Return of Aggregate Trial Results: The MRCT Center Toolkit

Carmen E. Aldinger, PhD, MPH
Program Manager
Multi-Regional Clinical Trials Center of
Brigham and Women’s Hospital and Harvard
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Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.
Objectives of this Session

• Evaluate best **methods to develop process and logistics** to return trial results to participants

• Identify key **data points to include** in aggregate data

• **Collaborate with existing transparency efforts** to optimize trial data usefulness in industry
A Word on Terminology

• Conference title and European Union refer to “lay summaries”

• We use the term “plain language:”
  – Feedback from patient groups indicated a more positive reaction to this term as compared to “lay” summary
Outline

• Rationale for returning aggregate results to participants

• Return of Results Guidance Document
  – Process flow of returning results
  – Methods for returning results
  – Content of results summaries
  – Health and numerical literacy

• Return of Results Toolkit
  – Templates for communicating study results
  – Neutral language guidance
  – Endpoint table

• Outlook and Collaboration
Rationale for returning aggregate results to participants
Declaration of Helsinki—
Ethical Principles for Medical Research Involving Human Subjects

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/
(last amended October 2013)

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:** 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.

EU Requires posting laypersons summary to EU Portal, expected to start in October 2018
EU Annex IV – Content of the Summary for Laypersons


1. Clinical trial identification
2. Name and contact details of the sponsor;
3. General information about the clinical trial;
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. Indication if follow up clinical trials are foreseen;
10. Indication where additional information could be found.

EU Consultation document (until August 31, 2016):
## Patient/Participant Perspective in the U.S.

<table>
<thead>
<tr>
<th>Patients / Study Volunteers</th>
<th>Research Professionals</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 90% want to know the results of their clinical trial&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• 98% of study staff would like to provide results to their volunteers&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>• 91% never hear back from study staff or sponsor&lt;sup&gt;2&lt;/sup&gt;</td>
<td>• 95% of research ethics board chairs strongly support (Canadian survey)&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>• If not informed, 68% would not participate in future trials&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

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4. CISCRP, personal communication
Multi-Regional Clinical Trials Center Response
Return of results: MRCT Center workgroup

**Academic/Medical Center:**
- Carmen Aldinger – MRCT Center
- Mark Barnes - Ropes & Gray, LLP / MRCT Center
- Barbara Bierer - Brigham & Women's Hospital/MRCT
- Assunta De Rienzo - Brigham & Women's Hospital
- Alla Digilova – MRCT Center
- Rebecca H Li – MRCT Center
- Holly Fernandez Lynch - Harvard Law School
- Pearl O'Rourke - Partners HealthCare
- Nesri Padayatchi - Univ. of KwaZulu-Natal
- Amish Shah - MRCT / Harvard Law School
- Zachary Shapiro – MRCT/ Harvard Law School
- Patrick Taylor - Children's Hospital, Boston
- Sarah White - Partners HealthCare
- Elizabeth Witte – Harvard Medical School
- Sabune Winkler – Harvard Medical School

**Industry/Trade Associations:**
- Salvatore Alesci – PhRMA
- Richard Bergstroem – EFPIA
- Elizabeth Garofalo - Novartis Pharma AG
- Laura Hagan - Merck Serano
- Sandra Hayes-Licitra – Johnson & Johnson
- Angelika Joos – Merck Sharp & Dohme
- Barbara Kress – Merck
- Sarah Larson – Biogen Idec
- David Leventhal – Pfizer
- Craig Lipset – Pfizer
- Laurie Myers – Merck (CO-CHAIR)

**Academic/Medical Center:**
- Alex Nasr – AbbVie
- Mary Ann Plummer – J&J (prior CO-CHAIR)
- Sandy Prucka – Lilly
- Ben Rotz – Lilly
- Beth Roxland – Johnson & Johnson
- Jessica Scott – GSK

**Institutional Review Boards:**
- David Forster - WIRB Copernicus Group
- Mary Oster – NE IRB
- Jim Saunders - NE IRB

**Nonprofit:**
- Behtash Bahador – CISC RP
- Phyllis Frosst - Personalized Medicine Coalition
- Zach Hallinan – CISC RP
- Marc Wilenzick – International AIDS Vaccine Initiative

**Patient Advocates:**
- Nicola Bedlington – European Patients Forum
- Deborah Collyar – PAIR (COCHAIR)
- David Haerry – European AIDS Treatment Group
- Cheryl Jernigan - Susan G. Komen
- Yann LeCam – EURODIS
- Marcello Losso - HIV RAMOS
- Jane Perlmutter – Gemini Group

**Research/Consulting Firms:**
- Barbara Godlew - The FAIRE Company, LLC
- Pierre Gervais - QT Research
- Paulo Lacativa - CCBR Clinical Research
- David Walling – Collaborative NeuroScience
Goals

• Develop standards and best practices.
• Ensure principles are respectful of global cultural expectations.
• Address perceived barriers to widespread implementation.

Rationale:

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 and increasing public trust.

Scope:
Communication and dissemination of *summary* research results to *individual* participants.
The MRCT Center Tools

An Return of Results Guidance Document including:

• Logistics and detailed processes for results sharing
• Content of research result summaries
• Cultural and health literacy considerations
• Timing


An Return of Results Toolkit including:

• Templates for Phase 1, 2 & 3, studies ending early
• Neutral language guide
• Endpoints language guide


Go to: mrctcenter.org -- Resources – Return of aggregate results
Process Flow for Returning Results

• **Pre-Study preparation**
  • Include data transparency in organizational preparation, policies, processes
  • Establish level/timing/delivery
  • Resource planning

• **Protocol Development**
  • Offer participants an opportunity to receive study results
  • Include a section on returning results in Informed Consent Form

• **During study conduct**
  • Consider letter of appreciation
  • Prepare for last study visit of participant
  • Keep intermittent engagement with participant thereafter

• **When study ends**
  • Prepare and review summary document
  • Adhere to global regulatory framework and health literacy principles
Methods of returning aggregate results

• **To Whom:**
  • All participants who have been enrolled and agreed to receive results

• **Several Methods of Return:**
  • Internet based methods (flexible, cost-effective, current, security may be important)
  • 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)

• **Timing:**
  • Within 1 year of completion or ‘end of study’ or publication
Participant Clinical Trial Results Summaries - Process

- Write in unbiased and not promotional language
- Obtain review by independent and objective editor(s) and patient representative(s)
- Translate into languages consistent with translations of informed consent
- Make available an individual from the study site or neutral informed third party to answer questions for participants
- Make provisions for vulnerable populations and other instances
- Consider as to whether to inform, and whom to inform, in the event of a participant’s death
- Use plain language (sixth to eight grade reading level)
- Apply health and numeracy principles
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.
Researchers were looking for a better way to treat knee pain in people with osteoarthritis. Osteoarthritis is a degenerative disease that involves the degradation of articular joints and subchondral bone, as a result of mechanical stress on the area.

In plain language:

- Osteoarthritis refers to a progressive joint disease or “wear and tear.” This is the most common illness of the joints. It occurs when the cartilage or cushion between joints breaks down. This leads to stiffness, swelling and pain.

Scores:
- Flesch Reading Ease: 72.5 (recommended between 60 and 70, the higher the score, the easier to understand)
- Flesch-Kincaid Grade Level: 5.5 (recommended 6-8; the lower the easier to understand)
Health Literacy Principles: Implementation

- Plain language
- Use active voice and short sentences
- Formatting to aid comprehension:
  - Presentation of the “big picture” before the details
  - Headlines to organize information
  - Descriptive headers and subheadings
  - Limited use of tables and charts
  - Minimum of 12-point font
  - Sufficient contrast between font and background color
  - Avoidance of text in ALL CAPS
  - Adequate “white space”
- For more information: Appendices 3 and 4 of Guidance Document
Example

Numeracy: Overview

• 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.
Numeracy Principles: Implementation

• Less is more – how critical are the numbers?
• Provide fewer choices – choose strategically which options to show
• Do the math – calculate or convert numbers, readers are unlikely to conduct even basic math
• Give numbers meaning and context – explain what numbers mean
• Use common terms and imaginable formats
• Use visuals
• Use whole numbers
• Use consistent denominators and timeframe
• Natural frequencies vs percentages – “1 out of 10” may be more useful than percentages because it gives context and imagery

Example

14%
Or
About 1 in 7
In 20% (or 1 in 5) of patients, tumors got at least 30% smaller.

In 80% (or 4 in 5) of patients, tumors did not get at least 30% smaller.
Return of results templates

Template for Communication of Study Results

**SPONSORS:** This template helps create clear summaries of clinical trials. Replace the {guidelines in red brackets} with your text; delete this heading.

If written to study participants, include the following:

Thank you for participating in this study.

You and other volunteers helped researchers answer important health questions.

Here we describe the results of this study.

If written for the general public, start here:

This summary was completed on [month/year]. Newer information since this summary was written may now exist. This summary includes only results from one single study.

Other studies may find different results.

**Phase 1 Study**

This study searched for a safe dose of [interventions/treatments] for people with [disease/condition].

[Place a simple title for the study in the box above. Sponsors may consider using the same simple title as in this registry. If drug names are used, list both generics and also where brand names® can be found.]

**Phase 2 and 3 Studies**

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.]

**Why the study was done**

**Phase 1 Study**

This was the first time this [treatment/drug/device/intervention] was studied in humans.

This study was done to find the highest [dose/amount] of the drug/treatment that people could take without having severe side effects. Side effects include unexpected medical

- Located in MRCT Return of Results Toolkit
- Templates for Phase 1, Phases 2 and 3, and Trials ending early
- Includes examples
- Incorporates principles of Health Literacy and Numeracy
Participant Clinical Trial Results Summaries - Content

• Thank You

• Title and purpose of the study

• Why the study was done

• Study information (patient population, drugs, start & end date, countries)

• How the study worked (how participants were divided into groups)

• Side effects

• Summary of results

• Final comments (official study title, where to get more information)
### Participant Clinical Trial Results Summaries - Content

<table>
<thead>
<tr>
<th>Content</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thank You</td>
<td><em>Thank you for participating in this study.</em>&lt;br&gt;As a clinical study participant, you belong to a large community of participants around the world. You help researchers answer important health questions and help them discover new medical treatments. ....</td>
</tr>
<tr>
<td>Title/Purpose of the study</td>
<td><strong>Phase 1 studies:</strong>&lt;br&gt;This study searched for a safe dose of <em>[interventions/treatments]</em> for people with <em>[disease/condition]</em>.&lt;br&gt;&lt;br&gt;<strong>Phase 2 and 3 studies:</strong>&lt;br&gt;This study compared <em>[interventions/treatments]</em> for people with <em>[disease/condition]</em>.</td>
</tr>
<tr>
<td>Why the study was done</td>
<td><strong>Phase 2 study:</strong>&lt;br&gt;This study was done to find out if patients’ conditions improved by using the <em>[drug(s)/device(s)/treatments/interventions]</em>.&lt;br&gt;&lt;br&gt;<strong>All phases of studies:</strong>&lt;br&gt;<em>A simple explanation of the disease/condition and what standard treatments may exist</em></td>
</tr>
</tbody>
</table>
## Participant Clinical Trial Results Summaries - Content

<table>
<thead>
<tr>
<th>Content</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Why the study was done (cont.)</td>
<td><strong>For clinical trials that stop early:</strong> This study was stopped earlier than planned. This can happen for many reasons.</td>
</tr>
<tr>
<td></td>
<td>This study stopped early because <em>[add one of the possible statements below, or your own simple explanation, to this sentence. If there is more than one reason, list all that apply.]</em></td>
</tr>
<tr>
<td></td>
<td>… too many participants had side effects (see below).</td>
</tr>
<tr>
<td></td>
<td>… <em>[drug generic name]</em> did not improve patient results.</td>
</tr>
<tr>
<td></td>
<td>… <em>[drug generic name]</em> was not as effective as expected <em>[comparator]</em>.</td>
</tr>
<tr>
<td></td>
<td>… <em>[drug generic name]</em> was much more effective than expected. <em>[if applicable, add]</em> The study was stopped so all participants had a chance to take <em>[drug generic name]</em>.</td>
</tr>
<tr>
<td></td>
<td>… not enough people joined the study.</td>
</tr>
<tr>
<td></td>
<td><em>[Include a statement about what will happen next. …]</em></td>
</tr>
<tr>
<td></td>
<td>• For side effects ..</td>
</tr>
<tr>
<td></td>
<td>• For efficacy ...</td>
</tr>
<tr>
<td></td>
<td>• For futility ...</td>
</tr>
<tr>
<td></td>
<td>• Low accrual: ....]</td>
</tr>
</tbody>
</table>
Example of Return of Results Template

• A Clinical Trial of a New Combination of Two Cancer Drugs for Breast Cancer
### Neutral Language Guide

<table>
<thead>
<tr>
<th>Language to avoid</th>
<th>Language to consider</th>
</tr>
</thead>
<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 &lt;drug A&gt; to prevent &lt;disease/condition&gt; is effective.</td>
<td>This study found that people with &lt;disease/condition&gt; who got &lt;drug A&gt; had &lt;primary endpoint&gt;.</td>
</tr>
<tr>
<td>This means that &lt;Drug A&gt; is better than &lt;Drug B&gt;.</td>
<td>In this study, people who got &lt;drug A&gt; had more &lt;study endpoint&gt; than some people who got &lt;Drug B&gt; with the same health conditions.</td>
</tr>
<tr>
<td>&lt;Drug A&gt; is better tolerated than &lt;Drug B&gt;.</td>
<td>In this study, fewer patients who took &lt;Drug A&gt; had &lt;list specific adverse events&gt; than patients who took &lt;Drug B&gt;.</td>
</tr>
</tbody>
</table>

Similar principles have been suggested by TransCelerate BioPharma:  
[Recommendations for Drafting Non-Promotional Lay Summaries of Clinical Trial Results](#)
Examples of translating into neutral language

• One promising finding was that tumors got at least 30% smaller in 20% of patients.
Examples of translating into neutral language

• One promising finding was that tumors got at least 30% smaller in 20% of patients.

• The study found that tumors got at least 30% smaller in 20% of patients.
  Or

• The study found that tumors got about one third (30%) smaller in one fifth (20%) of patients.
Examples of translating into neutral language

• This study proved that two thirds of the patients (66%) survived their breast cancer for at least one year after starting the study drugs.
Examples of translating into neutral language

• This study proved that two thirds of the patients (66%) survived their breast cancer for at least one year after starting the study drugs.

• In this study, two thirds of the patients (66%) survived their breast cancer for at least one year after starting the study drugs.
Endpoint Descriptions and Examples

• Toolkit lists common clinical trial endpoints
  – Definition with a general description
  – Examples of simple, plain language for research results summaries

• Endpoints included:

  **Composite Endpoint**
  - Non-Inferiority

  Dose Escalation
  - Patient-Reported Outcomes

  Exploratory Biomarker
  - Prevention / Incidence

  Mortality / Overall Survival
  - Progression-Free Survival

  Morbidity
  - Surrogate Endpoint
## Endpoint Descriptions and Examples

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Description of the type of endpoint</th>
<th>Example in simple, plain language</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>A composite endpoint, as the primary endpoint, combines multiple outcomes (e.g. death, getting sick again (relapse), serious event) and test results into one measure of how well the drug/therapy/device works. This is useful when there are many different outcomes that can happen during a trial. This can also be called a combined or multi-part endpoint.</td>
<td>“The XXX study measured [patients/people] to see if those in Group A (ABC treatment) or Group B (XYZ treatment) lived longer, had fewer heart attacks, or fewer hospital visits for heart failure. These events were measured together (combined) because each one is quite rare. Researchers also wanted to see if the drug worked in patients who had all 3 conditions. The study found that there was no change in the number of events for [patients/people] in Group A or Group B.”</td>
</tr>
</tbody>
</table>
## Endpoint Descriptions and Examples

| Endpoint                  | Description of the type of endpoint                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Example in simple, plain language                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Patient-Reported Outcomes | This study asked patients about their [list the main purpose of the questionnaire: e.g., symptoms, activity level, quality of life, income and/or happiness] and if the measurement changed based on whether a patient got A or B.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                          | The primary endpoint is less XXX based on the YYY scale. This scale measures ZZZ and how this changes over time.                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

“Patients answered questions to measure pain, stiffness, and how well people climbed stairs, stood or bent over. Questions were asked during each study visit.

About 50 in 100 people (50%) in Group A had less knee pain.

About 25 in 100 people (25%) in Group B had less knee pain.

This means that patients in Group A (x treatment) had less knee pain than patients in Group B (y treatment/placebo).”
• Write in plain language, short sentences, active voice
• Use headlines and “white space” to organize information
• Give numbers meaning and context
• Use the provided templates
• Write in neutral, non-promotional language
• Describe the study endpoint in simple language
• Return of results to participants may become the expectation and practice in clinical research.

• If similar to the U.S. studies, research participants world wide may want to receive information about the clinical trial to which they participated.

• Funding and resources for return of results and training for writing summary results should be provided as an anticipated component of human subjects research.

• Logistics, content, processes, standard methodologies and approaches must be delineated for populations in the US, UK, EU and beyond.
Collaboration with existing transparency efforts

- European Commission: “Summary of Clinical Trial Results for Laypersons” expected in early 2017
- CISCRP (Center for Information and Study on Clinical Research Participation): Trial Result Summaries
- TransCelerate: Recommendations for Drafting Non-Promotional Lay Summaries of Clinical Trial Results
- MRCT Center templates available for use
Next Steps for the MRCT Center Efforts

- Return of aggregate results
  - Released Guidance Document Version 2.1 and Toolkit Version 2.2
  - Apply principles and templates to a number of studies, collecting feedback from participants as to comprehension and preferences
- Adoption of guidance for non-Western cultures
- Return of individual level results (incidental findings, results of study arm, clinical and research findings)
Comments, questions and discussion

Carmen E. Aldinger, PhD, MPH
Program Manager

Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard
14 Story Street, 4th floor, Cambridge, MA 02138 USA
1-617-496-9807 caldinger@bwh.harvard.edu
http://MRCTcenter.org/