MULTI-REGIONAL CLINICAL TRIALS

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

Post-Trial Responsibilities to Research Participants

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MRCT Center
Post-Trial Responsibilities Workgroup

MRCT Center Mission

Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.

Problem Statement

- There are multiple terms employed on the topic of “post-trial responsibilities” and multiple interpretations of the ethical obligations associated with those terms.
- Specifically, there are multiple directives, based on ethical principles, related to:
  - Providing continued access to investigational products, medical care, and infrastructure for research participants under certain conditions
  - Providing investigational product to the host community or country
  - Providing other benefits to the host community or county
  - Providing information about research findings
- But there are no standards with regard to the practical application of those directives.

MRCT Center organized two efforts to fully understand the breadth and depth of PTR issues

Post-Trial Responsibilities Conference: Ethics and Implementation September 18, 2014

NIH, Industry, WMA, CIOMS, Academia, IRBs, Non-profits, Govt

Multi-Stakeholder Workgroup Launched February 2015

42 members from 8 countries

Biweekly meetings and In-person meeting

Presentation of PTR Framework: MRCT Annual Meeting 2015

>90 attendees

WMA, academia, NIH, Industry, IRBs, Non-profits, Govt., Patient Advocates and others

Post-Trial Responsibilities: MRCT Center PTR Workgroup

Carmen Aldinger, MRCT Center

Mark Barnes, MRCT Center, Ropes and Gray LLP

Eileen Bedell, Takeda Pharmaceuticals International, Inc.

Barbara E. Bierer, MRCT Center, Brigham and Women's Hospital, Harvard Medical School (Co-Chair)

Amanda Brown-Inz, MRCT Center

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 International, Inc.

Kate Heffernan, Verrill Dana LLP

Deborah Henderson, Merck & Co., Inc.

Joan Herbert, MMV, Bill and Melinda Gates Foundation

Patrick Kelly, Takeda Pharmaceuticals International, Inc.

Ariella Kelman, Genentech, Inc.

Laurie Letvak, Novartis International AG

Rebecca Li, MRCT Center, Brigham and Women's Hospital, Harvard Medical School

Susan Manoff, Merck & Co., Inc.

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, GlaxoSmithKline; formerly HIV Netherland Australia Thailand

Juliana Rossi, Eli Lilly and Company, Brazil

Beth Roxland, Johnson & Johnson

Jessica Scott, GlaxoSmithKline

Seema Shah, National Institutes of Health

Lana Skirboll, Sanofi

Sheldon Sloan, Johnson and Johnson

Hans Spiegel, Henry M. Jackson Foundation for the Advancement of Military Medicine

Walter Straus, Merck & Co., Inc.

Jeremy Sugarman, Johns Hopkins Berman Institute of Bioethics

Jocelyn Ulrich, PhRMA

Luann Van Campen, Eli Lilly and Company (Co-Chair)

Daniel Wang, Queen Mary University of London, United Kingdom

Jayne Ware, Merck & Co., Inc.

Mitchell Warren, AVAC

Marc Wilenzick, International AIDS Vaccine Initiative

Objectives: Deliverables

1. Common terminology:
   - Post trial responsibilities
   - Continued access to an investigational medic
   - Expanded access
2. A case studies/scenarios portfolio
3. Ethics and practical framework for PTR
   - **Guidance Document** – Guidance regarding responsibilities of all stakeholders within defined scope and based on basic ethical principles
   - **Toolkit** - Practical tool to assess PTR
   - **Principles Document** – Summarizing major concepts on PTR

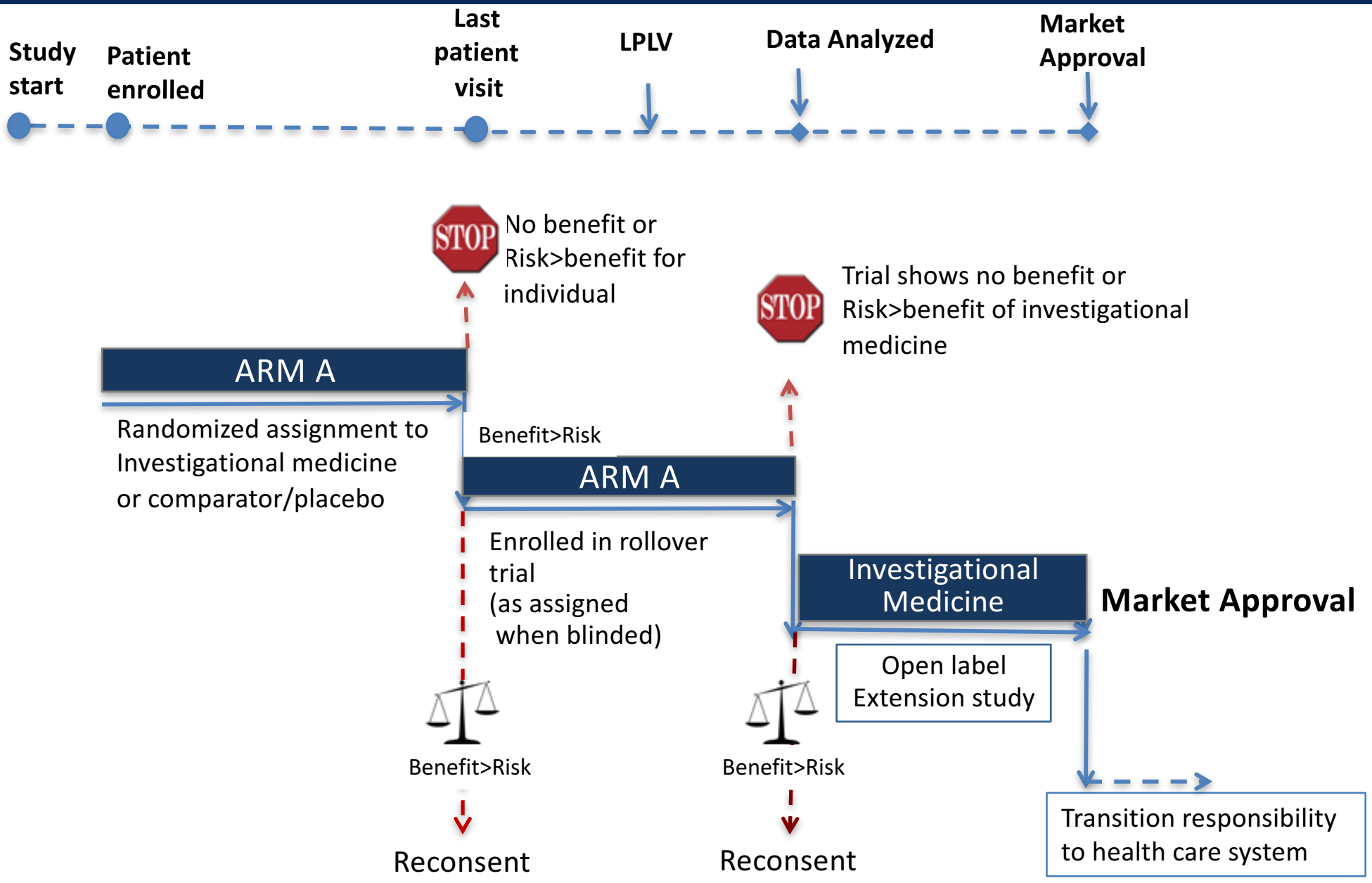
http://mrctcenter.org/projects/post-trial-responsibilities/

Scope of Project

Framework addresses PTR to *research participants* and stakeholder responsibilities associated with the benefits of:

- Access to intervention, either investigational medicine or comparators (primary post-trial benefit)
- Access to associated medical care (collateral post-trial benefit)
- Access to health care infrastructure (collateral post-trial benefit)

Post-trial responsibilities: to research participants on trial



The MRCT Center Framework

- **PTR Guidance Document**
  - History, Scope, Purpose, Approach, Process
  - Stakeholder Roles
  - Terminology
  - Overall Considerations (benefit-risk, planning, setting, scope, communication and informed consent)
  - Bioethics Principles
  - Stakeholder Responsibilities
  - MRCT Guidance on PTR (continued access to investigational medicines, medical care and infrastructure)

http://mrctcenter.org/wp-content/uploads/2016/12/2016-12-07-Post-Trial-Responsibilities-Guidance-Document.pdf

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MRCT Center Post-Trial Responsibilities Framework

Continued Access to Investigational Medicines

I. Guidance Document

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

December 1, 2016

Version 1.0

MRCT Center Guidance for Post-Trial Responsibilities – Version 1.0, December 1, 2016 Page 1

The MRCT Center Framework (Continued)

- **PTR Toolkit**
  - Conceptual Diagrams
  - Scenario Tables
  - Points to Consider
  - Case Studies
  - Country Regulations

The MRCT Center Framework (Continued)

- **PTR Principles Paper**
  - Principles for continued access to an investigational medicine
  - Criteria for continued access
  - Stages of continued access

Principles of Post-Trial Responsibilities: Continued Access to an Investigational Medicine

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (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 foundation of this guidance document is summarized in 12 principles:

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.
2. Provision of continued access is a bounded and not a limitless responsibility of any one stakeholder.
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.
4. Provision of continued access must be fair and not inadvertently advantage some and harm others.
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.
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.
8. Generally, informed consent for continued access should be solicited prior to provision of the medicine.
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.
10. Continued access to an investigational medicine should always be provided under mechanisms that satisfy local regulatory requirements for investigational medicines.
11. The sponsor is responsible for continuously monitoring whether there is an ongoing unmet medical need for the investigational medicine during the clinical trial and drug development program.
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.

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For more information about the MRCT Center and our resources visit:
mrctcenter.org/resources

Version: December 7, 2016

http://mrctcenter.org/wp-content/uploads/2016/12/2016-12-02-Post-Trial-Responsibilities-Document.pdf

Overview of PTR Framework

Approach and Process to Develop Framework

- Approach
  - The framework described t integrates both “case-based” (descriptive) and “principles-based” (normative) approaches to PTR
- Process
  - **First**, **cases** were solicited from the Workgroup to identify the major PTR issues. Cases were used to elicit the salient ethical issues related to PTR.
  - **Second**, the group identified **ethical principles** relating to PTR and how these principles relate to the primary stakeholder roles.
  - These principles and stakeholder roles were then applied to the master list of questions to develop the MRCT Framework (guidance and toolkit).
  - **Third**, the group produced a **series of recommendations**
    - Recommendations are being applied to the **case studies**.
    - Recommendations will be applied to a **new group of case studies**.

Delineating Primary Roles of Clinical Trial Stakeholders

Stakeholder	Role
Sponsor	Takes responsibility for, manages, and initiates clinical investigation
Sponsor-Investigator	Initiates and conducts an investigation
Biopharmaceutical or Device Company (for-profit sponsor)	Discovers, develops, manufactures, and commercializes products for the benefit of population
Non-profit Sponsor/ Funder	Discovers and develops products for the benefit of populations
Investigator/Physician	Ensures clinical care is deemed ethical; implements trial protocol
Research Participant	Adheres to clinical protocol; participates voluntarily
National Regulatory Authority	Assesses, licenses, controls, and surveys/monitors products
National Health Care Authority	Oversees all issues related to public health
Payer (private or government)	Ensures that clients receive coverage that provides for the payment of benefits as a result of sickness or injury
Healthcare Provider	Provides health care services

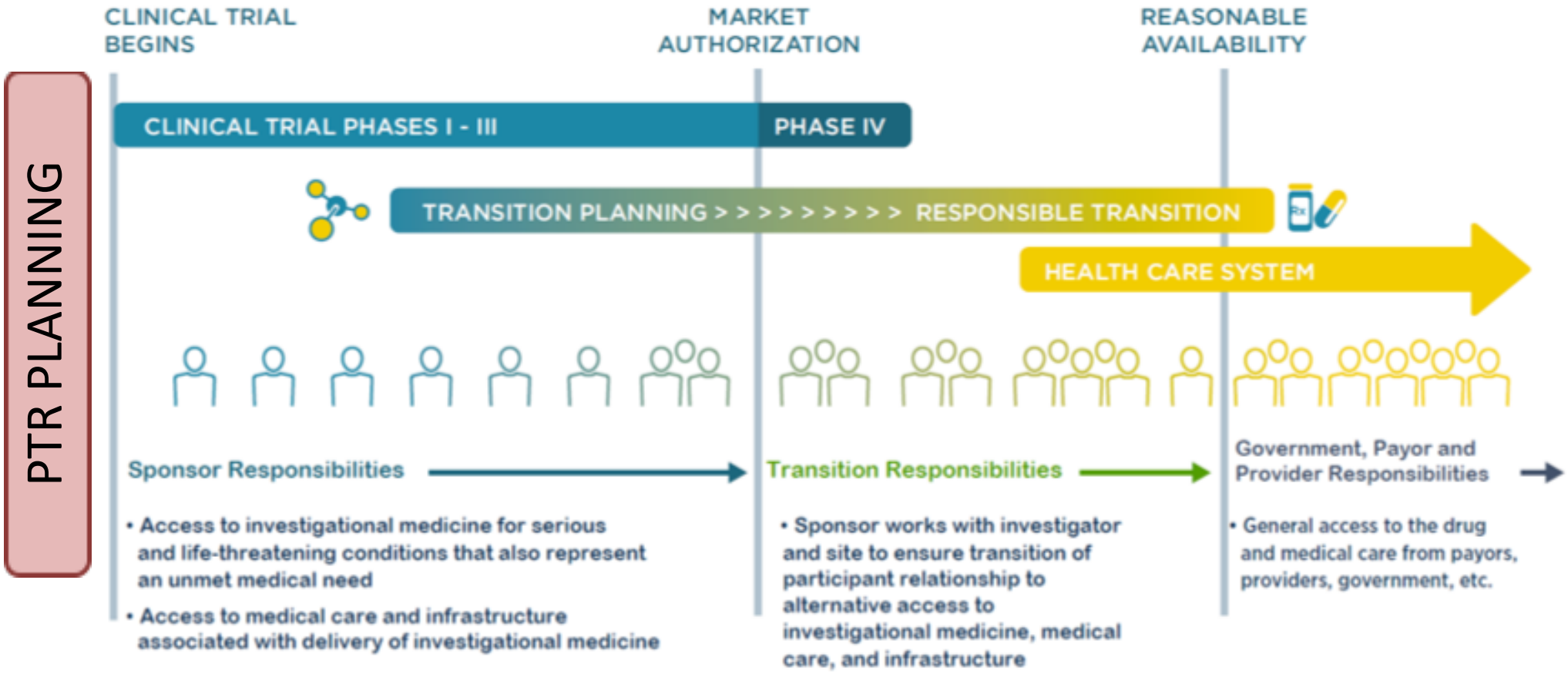
Bioethics Principles Informing PTR Framework

- Nonmaleficence (no intentional harm)
- Autonomy (participants consent voluntarily)
- Distributive Justice (using scare resources for PTR to research participants vs general public)
- Justice as Reciprocity (reciprocating patients for participating in trial)
- Beneficence (securing participants' well-being)

PTR is weighted by six inter-related important considerations

1. **Demonstrable clinical evidence** of benefit exceeding risk for an individual participant;
2. **Statistical evidence** of benefit exceeding risk in the overall study population;
3. Whether imminent **risk of death or serious harm** if the investigational medicine is discontinued;
4. The investigational medicine addresses an **unmet medical need** in that there are no suitable therapeutic alternatives available to participants,
5. The **sponsor is the sole source** of the investigational medicine and there is no alternative access to the product, and
6. The provision of continued access to the investigational medicine will not **adversely affect the viability of the research or the ability to complete the trial(s).**

Post-Trial Responsibilities, Investigational Medicine Approval Pathway: From Clinical Trials to General Access



Thank you