Operational Planning for Plain Language Summaries and Return of Results to Patients and Other Stakeholders

Barbara E. Bierer, MD

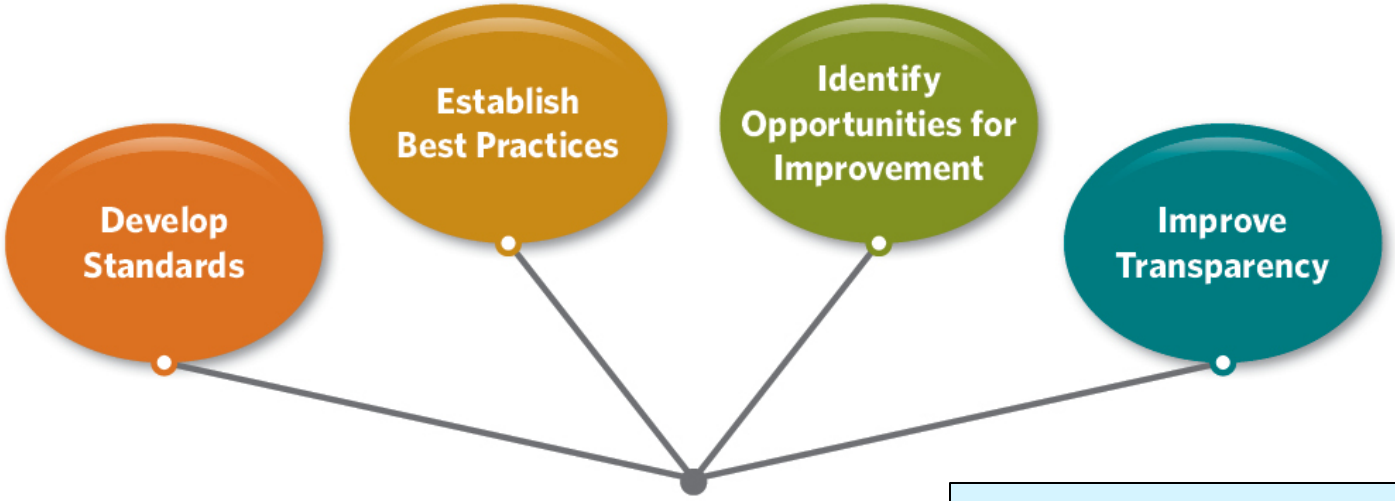
CBI Clinical Data Disclosure and Transparency
Philadelphia, PA
February 5-6, 2015

Agenda

Harvard MRCT Center – Mission
Overview of Project Scope and Deliverables
Process for Returning Results
Incorporation of Health and Cultural Literacy Principles
Timing of Returning Results
Special Considerations
Regulatory Agency questions
Collaborations
Next Steps

Collaborating to Improve Multi-Regional Clinical Trials

The MRCT Center's Purpose is *to improve the design, conduct, and oversight of multi-regional clinical trials, especially trials sited in or involving the developing world; to simplify research through the use of best practices; and to foster respect for research participants, efficacy, safety and fairness in transnational, trans-cultural human subjects research.*



Return of general research results is one of many Harvard MRCT initiatives

Return of results: current Harvard MRCT workgroup

Salvatore Alesci – PhRMA
Mark Barnes - Ropes & Gray, LLP
Richard Bergstreom – EFPIA
Deborah Collyar – PAIR (COCHAIR)
Alla Digilova – MRCT
David Forster - WIRB Copernicus Group
Elizabeth Garofalo - Novartis Pharma AG
Barbara Godlew - The FAIRE Company, LLC
Laura Hagan - Merck Serano
Sandra Hayes-Licitra – Johnson & Johnson
Angelika Joos – Merck Sharp & Dohme
Paulo Lacativa - CCBR Clinical Research
Yann LeCam – EURODIS
Rebecca H Li – MRCT
Marcello Losso - HIV RAMOS
Laurie Myers – Merck (CO-CHAIR)
Pearl O'Rourke - Partners HealthCare
Nesri Padayatchi - Univ. of KwaZulu-Natal
Mary Ann Plummer – (prior CO-CHAIR)
Ben Rotz – Lilly
Jim Saunders - NE IRB
Amish Shah - MRCT / HLS
Patrick Taylor - Children's Hospital, Boston
Sarah White - Partners HealthCare
Sabune Winkler – HMS

Behtash Bahador - CISCRP
Nicola Bedlington – European Patients Forum
Barbara Bierer - Brigham & Women's Hospital/MRCT
Assunta De Rienzo - Brigham and Women's Hospital
Dimitrios Dogas – MRCT
Phyllis Frosst - Personalized Medicine Coalition
Pierre Gervais - QT Research
David Haerry – European AIDS Treatment Group
Zach Hallinan – CISCRP
Cheryl Jernigan - Susan G. Komen
Barbara Kress – Merck
Sarah Larson – Biogen Idec
David Leventhal – Pfizer
Craig Lipset – Pfizer
Holly Fernandez Lynch - Harvard Law School
Alex Nasr – AbbVie
Mary Oster – NEIRB
Jane Perlmutter – Gemini Group
Sandy Prucka – Lilly
Beth Roxland – Johnson & Johnson
Jessica Scott – GSK
Zachary Shapiro – MRCT/ HLS
David Walling – Collaborative NeuroScience
Marc Wilenzick
Elizabeth Witte - HMS

Returning Results and the MRCT Mission

Goals: Returning Clinical Trial Results to study participants

- **Develop standards and best practices.**
- **Create a guidance document,** including templates.
- **Address perceived barriers** to widespread implementation.

Returning results allows sponsors and investigators to recognize and honor the essential contributions and volunteerism of clinical trial participants.

Expectations of academic, industry, not-for-profit sponsors similar

Returning results is a key aspect of **Improving Transparency** of clinical trials and **Increasing Public Trust.**

Scope:
Communication and dissemination of summary research results to individual participants

Why now?

Declaration of Helsinki

Paragraph 26:

> All medical research subjects should be given the option of being informed about the general outcome and results of the study.

http://www.wma.net/en/30publications/10policies/b3/

Why Now?

EU Parliament: **Regulation (EU) No 536/2014 (2014):**

Sponsor of a clinical trial must submit **"**a summary of the results of the clinical trial together with a summary that is understandable to a layperson, and the clinical study report, where applicable, within the defined timelines.**"**

Article 37:

4. Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial.

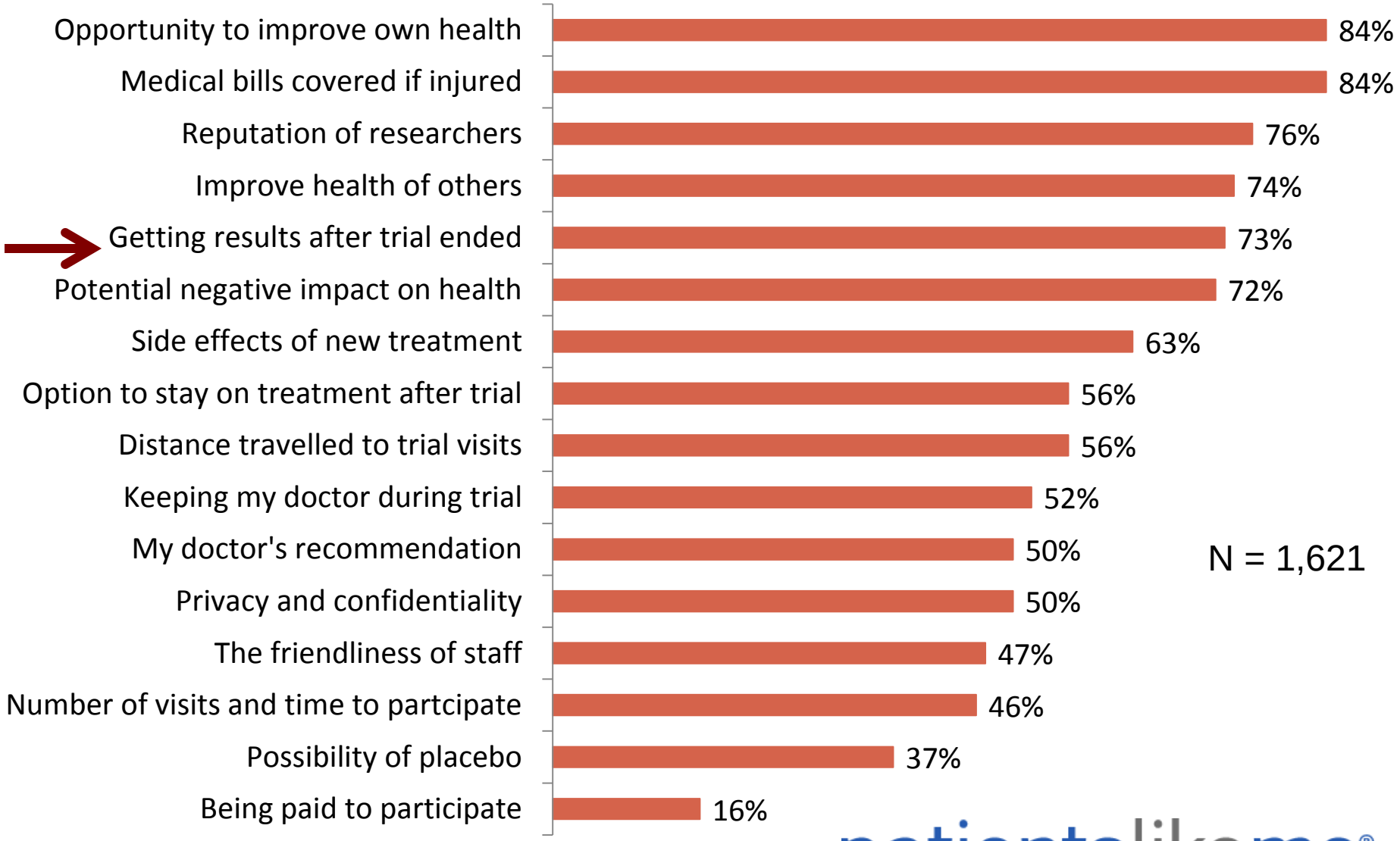
PhRMA EFPIA Principles for Responsible Clinical Trial Data Sharing

3. Sharing Results with Patients Who Participate in Clinical Trials

In order to help inform and educate patients about the clinical trials in which they participate, biopharmaceutical companies will work with regulators to adopt mechanisms for providing a factual summary of clinical trial results and make the summaries available to research participants.

http://www.phrma.org/sites/default/files/pdf/PhRMAPrinciplesForResponsibleClinicalTrialDataSharing.pdf

Factors important when considering research



Return of Results: Harvard MRCT Project

Potential audiences and scope:

1. **Communication and dissemination of *summary* research results:**
   - Through the scientific literature
   - To general public
   - To local community of the participants
   - **To individual participants**

2. Communication of ***individual*** results:
   - Specific results for each study participants (e.g. treatment arm assignment)
   - Incidental findings

Overview

- Return of results should become the expectation and practice in clinical research. The practice demonstrates:
  - Appreciation of the contributions and volunteerism of the individual participant and stewardship of the general public.
  - The core principle that each participant has a right to know the outcome of his or her participation (and his or her own information) and understand the results.
  - Participant has a right to choose whether to (and who can) have that information.
- Standard methodologies and approaches should be developed so that roles and responsibilities are clear, expectations are set and met, and multinational requirements appreciated from the outset.
- Funding for return of results should be provided as an anticipated component of human subjects research.

A Novel Approach to Returning Results

- **We have partnered with other working groups addressing returning results, including:**
  - Alliance for Clinical Trials in Oncology (Alliance)
  - CSCRIP Group
  - DIA Lay Summary Working Group
  - Pfizer Blue Button Project
  - NIH Alliance Working Group
  - Dana Farber Cancer Institute

- **Includes input from multiple stakeholder groups:**
  - Academics
  - Industry
  - Regulators
  - Patient-Advocates and patients
  - CROs
  - IRBs/ECs

The Harvard MRCT Deliverables

An **ROR Process Reference Guide** for groups wishing to return results including:

- Content (essential components, source documentation, cultural and health literacy considerations)
- Logistics and detailed processes for results sharing
- Timing
- Special considerations

An **ROR Users Toolkit** including:

- Templates for Phase1, Phase II/III, studies ending early
- Neutral language guide
- Endpoints language guide
- Useful Checklists

Returning Results: Perceived Barriers

- **Practical Considerations and Issues, including:**
  - Who, What, Where, When, and How
- **Logistics**
  - Costs
  - Methods
- **Content and Comprehension**
  - Content consistent with EMA
  - What do patients/participants want to know? And do they understand implications?
  - Understandable
- **Misinterpreting intent**
  - FDA and other regulators might view returning results as a promotional activity

Process Flow for Returning Results

Pre-Study preparation

- Organizational preparation, policies, processes
- Establish level/timing/delivery
- Resource planning

Protocol Development

- Describes ROR as voluntary process, including who what where when how
- Include ICF section description

During study conduct

- Letter of appreciation
- Last study visit of participant content
- Intermittent engagement with participant thereafter

When study ends

- Content of summary document (and health literacy principles)
- Adherence to global regulatory framework

Last study visit of participant

- What to anticipate after last study visit
- Advice regarding monitoring for adverse events, both rare and common, severe and serious, if appropriate
- If questions, or adverse events, whom to contact (and contact information)
- A reminder, if appropriate, that they may be contacted in the future if any adverse events are uncovered that might impact their health.
- Access to any benefits or care as a consequence of participation, if any
- Advice as to where to obtain further treatment and/or clinical care
- Information regarding personal data developed during the study, if appropriate
- Whether they would or would not like to receive summary study results at end of study.
- If opt in to receive RSS, how to access the information and when to anticipate the information. Ensure the format for the data will be accessible
- Contact information for the participant, if appropriate.
- Designation a third party to receive results, if desired

Aggregate Study Results: Suggestions

To Whom:

All participants that have been enrolled and, if appropriate, randomized

Method of Return:

- Interactive methods (e.g., face-to-face meeting(s), telephone call(s), two-way online meeting(s), dynamic email exchange, etc.,)
- One-way communications (video summary, automated phone message, printed materials)
- Internet based methods (flexible, cost-effective, current, security may be important)
  - Open models
  - Password protected or other

Timing

Timing of Return of Results: Suggestions

Trial Type	Timing	Source Document	Action
Regulated trials (typically industry sponsored interventional studies) Consistent with EMA regulation	Within 1 year of completion or 'end of study' defined as 1 year after LSLV	Clinical study report (CSR) or ICHE3 synopsis (CSR synopsis)	• Return RRS to trial participants • Post non-technical summary on CT.gov, EudraCT (not required or supported to-date) • Harmonization across sites
Academic / non-regulated trials	Within 1 year of the study close by the IRB or final data analysis or concurrent with the release of the first study publication	Publication	• Return RRS to trial participants including unpublished trials
Longitudinal / observational studies	Concurrent with the release of each major study publication	Publication	• Return RRS to trial participants and after each update

Creation of Summary

- Summary must be unbiased and not promotional
- Summary to be reviewed by independent and objective editor(s) and patient representative(s)
- Plain language (sixth-eight grade reading level) and apply health literacy principles.
- Translation into additional languages consistent with translations of informed consent
- An individual from the study site or neutral informed third party should be available to answer questions for participants
- Provisions should be made for vulnerable populations and other instances
- Consideration as to whether to, and whom to, inform in the event of a participants death

Content Annex V – EU Layperson Summary

http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.158.01.0001.01.ENG

1. Clinical trial identification
2. Name and contact details of the sponsor;
3. Main objectives
4. Population of subjects (include eligibility criteria);
5. Investigational medicinal products used;
6. Description of adverse reactions and frequency;
7. Overall results of the clinical trial;
8. Comments on the outcome of the clinical trial;
9. Whether follow up clinical trials are foreseen;
10. Where additional information could be found.

Health Literacy

- Emphasis on **health literacy**
  - Health Literacy is not the same as literacy level or ability to read.
    - Health Literacy: “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.”[1]
  - Even those with adequate health literacy can struggle at times to understand health information, and appreciate clear communication.
  - Guidance: testing for readability; visuals; and writing style.
- Emphasis on **numeracy**
- Emphasis on **cultural literacy**

1. U.S. Department of Health and Human Services (HHS). Healthy People 2010. Washington, DC: U.S. Government Printing Office. 2000.

Neutral Language

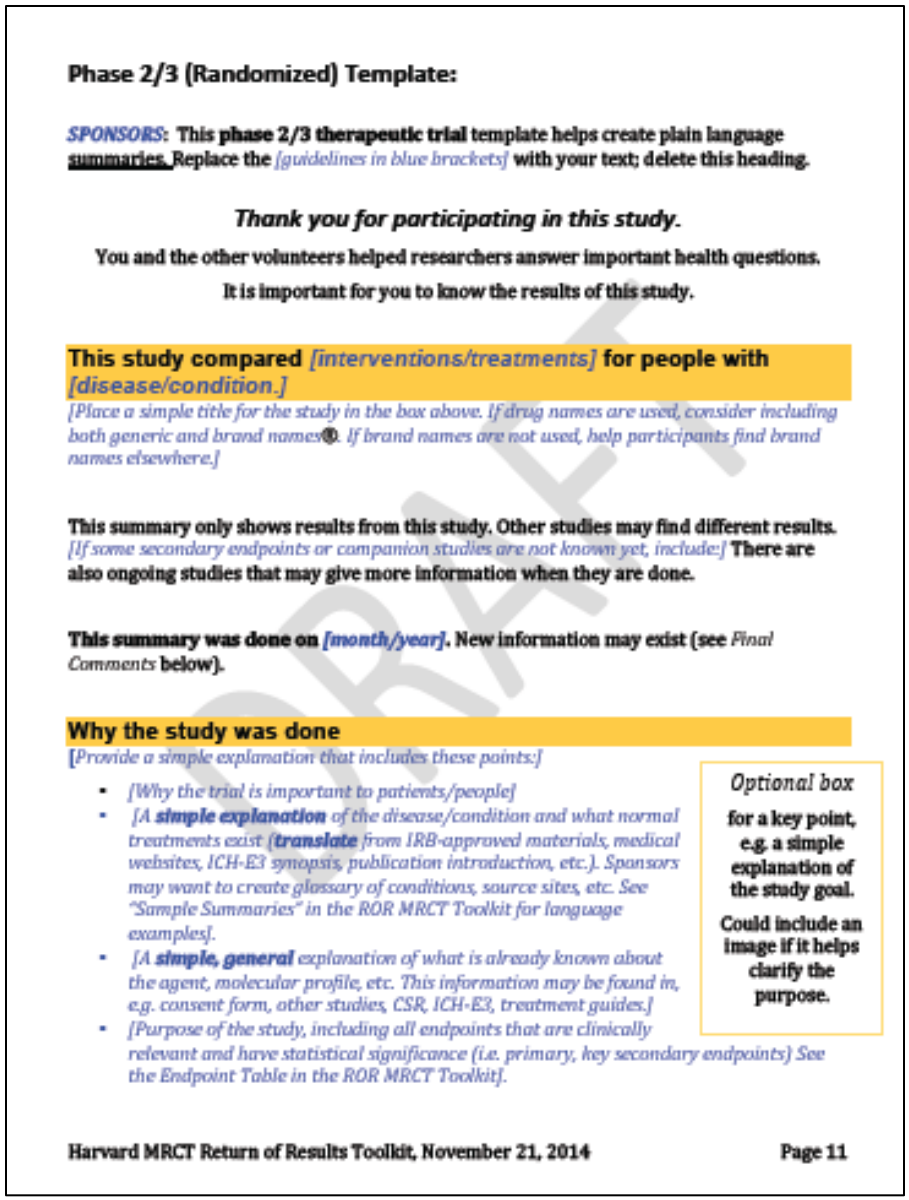
Language to avoid	Language to consider
This study proved…	This study found that... This does not mean everyone in that group had these results.
This study proved that using <*Drug A*> to prevent <*disease*> is effective.	This study found that people with <*disease*> who got <*Drug A*> had <*primary endpoint*>.
The combination treatment of <*Drug A and B*> may also help alleviate <*a different disease/condition than what was studied*>	When <*Drug A and B*> are used together, people in this study had <*study endpoint*> .
This means that <*Drug A*> is better than <*Drug B*>.	In this study, people who got <*Drug A*> had more <*study endpoint*> than some people who got <*Drug B*> if they had the same health conditions.
<*Drug A*> works better than <*Drug B*>, but some people didn't tolerate it as well.	In this study, more people got <*study endpoint*> with <*Drug A*>. They also had more adverse events that interfered with their daily lives, like <*specific adverse events*>.
<*Drug A*> is better tolerated than Drug B	In this study, fewer patients who took <*Drug A*> had <*list adverse events*> than patients who took

FDAs points to consider:

- Truthful accurate and non-misleading information about trial results that may benefit participants
- The language should be simple and factual, neutral in tis description
- The information should not be selective
- The information cannot make pre-approval claims of safety or effectiveness in a promotional context (?company website)

Adapted from R Moscicki, 5 Feb 2015

MRCT Center Templates



Phase 2/3 (Randomized) Template:

***SPONSORS*: This phase 2/3 therapeutic trial template helps create plain language summaries. Replace the *[guidelines in blue brackets]* with your text; delete this heading.**

Thank you for participating in this study.

You and the other volunteers helped researchers answer important health questions.

It is important for you to know the results of this study.

This study compared *[interventions/treatments]* for people with *[disease/condition.]*

[Place a simple title for the study in the box above. If drug names are used, consider including both generic and brand names®. If brand names are not used, help participants find brand names elsewhere.]

This summary only shows results from this study. Other studies may find different results. *[If some secondary endpoints or companion studies are not known yet, include:]* **There are also ongoing studies that may give more information when they are done.**

This summary was done on *[month/year]*. New information may exist (see *Final Comments* below).

Why the study was done

[Provide a simple explanation that includes these points:]

- *[Why the trial is important to patients/people]*
- *[A **simple explanation** of the disease/condition and what normal treatments exist (**translate** from IRB-approved materials, medical websites, ICH-E3 synopsis, publication introduction, etc.). Sponsors may want to create glossary of conditions, source sites, etc. See "Sample Summaries" in the ROR MRCT Toolkit for language examples].*
- *[A **simple, general** explanation of what is already known about the agent, molecular profile, etc. This information may be found in, e.g. consent form, other studies, CSR, ICH-E3, treatment guides.]*
- *[Purpose of the study, including all endpoints that are clinically relevant and have statistical significance (i.e. primary, key secondary endpoints) See the Endpoint Table in the ROR MRCT Toolkit].*

Optional box

for a key point, e.g. a simple explanation of the study goal.

Could include an image if it helps clarify the purpose.

Harvard MRCT Return of Results Toolkit, November 21, 2014 **Page 11**

- Located in ROR Toolkit
- Includes EMA required elements
- Examples
- Incorporates principles of Health Literacy and Numeracy
- Templates created for Phase I, Phase II/III, Trials ending early and Observational studies

Endpoint Descriptions and Examples

Endpoint
Composite
Surrogate
Mortality
Morbidity
Progression-free survival (or disease-free survival)
Patient-Reported Outcome on symptoms or functions (e.g., pain)
Exploratory Biomarker / Pharmacogenomics
Prevention or incidence endpoint
Non-inferiority endpoints

Endpoint Descriptions and Examples

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

Mortality Endpoint Description and Example

Endpoint Description	Example in plain language
The goal of this trial is to see if giving drug X (or treatment ABC) or Y (or treatment XYZ) will help patients with a particular disease live longer.	NO EFFECT - Patients in both groups lived about the same amount of time, whether they got drug X or Y (or treatments ABC or XYZ). EFFECT – People in Group A (ABC treatment) lived about 15 months. (some people lived less than 15 months and some lived longer than 15 months.) People in Group B (XYZ treatment) (that included a sugar substitute instead of the active drug) lived about 12 months (some people lived less than 12 months and some lived longer than 12 months. This means that people in Group A (ABC treatment) lived about 3 months longer than people in Group B. This result was different enough that it is unlikely to have happened by chance alone.

Special Considerations

- Trials that close early
  - Futility
  - Efficacy
  - Safety
  - Low accrual
- Observational, long-term follow-up, and extension studies
- Notification of results to a 3rd party designated by the participant
- Vulnerable populations
- Legally Authorized Representatives and other designated parties
- Return of Results in the event of participant death
- Assent for Return of Results to Children
- Complexities of the Global Context

Role of the IRB/RECs: Special Considerations

- If return of results is planned, the ICF should include that statement and the plan, and the IRB/REC should review.
- If returning results occurs when the study is still open, the IRB/REC should review the materials (ICH E6).
- When a study is closed, the IRB/REC does not have jurisdiction and will likely not wish to review materials; patients/participants are not considered “human subjects”. Note that definition of “end of study” may vary by sponsor and regulatory authority.
- Many investigators think it would be helpful for the IRB/REC to know plan for communicating the results, and the content of that communication, at the same time the subjects are provided the results but not as a mandatory process. In this situation, the role of the IRB/REC should be decided beforehand
- IRB/RECs vary significantly. Sponsors and investigators should ask the IRB/REC of record early in the process. Guidance for IRB provided

Studies that *may* not warrant return of results

- Results indeterminate or not powered to deliver “results:”
  - Exploratory tissue and blood studies
  - Pilot proof of concept studies
  - Some minimal risk studies may be of insufficient scientific rigor to justify the return of results, such as research required of students in order to graduate.
- Tissue banking and bio banking activities
- Research conducted under a waiver of consent
- Exempt studies
- Cluster randomized studies
- Pragmatic clinical trials.
- Studies of illegal or socially unacceptable behavior such as illegal drug use or prostitution, where providing results may create the potential for a breach of confidentiality and subsequent harm.
  - Studies with certificates of confidentiality
  - Small studies with limited numbers of subjects may compromise privacy

Promotional activity and Agency concerns

- Regulatory requirements prohibit any type of promotional communication prior to FDA (and other regulatory agencies) marketing approval
- What constitutes “promotional language” in describing results?
- Will the FDA (and other regulatory agencies) provide guidance on what the agency considers “promotional” in a timely fashion?
- If not, does the FDA (and other regulatory agencies) plan to review –or require review of – each participant summary prior to release?
  - Will the review be timely?
  - Will the review differ for different phases of drug development (Phase1 vs Phase III, etc)?

Collaborations

- Our current Guide and Toolkit are designed for all sponsors (PI-initiated, industry, NIH) to use in all trial types (all phases, FDA- and EMA-regulated, comparative effectiveness, biobanking, etc)
- Harmonization and consistency is critically important.
- We have discussed with TransCelerate, EFPIA and PhRMA a potential collaboration to disseminate our work further through their efforts. We have approached NIH to partner in this transparency effort.
- We invite additional collaborators and partners.

Summary

- Return of results should become the expectation and practice in clinical research. It is the right thing to do.
- Logistics, Content, Process and Standard methodologies and approaches have been delineated. These methods are efficient, roles and responsibilities are clear, expectations are outlined, and multinational requirements have been incorporated.
- Funding for return of results should be provided as an anticipated component of human subjects research.
- Research participants clearly want to receive information about the clinical trial to which they participated. There is no reason not to do so.

Thank you

Barbara E. Bierer
bbierer@partners.org
mrct@harvard.edu

Laurie Myers
laurie_myers@merck.com

Rebecca Li
Rebecca_Li@harvard.edu

Mark Barnes
mrct@harvard.edu