Return of Results Initiative
5 November 2014
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Today’s 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 (EMA, FDA) questions
Discussion
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.

Develop Standards

Establish Best Practices

Identify Opportunities for Improvement

Improve Transparency

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

Goal today: your feedback, comments, and suggestions. We will then incorporate your suggestions to version 2.
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, and expectations are set and met.

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:
  o Academics
  o Industry
  o Regulators
  o Patient-Advocates and patients
  o CROs
  o IRBs/ECs
The Harvard MRCT Deliverables

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

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

An **ROR Users Toolkit** including:

- Templates for Phase I, Phase II/III, studies ending early
- Neutral language guide
- Useful Checklists
Returning Results: Perceived Barriers

Practical Considerations and Issues, including:

- Timing of release of study results
- Designating responsible party to deliver results (sponsor, study team, provider)
- Designated third party receipt of results (participant death, LAR, parent)
- Follow-on questions from and information required by participants
- Resource requirements for process

Logistics

- Cost implications of returning results (mail vs. web or online portal; IT vs other)
- How best to communicate? (online vs. in-person vs. paper-based delivery)
- Role of IRBs/Ethics Committee

Comprehension

- What do patients/participants want to know? And do they understand implications?
- Language in letter should not be too scientific for non-scientists to understand

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
Creation of Summary

• To ensure that the summary is unbiased and not promotional, an independent and objective editor or editorial panel, and patient(s) or patient representative(s), should translate technical results into plain language (sixth-eight grade reading level) and apply health literacy principles. Content summary should be reviewed for accuracy.

• Translation into additional languages should be undertaken consistent with translations of informed consent

• An individual from either the study site (e.g. investigator, study team) or neutral informed third party should be available to answer questions for participants after receipt of study results

• 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
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.

Incorporation of Health and Cultural Literacy

**Health Literacy** is not the same as literacy level or ability to read. Health Literacy refers to the capacity to make sound health decisions in the context of everyday life – at home, in the community, at the workplace, in the healthcare system, in the market place, and in the political arena.

**Numeracy** is the ability to use probability and basic mathematical concepts, necessary to function effectively in the health care environment and act appropriately on health care information (whole numbers, important information only, do the math, use visuals, explain concepts of risk and probability)

**Cultural literacy**: To avoid informational disparities among underrepresented populations sponsors should ensure processes for ROR reflect cultural literacy principles (translation, back translation, medical terms in native language, cultural norms and appropriateness.)
<table>
<thead>
<tr>
<th>Language to avoid</th>
<th>Language to consider</th>
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<tbody>
<tr>
<td>This study proved...</td>
<td>This study found that... This does not mean everyone in that group had these results.</td>
</tr>
<tr>
<td>This study proved that using <code>&lt;Drug A&gt;</code> to prevent <code>&lt;disease&gt;</code> is effective.</td>
<td>This study found that people with <code>&lt;disease&gt;</code> who got <code>&lt;Drug A&gt;</code> had <code>&lt;primary endpoint&gt;</code>.</td>
</tr>
<tr>
<td>The combination treatment of <code>&lt;Drug A and B&gt;</code> may also help alleviate <code>&lt;a different disease/condition than what was studied&gt;</code></td>
<td>When <code>&lt;Drug A and B&gt;</code> are used together, people in this study had <code>&lt;study endpoint&gt;</code>.</td>
</tr>
<tr>
<td>This means that <code>&lt;Drug A&gt;</code> is better than <code>&lt;Drug B&gt;</code>.</td>
<td>In this study, people who got <code>&lt;Drug A&gt;</code> had more <code>&lt;study endpoint&gt;</code> than some people who got <code>&lt;Drug B&gt;</code> if they had the same health conditions.</td>
</tr>
<tr>
<td><code>&lt;Drug A&gt;</code> works better than <code>&lt;Drug B&gt;</code>, but some people didn’t tolerate it as well.</td>
<td>In this study, more people got <code>&lt;study endpoint&gt;</code> with <code>&lt;Drug A&gt;</code>. They also had more adverse events that interfered with their daily lives, like <code>&lt;specific adverse events&gt;</code>.</td>
</tr>
<tr>
<td><code>&lt;Drug A&gt;</code> is better tolerated than Drug B.</td>
<td>In this study, fewer patients who took <code>&lt;Drug A&gt;</code> had <code>&lt;list adverse events&gt;</code>, than patients who took...</td>
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Harvard MRCT Templates

3 - Return of Results Sample Template Forms
   a. Template for Return of Results

   Thank you for participating in this study.
   You and the other volunteers made a difference!

   [Simple title] e.g. “Use of [drug generic (brand name)
   oldermycin (Standard®) and XYZinib (Newbie®) in
   [disease/condition]”
   [Provide a simple title for the study with the disease/condition and type of
   intervention studied. Consider a relevant image, icon, etc.]
   e.g. “This study compared drug treatments called [list drugs or therapies tested
   with generic (and brand® names)] in people with [disease/condition, with sub-
   type if applicable].”

   Why the study was done
   [Provide a simple explanation that includes these points:]
   • [Context with a simple explanation of the type of disease/condition
   and what normal treatments exist (often found in consent form or
   publication’s introduction)]
     e.g. “[specific disease/condition] is a [common/uncommon]
     [disease/condition]. About [N] people in [country/the world] have
     [specific disease/condition].”
   • [What is already known about the agent, molecular profile, etc.
     (often found in consent form)]
     e.g. “[drug/device/intervention/marker] has been tested in other
     [diseases/conditions]. It works to treat [specific disease/condition]
     in [specific population/disease/preclinical model].”
   • [Purpose of the study, including all endpoints that have a clinical outcome]
     e.g. “This study was done to find out if [drug/device/intervention/marker by
     generic and brand name®] [primary endpoint that worked longer/helped
     people live longer/lowered side effects or risk/improved safety].
     Researchers also wanted to find out if [secondary endpoint(s) that worked
     longer/helped people live longer/lowered side effect or risk/improved
     safety] and [more endpoints that have clinical outcomes].”
   • [Why these endpoints are important to patients]
     e.g. “This is important because current treatments for people with
     [disease/condition] only help about 2 out of 10 people (21%) live longer
     and they cause side effects like [list main/major side effects of standard
     treatment(s)].”
     [OR- “...there are no effective treatments for people
     with [disease/condition].”]

   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.

   Optional box
   or image
   for a specific
   information
   point, e.g. dates,
   locations, or
   number of
   participants.

   Study information

• 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
# Timing of Return of Results: Suggestions

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Timing</th>
<th>Source Document</th>
<th>Action</th>
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</thead>
</table>
| **Regulated trials** (typically industry sponsored interventional studies) | Within 1 year of CSR completion or ‘end of study’                    | Clinical study report (CSR)              | • Post non-technical summary on CT.gov, EudraCT  
• Return RRS to trial participants  
• Harmonization essential |
| **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                                |
| **Longitudinal / observational studies**       | Concurrent with the release of each major study publication            | Publication                               | • Return RRS to trial participants                                |
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.
Studies that *may* not warrant return of results

- Results indeterminate or not powered to deliver “results:”
  - Phase I PK studies in healthy volunteers
  - 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 FDA 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 (Phase I vs Phase III, etc)?
Return of results: current Harvard MRCT workgroup

Salvatore Alesci – PhRMA
Mark Barnes - Ropes & Gray, LLP
Richard Bergstrom - 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
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