Toolkit and Guidance for Implementation of Returning Results to Study Participants
Laurie Myers, Merck & Co., Inc, USA
Co-Chair, Return of Results Working Group, The MRCT Center at Harvard

EFGCP Workshop: “Communicating Clinical Trial Results to Meet Public Needs”
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Disclaimer

• I am here today representing the work done on return of results by the MRCT Center at Harvard working group, which I co-chaired.

• The views and opinions expressed in the following slides should not be attributed to my employer, MSD.
Objective of Today’s Presentation

• Provide overview of the MRCT Center at Harvard, including membership of working group on result summaries
• Describe goals of the return of results working group
• Provide brief overview of guidance document and templates
• Share next steps (US and Europe)
• Answer questions

This document is not intended to be prescriptive, creating a new mandate. It is meant to be a starting point, which can be used in its existing form, or modified.

It is a guidance document only, which any organization may customize to meet its own needs.
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 results is one of many MRCT Center initiatives.
A Global Approach to Returning Results

- Membership of the return of results group includes academics, industry, regulators, patient advocates and patients, CROs, and IRBs/ECs.

- We have partnered with other groups addressing returning results, including Dana Farber Cancer Institute, NIH Alliance Working Group, DIA Lay Summary Working Group, the Alliance for Clinical Trials in Oncology, and CISCRP.

- The working team began as a US working group only. Subsequently established communication channels with EU based stakeholders.

- The MRCT working group modified the templates to meet the requirements of Regulation (EU) No 536/2014 (2014).

- The version reflecting EU requirements is available today on the Harvard MRCT website.

- Additional feedback is encouraged; the working group will incorporate input from European stakeholders and update the document.
# Return of Results: MRCT Center Workgroup

<table>
<thead>
<tr>
<th>Name</th>
<th>Organization</th>
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<tbody>
<tr>
<td>Carmen Aldinger</td>
<td>MRCT Center</td>
</tr>
<tr>
<td>Salvatore Alesci</td>
<td>PhRMA</td>
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<td>Mark Barnes - Ropes &amp; Gray, LLP</td>
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<tr>
<td>Richard Bergstream</td>
<td>EFPIA</td>
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<tr>
<td>Deborah Collyar – PAIR (Co-Chair)</td>
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<tr>
<td>Alla Digilova</td>
<td>MRCT Center</td>
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<tr>
<td>Elizabeth Frank-Dana-Farber Cancer Institute (patient advocate)</td>
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<tr>
<td>David Forster</td>
<td>WIRB Copernicus Group</td>
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<tr>
<td>Elizabeth Garofalo</td>
<td>Novartis Pharma AG</td>
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<td>Barbara Godlew</td>
<td>The FAIRE Company, LLC</td>
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<td>Laura Hagan</td>
<td>Merck Serano</td>
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<td>Sandra Hayes-Licitra</td>
<td>Johnson &amp; Johnson</td>
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<tr>
<td>Angelika Joos</td>
<td>Merck Sharp &amp; Dohme</td>
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<tr>
<td>Paulo Lacatava</td>
<td>CCBR Clinical Research</td>
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<td>Yann LeCam</td>
<td>EURODIS</td>
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<td>Rebecca H Li</td>
<td>MRCT Center</td>
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<td>Marcello Losso</td>
<td>HIV RAMOS</td>
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<td>Laurie Myers</td>
<td>Merck (Co-Chair)</td>
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<tr>
<td>Pearl O'Rourke</td>
<td>Partners HealthCare</td>
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<tr>
<td>Nesri Padayatchi</td>
<td>Univ. of KwaZulu-Natal</td>
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<tr>
<td>Mary Ann Plummer – (prior Co-Chair)</td>
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<td>Ben Rotz</td>
<td>Merck</td>
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<td>Jim Saunders</td>
<td>NE IRB</td>
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<td>Amish Shah - MRCT / HLS</td>
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<tr>
<td>Patrick Taylor</td>
<td>Children's Hospital, Boston</td>
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<tr>
<td>Sarah White</td>
<td>Partners HealthCare</td>
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<td>Sabune Winkler</td>
<td>HMS</td>
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<td>Behtash Bahador</td>
<td>CISCRP</td>
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<tr>
<td>Nicola Bedlington</td>
<td>European Patients Forum</td>
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<tr>
<td>Barbara Bierer</td>
<td>Brigham &amp; Women's Hospital/ MRCT Center</td>
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<tr>
<td>Assunta De Rienzo</td>
<td>Brigham and Women's Hospital</td>
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<td>Dimitrios Dogas</td>
<td>MRCT Center</td>
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<td>Phyllis Frost</td>
<td>Personalized Medicine Coalition</td>
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<td>Pierre Gervais</td>
<td>QT Research</td>
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<td>David Haery</td>
<td>European AIDS Treatment Group</td>
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<td>Zach Hallinan</td>
<td>CISCRP</td>
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<td>Cheryl Jernigan</td>
<td>Susan G. Komen</td>
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<td>Barbara Kress</td>
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<td>Sarah Larson</td>
<td>Biogen Idec</td>
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<td>David Leventhal</td>
<td>Pfizer</td>
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<td>Craig Lipset</td>
<td>Pfizer</td>
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<tr>
<td>Holly Fernandez Lynch</td>
<td>Harvard Law School</td>
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<td>Alex Nasr</td>
<td>AbbVie</td>
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<td>Mary Oster</td>
<td>NEIRB</td>
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<td>Jane Perlmutter</td>
<td>Gemini Group</td>
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<td>Sandy Prucka</td>
<td>Lilly</td>
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<td>Beth Roxland</td>
<td>Johnson &amp; Johnson</td>
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<td>Jessica Scott</td>
<td>GSK</td>
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<td>Zachary Shapiro</td>
<td>MRCT Center/ Harvard Law School</td>
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<tr>
<td>David Walling</td>
<td>Collaborative NeuroScience</td>
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<td>Marc Wilenzick</td>
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<td>Elizabeth Witte</td>
<td>HMS</td>
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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**
The MRCT Center Deliverables

**MRCT Center Return of Results Guidance** for groups wishing to return results including:

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

**MRCT Center Return of Results Toolkit** including:

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

http://mrct.globalhealth.harvard.edu/file/377001

http://mrct.globalhealth.harvard.edu/file/377016
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
• Adherence to global regulatory framework
Aggregate Study Results: Suggestions

To Whom:

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

Several Methods 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 (e.g. 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
Last Study Visit of Participant

• What to anticipate after last study visit
• Monitoring for adverse events, and contact information if questions
• 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
• Personal data collected during the study, if appropriate
• Participant choice whether or not to receive summary study results, and how they will receive/access
• Contact information for the participant
• Designation a third party to receive results, if desired
Creation of Summary: Suggestions

• Summary must be unbiased and not promotional

• Summary reviewed by independent editor(s) and patient representative(s)

• Health literacy principles, including clear language

• Translation into other languages (consistent with 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 participant’s death
Health Literacy Overview

• Emphasis on **health literacy**

  • Health Literacy is not the same as one’s 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.” (Consensus Paper 2013, Making Health Literacy a Priority in EU Policy)

  • Even those with adequate health literacy can struggle at times to understand health information, and appreciate clear communication.

  • The complexity of the healthcare system can challenge everyone!
Health Literacy Overview

• Application of “universal health literacy precautions” facilitates understanding.
  • Tools such as CDC Clear Communication Index may be used to measure successful application of health literacy principles
    www.cdc.gov/ccindex

• Input of patients/participants critical:
  • Development of the content
  • Comprehension testing of the summary

• Additional links/information may be offered to participants who would like additional detail.
Health Literacy Principles (Implementation)

- Plain language
- Use active voice and short sentences
- Formatting to aid comprehension:
  - Headlines to organize information
  - Presentation of the “big picture” before the details
  - Descriptive headers and subheadings
  - Limited use of tables and charts
  - Adequate “white space”
  - Minimum of 12-point font
  - Sufficient contrast between font and background color
  - Avoidance of text in “all caps”
Numeracy

- The ability to use basic probability and mathematical concepts to explain mathematical and statistical terms.
- Numeracy principles in health literacy focus on simple explanations, instead of using complex fractions, percentages or statistical terms.
- Consider when to include numbers—don’t ignore them!
  - Give people the information they need to make their own choices.
  - Providing necessary numbers can increase comprehension.
Less is more – how critical are the numbers?

- Omitting unrelated numbers can lead to improved comprehension and higher quality choices.
- The depth of necessary data may differ. For example, a cancer patient choosing a treatment type will need data regarding effectiveness and survival rates, where a patient wanting to learn how to use an inhaler does not need data on asthma prevalence.
- In other words, “give the right tool at the right time”.
Numeracy Example

14%
Or
About 1 in 7
MRCT Center Templates

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

<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 <em>Drug A</em> to prevent <em>disease</em> is effective.</td>
<td>This study found that people with <em>disease</em> who got <em>Drug A</em> had <em>primary endpoint</em>.</td>
</tr>
<tr>
<td>The combination treatment of <em>Drug A and B</em> may also help alleviate <em>a different disease/condition than what was studied</em></td>
<td>When <em>Drug A and B</em> are used together, people in this study had <em>study endpoint</em>.</td>
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## Endpoint Descriptions and Examples

<table>
<thead>
<tr>
<th>Endpoint</th>
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<tbody>
<tr>
<td>Composite</td>
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<tr>
<td>Surrogate</td>
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<tr>
<td>Mortality</td>
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<tr>
<td>Morbidity</td>
</tr>
<tr>
<td>Progression-free survival (or disease-free survival)</td>
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<tr>
<td>Patient-Reported Outcome on symptoms or functions (e.g., pain)</td>
</tr>
<tr>
<td>Exploratory Biomarker / Pharmacogenomics</td>
</tr>
<tr>
<td>Prevention or incidence endpoint</td>
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<tr>
<td>Non-inferiority endpoints</td>
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# Endpoint Descriptions and Examples

## Mortality Endpoint Description and Example

<table>
<thead>
<tr>
<th>Endpoint Description</th>
<th>Example in plain language</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>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.)</td>
</tr>
<tr>
<td></td>
<td>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.)</td>
</tr>
</tbody>
</table>
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
Collaborations – Next Steps

• Our current Guide and Toolkit are designed for all sponsors (PI-initiated, industry, NIH) to use in all trial types (all phases, FDA- and EU, comparative effectiveness, biobanking, etc).

• Effort made to create harmonized document that will meet the needs of the US and Europe.

• We invite additional collaborators, and welcome your feedback. We will use this feedback to create an updated version.

• Link to MRCT Return of Results overview: http://mrct.globalhealth.harvard.edu/return-results
  Guidance document: http://mrct.globalhealth.harvard.edu/file/377001
  Toolkit (with Templates): http://mrct.globalhealth.harvard.edu/file/377016

• Provide feedback to: Carmen Aldinger (carmen_aldinger@harvard.edu)
Thank you

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

Laurie Myers
laurie_myers@merck.com

Rebecca Li
Rebecca_Li@harvard.edu

Deborah Collyar
Deborah@tumortime.com

Mark Barnes
mrct@harvard.edu
APPENDIX
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
## 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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</table>
| **Regulated trials**  
(typically industry sponsored interventional studies) | 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 |
| Consistent with EU regulation                           |                                                                       |                                                      |                                                                      |
| **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 | Manuscript or Publication                            | - Return RRS to trial participants including unpublished trials       |
| **Longitudinal / observational studies**                | Concurrent with the release of each major study publication            | Manuscript or Publication                            | - Return RRS to trial participants and after each update              |