Post-Trial Responsibilities to Research Participants

Rebecca Li, PhD, Executive Director
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MRCT Center
Post-Trial Responsibilities Workgroup
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 medicine
   • 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/
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

**Study start**

**Patient enrolled**

**Last patient visit**

**LPLV**

**Data Analyzed**

**Market Approval**

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**ARM A**

Randomized assignment to Investigational medicine or comparator/placebo

Benefit>Risk

Enrolled in rollover trial (as assigned when blinded)

Benefit>Risk

Reconsent

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**Investigational Medicine**

Open label Extension study

Benefit>Risk

Reconsent

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Stop

No benefit or Risk>benefit for individual

Stop

Trial shows no benefit or Risk>benefit of investigational medicine

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Transition responsibility to health care system
• 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)

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

Overview of PTR Framework
Approach and Process to Develop Framework

• **Approach**
  - The framework described 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

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

- Nonmaleficence (no intentional harm)
- Autonomy (participants consent voluntarily)
- Distributive Justice (using scarce 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

**Sponsor Responsibilities**
- Access to investigational medicine for serious and life-threatening conditions that also represent an unmet medical need
- Access to medical care and infrastructure associated with delivery of investigational medicine

**Transition Responsibilities**
- Sponsor works with investigator and site to ensure transition of participant relationship to alternative access to investigational medicine, medical care, and infrastructure

**Government, Payor and Provider Responsibilities**
- General access to the drug and medical care from payors, providers, government, etc.
Thank you