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MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Writing Plain Language Summaries in Accordance with the new EU Guidelines

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Our Mission

Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.

Objectives of today's presentation

- Review the new EU guideline's recommendations for summarizing clinical trial results for laypeople
- Learn how to return results consistent with the EU guidelines, utilizing the MRCT Center Toolkit and Guidance Document
- Apply health literacy, numeracy and readability standards to plain language summaries
- Weigh the benefits of planning for plain language summaries in the early stages and throughout the clinical trial

Rationale for returning plain language summaries to participants

A Word on Terminology

- In the U.S., change in progress from “lay summaries” to “plain language summaries” (PLS)
- We use the term “plain language:”
  - Feedback from patient groups indicated a more positive reaction to this term as compared to “lay” summary
- EU Guideline refers to “Summaries of Clinical Trial Results for Laypersons”

European Regulation

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

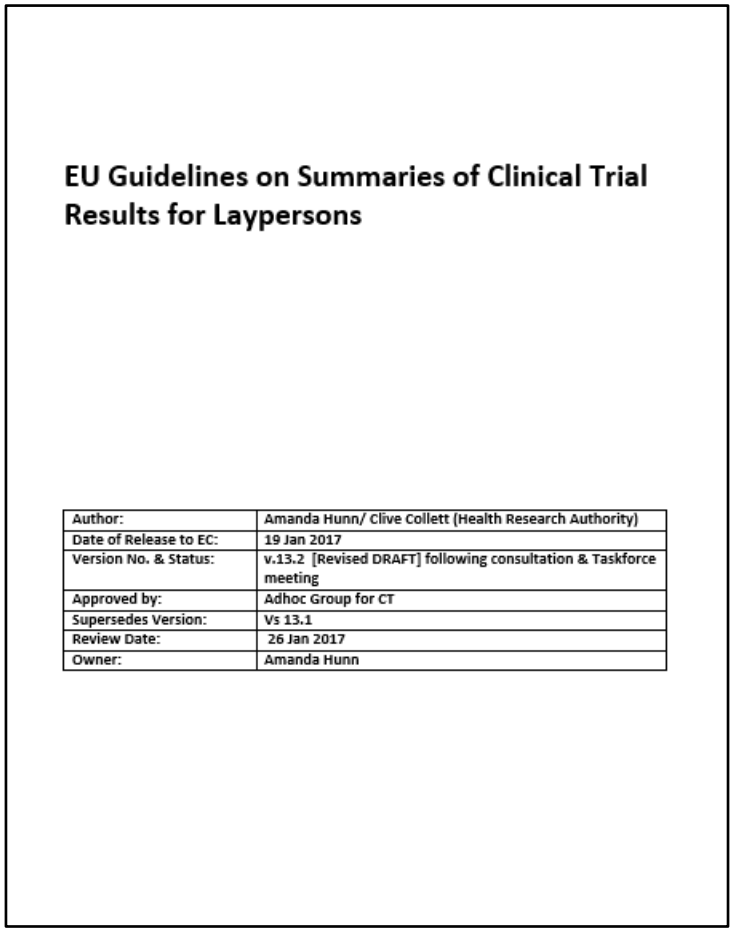
Sponsor of a clinical trial must submit "a summary of the results of the clinical trial together with a summary that is understandable to a layperson, and the clinical study report, where applicable, within the defined timelines."

Article 37: 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 beginning in Oct 2018

EU Guidelines on Summaries of Clinical Trial Results to Laypersons

- Has been approved by ad-hoc committee in January 2017
- Has not been publicly released



EU Guidelines on Summaries of Clinical Trial Results for Laypersons

Author:	Amanda Hunn/ Clive Collett (Health Research Authority)
Date of Release to EC:	19 Jan 2017
Version No. & Status:	v.13.2 [Revised DRAFT] following consultation & Taskforce meeting
Approved by:	Adhoc Group for CT
Supersedes Version:	Vs 13.1
Review Date:	26 Jan 2017
Owner:	Amanda Hunn

Patient/Participant Perspective in the U.S.

Patients / Study Volunteers	Research Professionals
• 90% want to know the results of their clinical trial[1] • 91% never hear back from study staff or sponsor[2] • If not informed, 68% would not participate in future trials[3]	• 98% of study staff would like to provide results to their volunteers[4] • 95% of research ethics board chairs strongly support (Canadian survey)[5]

Recent small studies with participants and patients of comprehensive and integrative medicine from New England confirmed: 89—90 % want researchers to share results, 16—37 % received their results

1. Shalowitz and Miller. 2008. *PLoS Medicine.* 5:714-720.
2. Getz et al. 2012. *Expert Rev. Clin. Pharmacol.* 5(2):149-156.
3. Sood et al. 2009. *Mayo Clinic Proceedings.* 84(3):243-247.
4. Dixon-Woods et al. 2006. *BMJ.* 332:206-210.
5. MacNeil and Fernandez. 2007. *J Med Ethics.* 33:549-553.

Multi-Regional Clinical Trials Center Response

The MRCT Center Tools

- **Return of Aggregate Results Guidance Document**

  (Version 3.0, March 2017)

  http://mrctcenter.org/wp-content/uploads/2017/04/2017-03-20-MRCT-Return-of-Aggregate-Results-Guidance-Document-Version-3.0.pdf

- **Return of Aggregate Results Toolkit**

  (Version 3.0, March 2017)

  http://mrctcenter.org/wp-content/uploads/2017/03/2017-03-13-MRCT-Return-of-Aggregate-Results-Toolkit-3.0.pdf

- **Return of Aggregate Results to Participants Principles**

  (Version 1.0, December 2016)

  http://mrctcenter.org/wp-content/uploads/2017/04/2016-12-02-Return-of-Aggregate-Results-to-Participants-4-Pager.pdf

Return of Aggregate Results Guidance Document

- **Version 3.0 released in March 2017**

  Major changes:

  - Changed terminology to Plain Language Summaries (PLS)
  - Changed headings for PLS to correspond with EU Guidelines
  - Revised Basic Principles

  Content:

  - Overview, including role of IRB/REC
  - Organizational process and logistics
  - Content of plain language summaries
  - Special considerations
  - Appendices, including Health Literacy and Numeracy

  Link:

  http://mrctcenter.org/wp-content/uploads/2017/04/2017-03-20-MRCT-Return-of-Aggregate-Results-Guidance-Document-Version-3.0.pdf

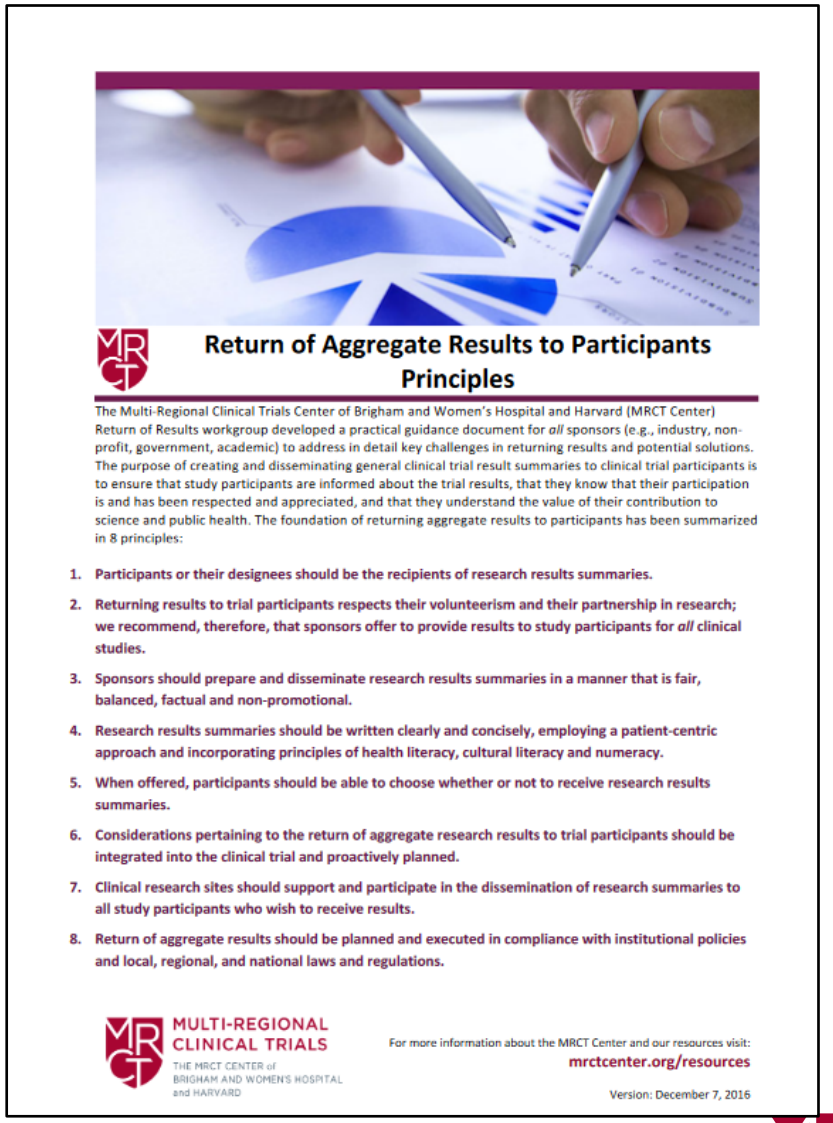
Return of Aggregate Results Principles

- **Released in December 2016**

  Content

  - 8 Principles that summarize the foundation of returning aggregate results to participants

  Link: http://mrctcenter.org/wp-content/uploads/2017/04/2016-12-02-Return-of-Aggregate-Results-to-Participants-4-Pager.pdf



Return of Aggregate Results to Participants Principles

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) Return of Results workgroup developed a practical guidance document for *all* sponsors (e.g., industry, non-profit, government, academic) to address in detail key challenges in returning results and potential solutions. The purpose of creating and disseminating general clinical trial result summaries to clinical trial participants is to ensure that study participants are informed about the trial results, that they know that their participation is and has been respected and appreciated, and that they understand the value of their contribution to science and public health. The foundation of returning aggregate results to participants has been summarized in 8 principles:

1. **Participants or their designees should be the recipients of research results summaries.**
2. **Returning results to trial participants respects their volunteerism and their partnership in research; we recommend, therefore, that sponsors offer to provide results to study participants for *all* clinical studies.**
3. **Sponsors should prepare and disseminate research results summaries in a manner that is fair, balanced, factual and non-promotional.**
4. **Research results summaries should be written clearly and concisely, employing a patient-centric approach and incorporating principles of health literacy, cultural literacy and numeracy.**
5. **When offered, participants should be able to choose whether or not to receive research results summaries.**
6. **Considerations pertaining to the return of aggregate research results to trial participants should be integrated into the clinical trial and proactively planned.**
7. **Clinical research sites should support and participate in the dissemination of research summaries to all study participants who wish to receive results.**
8. **Return of aggregate results should be planned and executed in compliance with institutional policies and local, regional, and national laws and regulations.**

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For more information about the MRCT Center and our resources visit:
mrctcenter.org/resources

Version: December 7, 2016

Principles for returning aggregate results

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Principles for returning aggregate results (cont.)

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Return of Aggregate Results Toolkit

- **Version 3.0 released in March 2017**

  Major changes:

  - Revised Template for Communication of Study Results to correspond with headings of EU Guidance

  Content:

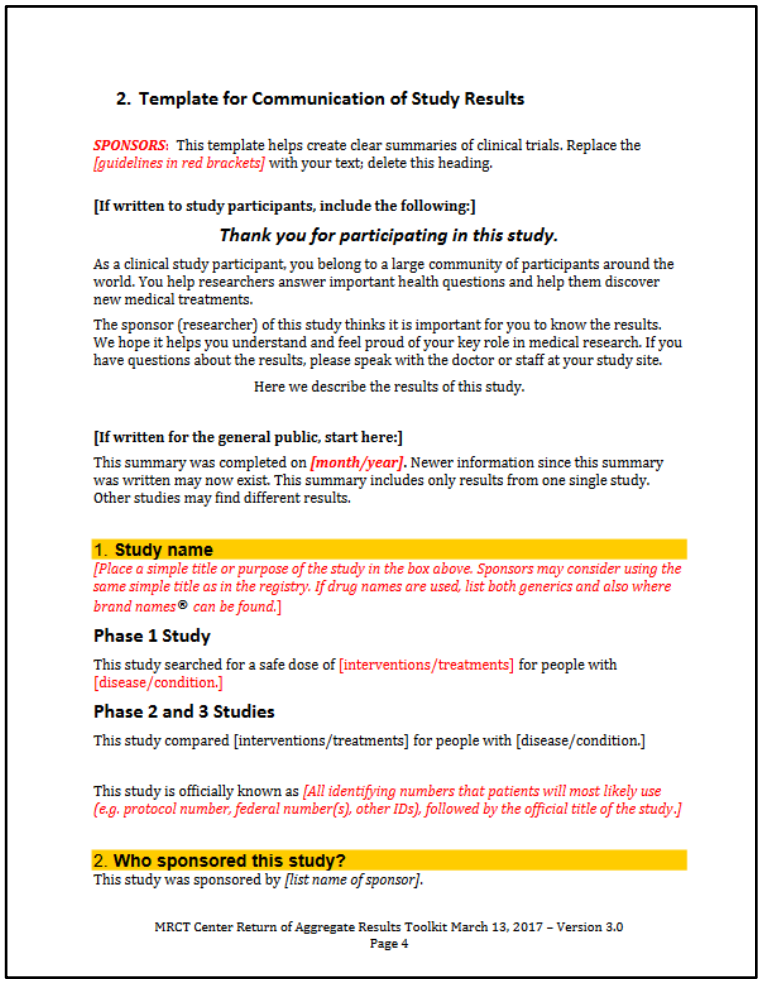
  - Template for communication of study results
  - Checklist for plain language summaries reviewers
  - Endpoint table with sample language
  - Neutral language guidance
  - Ethics committee checklist for aggregate plain language summaries
  - Examples from external sources

  Link:

  http://mrctcenter.org/wp-content/uploads/2017/03/2017-03-13-MRCT-Return-of-Aggregate-Results-Toolkit-3.0.pdf

Toolkit: Template for Communication of Study Results

1. Study name
2. Who sponsored this study?
3. General information about the clinical trial
4. What patients/people were included in this study?
5. Which medicines [or vaccines] were studied?
6. What were the side effects?
7. What were the overall results of the study?
8. How has this study helped patients and researchers?
9. Are there plans for future studies?
10. Where can I find more information about this study?



2. 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.

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.

The sponsor (researcher) of this study thinks it is important for you to know the results. We hope it helps you understand and feel proud of your key role in medical research. If you have questions about the results, please speak with the doctor or staff at your study site.

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.

1. Study name

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

Phase 1 Study

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

Phase 2 and 3 Studies

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

This study is officially known as *[All identifying numbers that patients will most likely use (e.g. protocol number, federal number(s), other IDs), followed by the official title of the study.]*

2. Who sponsored this study?

This study was sponsored by *[list name of sponsor].*

MRCT Center Return of Aggregate Results Toolkit March 13, 2017 – Version 3.0
Page 4

Essential Elements of Plain Language Summaries

1. Study name
   - Plain, simple language
   - Full title is required by U.K. guidelines
   - Summary includes only results from one single study
2. Who sponsored this study?
   - List all sponsors
   - Contact information
3. General information about the clinical trial
   - Start and stop dates
   - Countries
   - Why the study was important

Essential Elements of Plain Language Summaries (cont.)

4. What patients/people were included in this study?
   - Number enrolled, age and gender
   - Description of specific population and how chosen
   - Results apply only to this population
5. What medicines [or vaccines] were studied?
   - Simple explanation of study arms, consider graphic
   - Clarify that this is only one study in drug development process
6. What were the side effects?
   - Common and serious medical issues

Essential Elements of Plain Language Summaries (cont.)

7. What were the overall results of the study?
   - Take-home message (like abstract to a paper)
   - Results per study arm
   - Neutral (non-promotional), simple language
8. How has this study helped patients and researchers?
   - Research helps future patients
   - Results applicable to the specific population studied
   - Limitations of the study
9. Are there plans for further studies?
   - Information about related trials, ongoing or planned

Essential Elements of Plain Language Summaries (cont.)

10. Where can I find more information about this study?
    - Official number and title
    - Links to related (non-promotional/generic) websites

- Don’t forget:
    - Thank you
    - Date

Link to sample summary

- A Pilot Study on a Mind-Body Intervention for Irritable Bowel Syndrome and Inflammatory Bowel Disease

Health Literacy Principles: Overview

- Plain language – check reading scores
- 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
  - Adequate “white space”
  - Minimum of 12-point font
  - Sufficient contrast between font and background color
  - Avoidance of text in ALL CAPS
- For more information: Appendices 3 and 4 of Guidance Document

Example of translating into plain language

- 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 / Numeracy Resources added

- Pleasant, A., Rooney, M., O'Leary, C., Myers, L., & Rudd, R. (2016). Strategies to Enhance Numeracy Skills. Discussion Paper. National Academy of Medicine. https://nam.edu/strategies-to-enhance-numeracy-skills/

- Rudd, R. (2016). Numbers Get In The Way. Commentary. National Academy of Medicine. https://nam.edu/numbers-get-in-the-way/

From: *Strategies to Enhance Numeracy Skills*

- Marry words and numbers to provide a complete understanding
- Do the math
- Be consistent
- Present only the most necessary information, but enough to be fully understood
- Be visual – use images and shapes to reflect the meaning of the numbers
- Be aware of how you present or describe a risk
- Check in early and often

From: https://nam.edu/wp-content/uploads/2016/05/Strategies-to-Enhance-Numeracy-Skills.pdf
(Accessed: June 16, 2017)

Planning for plain language summaries throughout the clinical trial process

- Before the study starts
  - Update organizational policies, processes, procedures
  - Establish level / timing / delivery method of PLS
  - Budget for PLS
  - Develop and incorporate PLS into study documents (e.g., informed consent, communication and publication plan)
  - Build staff capacity

Planning for plain language summaries throughout the clinical trial process (cont.)

- Protocol development
  - Anticipate that participants will be given an opportunity to receive study results
- Informed consent development
  - Include a general statement that explains the intent to provide PLS
  - Example: “In the future, you can decide whether or not you wish to receive the general results of the study. You do not need to decide now about this."
- Resource planning
  - Discuss and agree upon resources for PLS execution

Planning for plain language summaries throughout the clinical trial process (cont.)

- During study conduct
  - Discuss Informed Consent with participant: process and anticipated timing of PLS
  - Prepare for participant end-of-study visit: written summary, including opt-in or opt-out for receiving aggregate results; if opted-in, how to access PLS when available
  - Stay connected with participant; e.g., thank you letter after ICF is signed, letter of appreciation after last visit, annual holiday card, periodic letters explaining stage of the study

Planning for plain language summaries throughout the clinical trial process (cont.)

- After study ends or all data for primary endpoint concluded
  - Develop PLS according to template
  - Have PLS reviewed by clinical trial team and medical communications group, and, optimally, internal and/or external reviewers with varied backgrounds
  - Identify study participants who agreed to receive PLS and notify them

New Resources

- Trial Scope
  - Searchable Portal for trial results summaries (search by keyword, condition, location, first or last visit date)
  - https://www.trialsummaries.com/Home/LandingPage

- Health Literacy Media
  - Write, edit, review and design health materials in plain language
  - Conduct national and international initiatives that apply health literacy best practices, etc.
  - http://www.healthliteracy.media/

Summary

- Create plain language summaries (PLS) according to template with new headings
- Integrate plans for PLS before the study begins, throughout the study, and after study ends
- Apply health literacy and numeracy principles
- Utilize available resources

Outlook

- Return of results to participants may become the expectation and practice in clinical research.

- 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 inside and outside of US, UK and EU.

Next Steps for the MRCT Center Efforts

- Recommendations Document and Toolkit for Return of Individual Results
- Results from small studies on return of results in integrative medicine, using PLS template
- E-Learning course for return of aggregate results
- Updates for Return of Aggregate Results Recommendations Document and Toolkit, as needed

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Comments, questions and discussion

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Go to "Resources" – "Return of Aggregate Results"