Allergy and Infectious Diseases (NIADID), 2013) and (European Commission, 2006b).

Post-trial access to an investigational medicine: The term "post-trial access" has varied meanings, often resulting in confusion and misunderstanding. Sometimes the term is used to indicate provision of access to an investigational medicine with evidence of benefit for individuals who have participated in a clinical trial and still need it. Alternatively, it is used to indicate community access to a proven effective product. For the avoidance of confusion, we

[39] Occasionally, sponsors have used "expanded access" as the protocol mechanism to provide continued access to an investigational medicine.
[40] The Workgroup could identify no case examples in which continued access to an investigational vaccine would be appropriate. In the limited case in which a second dose of a vaccine ("booster") would not have been planned in the first trial but nevertheless thought necessary to be given, a second clinical study would be indicated. Therefore, the special case of investigational vaccines is not further considered here.
[41] As noted previously, post-trial responsibilities in the case of investigational devices will be the subject of a follow on MRCT Center project and is not further considered here.

use the term "continued access" to indicate access to an investigational medicine (or under certain conditions, to comparator) to individuals who participated in a trial.[42]

Post-trial responsibilities (PTR): PTR should be interpreted to include a broad set of potential responsibilities when an individual has completed trial participation or at the conclusion of a clinical trial, including but not restricted to continued access. PTR may also include, for instance, communicating the results of aggregate (summary) and/or individual results to participants, transitioning research participants to other venues for obtaining, clinical care and treatment, provision of counseling, and/or the obligation to provide benefits to the community and country in which the clinical trials were conducted.

Post-trial responsibility mechanisms: We use this term to refer to the specific practices that are used in order to comply with continued access. The same responsibility might be met by different mechanisms in different settings and for different individual participants. Different PTR mechanisms may need to be used and coordinated in order to secure access to individual research participants. PTR mechanism should be distinguished in two broad groups: pre- and post-commercialization mechanisms because national regulations differ between a licensed and unlicensed medical product. 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. Post-commercialization mechanism may include appropriate referral to public health system, patient assistance programs, personal health insurance, etc.[43] Different mechanisms may also be used to comply with local laws and regulations.

Standard of care: A diagnostic and treatment process that a clinician should follow for a certain type of patient, illness, or clinical circumstance. In legal terms, the level at which the average, prudent provider in a given community would practice. It is how similarly qualified practitioners would have managed the patient's care under the same or similar circumstances (MedicineNet, 2016).

[42] Note, in this document the term "continued access" means access to an investigational medicine, and that access may trigger access to necessary health care and infrastructure required to provide that investigational medicine, as described in the body of the text.

[43] For a reference to the term "mechanism" in PTR literature and a list of pre-commercialization and post-commercialization see Millum, J. (2011). Also, see MRCT PTR Toolkit, Section 4A, for an overview of post-trial mechanisms. As mentioned, this guidance and toolkit mainly address the issues attendant in continued access to investigational medicines, not post-commercialization.

APPENDIX B: General Terminology and Definitions

Chronic disease: The U.S. National Center for Health Statistics defines a chronic disease as one lasting three months or more that generally cannot be cured by medication and does not spontaneously remit. The U.S. Department of Health and Human Services defines a chronic condition as one that lasts a year or more and requires ongoing medical attention and/or limits activities of daily living. Definitions of chronic disease vary widely in several aspects including duration or latency, disease nature, ability to cure, or functional limitation (Goodman et al., 2013).

Clinical Trial: We use this term to refer to interventional studies involving clinical treatment of participants.

Rare Disease: A disorder or condition that affects fewer than 200,000 people in the US (Public Law, 1983). The EU also incorporates in its definition some tropical diseases that are primarily found in developing nations.

Serious disease or condition: The U.S. Food and Drug Administration (US FDA) defines a serious disease or condition as " ... a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one." (United States Food and Drug Administration, 2015b, 21 C.F.R. § 312.300b1)

Stakeholder: A "stakeholder" is here defined as, "a person or group with an interest or concern in something; one who is involved in or affected by a course of action." (Dictionary.com, 2016)

Unmet medical need: The US FDA defines "unmet medical need" as "a condition whose treatment or diagnosis is not addressed adequately by available therapy" (United States Food and Drug Administration, 2014). This condition includes an immediate need or a long-term need for a population or society. Similarly, unmet medical need is defined by the European Parliament and of the Council as "a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorized in the community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected" (European Commission, 2006a)

REFERENCES

Appelbaum, P. S.; Roth, L. H.; Lidz, C. W.; Benson, P.; Winslade, W. (1987). "False hopes and best data: Consent to research and the therapeutic misconception". *The Hastings Center report*. 17: 20–24. PMID 3294743.

Argentina National Administration of Drugs, F., and Medical Devices (ANMAT). (2010). Disposicion 6677/2010,SectionB,4.11(f).Availableathttp://infoleg.mecon.gov.ar/infolegInternet/anexos/170000-174999/174557/norma.htm. Accessed 22 August 2016.

Argentina National Administration of Drugs, F., and Medical Devices (ANMAT). (2013). Circular No. 9. Available at https://www.scribd.com/doc/74882826/Circular-No-9-2009-SIDA-Protocolos-Bloch. Accessed 23 August 2016.

Canada Panel on Research Ethics. (2010). Tri-Council Policy Statement (2nd ed.): Clinical Trials. Available athttp://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter11-chapitre11/. Accessed 22 August 2016.

Cash, D. W., Adger, W. N., Berkes, F., Garden, P., Lebel, L., Olsson, P., et al. (2006). Scale and Cross-Scale Dynamics: Governance and Information in a Multilevel World. *Ecology and Society, 11*(2).

Ciaranello, A. L., Walensky, R. P., Sax, P. E., Chang, Y., Freedberg, K. A., & Weissman, J. S. (2009). Access to medications and medical care after participation in HIV clinical trials: a systematic review of trial protocols and informed consent documents. *HIV Clin Trials, 10*(1), 13-24. doi:10.1310/hct1001-01310.1310/hct1001-13

CIOMS. (2002). International Ethical Guidelines for Biomedical Research Involving Human Subjects. Available at http://www.cioms.ch/publications/layout_guide2002.pdf. Accessed 19 August 2016.

Claxton, G., & Lundy, J. (2008). How Private Health Coverage Works: A Primer, 2008 Update. Kaiser Family Foundation. Available at https://kaiserfamilyfoundation.files.wordpress.com/2013/01/7766.pdf. Accessed 22 August 2016.

Council for International Organizations of Medical Societies (CIOMS). (2002). International Ethical Guidelines for Biomedical Research Involving Human Subjects. Available at http://www.cioms.ch/publications/layout_guide2002.pdf. Accessed 19 August 2016.

Council for International Organizations of Medical Societies (CIOMS). (2016). International Ethical Guidelines for Health-related Research Involving Humans. Available at http://cioms.ch/ethical-guidelines-2016/WEB-CIOMS-EthicalGuidelines.pdf. Accessed June 26, 2017.

Daniels, N. (2007). *Just Health: Meeting Health Needs Fairly*. Cambridge: Cambridge Univesity Press.

Dictionary.com. (2016). Stakeholder. Available at http://www.dictionary.com/browse/stakeholder. Accessed 22 August 2016.

Diretoria Colegiada da Agencia Nacional de Vigilancia Sanitaria (Anvisa). (2013). Resolucao – RDC No. 38. Available at http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2013/rdc0038_12_08_2013.html. Accessed 22 August 2016.

Emanuel, E. J., Wendler, D. D., & Grady, C. C. (2008). An Ethical Framework for Biomedical Research. In E. J. Emanuel, C. C. Grady, R. A. Crouch, R. K. Lie, F. G. Miller, & D. D. Wendler (Eds.), *The Oxford Textbook of Clinical Research Ethics* (pp. 123 – 135). New York: Oxford University Press.

European Commission. (2006a). Commission Regulation No. 507 | 2006, on the conditional marketing authorisation for medicinal products for human use. Available at http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_507/reg_2006_507_en.pdf. Accessed 22 August 2016.

European Commission. (2006b). Definition of Investigational Medicinal Products (IMPs) and Definition of Non Investigational Medicinal Products (NIMPs). Available at http://ec.europa.eu/health/files/pharmacos/docs/doc2006/07_2006/def_imp_2006_07_27_en.pdf. Accessed 22 August 2016.

Goodman, R. A., Posner, S. F., Huang, E. S., Parekh, A. K., & Koh, H. K. (2013). Defining and Measuring Chronic Conditions: Imperatives for Research, Policy, Program, and Practice. *Preventing Chronic Disease, 10*, E66. doi:10.5888/pcd10.120239

Goodyear, M. D., Lemmens, T., Sprumont, D., & Tangwa, G. (2009). Does the FDA have the authority to trump the Declaration of Helsinki? *Bmj, 338*, b1559. doi:10.1136/bmj.b1559

Grady, C. (2005). The challenge of assuring continued post-trial access to beneficial treatment. *Yale J Health Policy Law Ethics, 5*(1), 425-435.

Indian Council of Medical Research. (2006). Ethical Guidelines for Biomedical Resaerch on Human Participants. Available at http://icmr.nic.in/ethical_guidelines.pdf. Accessed 22 August 2016.

Klopfenstein, M., Van Campen, L. E., & Garnett, T. (2015). Expanded Access Programs: Ethical and Practical Considerations for Biopharmaceutical Sponsors. *Therapeutic Innovation & Regulatory Science, 49*(3), 352-358. doi:10.1177/2168479015578154

Macklin, R. (2008). Appropriate Ethical Standards. In E. J. Emanuel, C. C. Grady, R. A. Crouch, R. K. Lie, F. G. Miller, & D. D. Wendler (Eds.), *The Oxford Textbook of Clinical Research Ethics* (pp. 711–718). New York: Oxford University Press.

MedicineNet. (2016). Standard of care. Available at http://www.medicinenet.com/script/main/art.asp?articlekey=33263 Accessed 22 August 2016.

Merritt, M., & Grady, C. (2006). Reciprocity and post-trial access for participants in antiretroviral therapy trials. *Aids, 20*(14), 1791-1794. doi:10.1097/01.aids.0000244197.88134.45

Ministry of Health Department of Health Planning and Research: National Health Research Ethics Committee of Nigeria. (2007). National Code of Health Research Ethics. Available at http://www.nhrec.net/nhrec/NCHRE_10.pdf. Accessed 22 August 2016.

MRCT Center. (2014). Proceedings of the Post-Trial Responsibilities: Ethics and Implementation, Harvard Law School, Cambridge, MA. Available at http://mrctcenter.org/news/mrct-post-trial-responsibilities-conference-proceedings-available/ Accessed 22 August 2016.

Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center). (2014). MRCT Ethics Essential Elements and Points to Consider Reference Document. Available at http://mrctcenter.org/wp-content/uploads/2015/11/2014-11-14_toolkit_essentialelementsofethics_108_pg.pdf. Accessed 22 August 2016.

Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center). (2017a). MRCT Return of Aggregate Results Guidance Document Version 3.0. Available at http://mrctcenter.org/wp-content/uploads/2017/04/2017-03-20-MRCT-Return-of-Aggregate-Results-Guidance-Document-Version-3.0.pdf. Accessed

Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center). (2017b). MRCT Return of Aggregate Results Toolkit. Available at http://mrctcenter.org/wp-

content/uploads/2017/03/2017-03-13-MRCT-Return-of-Aggregate-Results-Toolkit-3.0.pdf. Accessed April 18, 2017.

Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center). (2017c). Return of Individual Results to Participants: Principles. Available at http://mrctcenter.org/wp-content/uploads/2017/03/2017-02-14b-IRR-Principles-Final.pdf. Accessed June 26, 2017.

National Bioethics Advisory Commission. (2001). *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries, Executive Summary*. Retrieved from https://bioethicsarchive.georgetown.edu/nbac/clinical/ExecSum.pdf

National Institute of Allergy and Infectious Diseases (NIADID). (2013). Microbiology and Infectious Diseases Clinical Research — Investigational Products. Available at https://www.niaid.nih.gov/labsandresources/resources/dmidclinrsrch/Pages/investigational.aspx. Accessed 22 August 2016.

National Institutes of Health. (2015). Clinical Trials Glossary of Common Terms. Available at http://www.nih.gov/health/clinicaltrials/glossary.htm. Accessed 22 August 2016.

Nuffield Council on Bioethics. (2005). What happens once research is over? *The Ethics of Research Related to Healthcare in Developing Countries.* Available at http://nuffieldbioethics.org/report/research-developing-countries-followup/chapter-downloads/and http://nuffieldbioethics.org/wp-content/uploads/2014/07/HRRDC-Follow-up-Chapter-4-What-happens-once-research-is-over.pdf. Accessed June 26, 2017.

Otterson, T., & Norheim, O. F. (2014). Making Fair Choices on the Path to Universal Health Coverage. *World Health Organization Bulletin, 92*(6), 389. doi:http://dx.doi.org/10.2471/BLT.14.139139

Padian, N. (2014). *Post-Trial Responsibilities* Presented at the Conference on Post-Trial Responsibilities: Ethics and Implementation, Harvard Law School, Cambridge, MA. Available at http://mrctcenter.org/resources/2014-09-18-presentation-harvard-mrct-post-trial-responsibilities-conference-session-3/ Accessed 23 August 2016.

Portugal National Authority of Medicines and Health Products (INFARMED). (2004). Law 46. Available at http://www.fcsaude.ubi.pt/comissaoetica/docs/Lei_2004_46.pdf. Accessed 22 August 2016.

Presidential Commission for Study of Bioethical Issues. (2011). Moral Science: Protecting Participants in Human Subjects Research. Available at http://bioethics.gov/sites/default/files/Moral Science June 2012.pdf. Accessed 22 August 2016.

Ravinetto, R., De Nys, K., Boelaert, M., Diro, E., Meintjes, G., Adoke, Y., et al. (2015). Sponsorship in non-commercial clinical trials: definitions, challenges and the role of Good Clinical Practices guidelines. *BMC International Health and Human Rights, 15*(1), 1-7. doi:10.1186/s12914-015-0073-8

Shah, S. (18 September 2014). *Post-trial Obligations: Policy Approaches Around the Globe*. Presented at the Conference on Post-Trial Responsibilities: Ethics and Implementation, Harvard Law School, Cambridge, MA.

South Africa Department of Health. (2006). South African Good Clinical Practice Guidelines. Available at http://www.kznhealth.gov.za/research/guideline2.pdf. Accessed 22 August 2016.

The Free Medical Dictionary by Farlex. (2016). Health Care Provider. Available at http://medical-dictionary.thefreedictionary.com/health+care+provider. Accessed 22 August 2016.

UNAIDS. (2012). Ethical considerations in biomedical HIV prevention trials. Available at http://www.unaids.org/sites/default/files/media_asset/jc1399_ethical_considerations_en_0.pdf. Accessed 22 August 2016.

UNESCO. (2005). Universal Declaration on Bioethics and Human Rights. Available at http://unesdoc.unesco.org/images/0014/001428/142825e.pdf. Accessed 25 August 2016.

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. doi:10.1200/JCO.2012.47.1227

United States Food and Drug Administration. (2009). Guidance for Industry Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects. Available at http://www.fda.gov/downloads/Drugs/.../Guidances/UCM187772.pdf. Accessed 22 August 2016.

United States Food and Drug Administration. (2014). Guidance for Industry — Expedited Programs for Serious Conditions – Drugs and Biologics. Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf. Accessed 22 August 2016.

United States Food and Drug Administration. (2015a). Guidance Documents — Acceptance of Foreign Clinical Studies. Available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm124932.htm. Accessed 22 August 2016.

United States Food and Drug Administration. Investigational Drug Application, 21 C.F.R. § 312 (2015b). Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312 Accessed 22 August 2016.

United States Food and Drug Administration. (2016). Investigational New Drug (IND) Application. Available at http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm. Accessed 22 August 2016.

Wang, D. (2013). "Courts as healthcare policy-makers: the problem, the responses to the problem and problems in the responses". Available at http://hdl.handle.net/10438/11198. Accessed 22 August 2016.

World Health Organization. (2011). Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants. Available at http://apps.who.int/iris/bitstream/10665/44783/1/9789241502948_eng.pdf?ua=1&ua=1&ua=1. Accessed 22 August 2016.

World Health Organization. (2015). Vaccine Regulation, National Regulatory Authorities. Available at http://www.who.int/immunization_standards/vaccine_regulation/en/. Accessed 22 August 2016.

World Medical Association. (1964; Amended 2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Available at http://www.wma.net/en/20activities/10ethics/10helsinki/15publicconsult/DoH-draft-for-public-consultation_annotated.pdf. Accessed 19 August 2016.