Voice of the Patient – Returning Aggregate Results through Plain Language Summaries

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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.
Goals

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

Rationale:
Returning results is a key aspect of improving transparency and increasing public trust, and fundamentally, recognizes and honors the contributions of clinical trial participants.

Scope:
Communication and dissemination of summary or aggregate research results.

Similar expectations of academic, industry, not-for-profit sponsors.
**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
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- Holly Fernandez Lynch - Harvard Law School
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- Amish Shah - MRCT / Harvard Law School
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- Sarah White - Partners HealthCare
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- Sandra Hayes-Licitra – Johnson & Johnson
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- David Leventhal – Pfizer
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- Laurie Myers – Merck (CO-CHAIR)

**Institutional Review Boards:**
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- Mary Oster – NE IRB
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- Zach Hallinan – CISCRP
- Marc Wilenzick – International AIDS Vaccine Initiative

**Patient Advocates:**
- Nicola Bedlington – European Patients Forum
- Deborah Collyar – PAIR (CO-CHAIR)
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- Yann LeCam – EURODIS
- Marcello Losso - HIV RAMOS
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- David Walling – Collaborative NeuroScience

Alex Nasr – AbbVie
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Sandy Prucka – Lilly
Ben Rotz – Lilly
Beth Roxland – Johnson & Johnson
Jessica Scott – GSK
Return of Aggregate Results — Principles

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.

http://mrctcenter.org/projects/return-of-results-to-participants/
MRCT Center Deliverables

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

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

Pre-Study preparation
- Protocol Development
  - Study Design
  - Protocol Development

Protocol Development
- IRB & Other Regulatory Requirements
- Identify and Recruit
- Collect Data
- Last Patient
  - Last Visit
- Close-out

During study conduct

When study ends
- Communicate Results
- Analyze Data
- Interpret Results

New Idea
- Address whether, what, when and how to return results
- IRB review and approval
- Introduce PLS
- Manage expectations
- Engage and communicate

Organizational Preparation
- Level, timing, methodologies
- Prepare summary, aligned with IC, CSR, Manuscript
- Web site or individual outreach through PIs/sites
- Follow up

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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 (EMA, one year from LPLV)
Participant Clinical Trial Results Summaries - Process

- Write in unbiased and non-promotional language
- Obtain review by independent, objective editor(s) and patient rep(s)
- Incorporate the patient’s voice into the summary
- 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
Returning results in plain language allows for investigators and sponsors to honor the essential contributions and voluntarism of study participants.

**Health Literate Communications: Summary is only one example**

- **Study Design**
- **Protocol Development**
- **Identify and Recruit**
- **Collect Data**
- **Last Patient Last Visit**
- **Close-out**
- **Analyze Data**
- **Interpret Results**
- **Communicate Results**

**New Idea**

- **Informed Consent**
- **Data Collection**
- **Individual**
- **Education**
- **Summary**

**11 April 2019**

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A systems approach

- Corporate and individual commitment to communication and, I would argue, participant engagement throughout the process

- Trials engineered to deliver results that are important to the participants and patients and their loved ones, and to society

- Process—like any other—that requires dissection, analysis, and reengineering
  - Plain language: terms, use and meaning in relevant culture
  - Design, visualization, numeracy
  - Education and training of all involved
  - Commitment to provide the resources required
  - Tools and resources to simplify where possible
  - Iterative quality improvement
  - Incentive structures for desired behaviors
  - Oversight, metrics, tracking, and transparency built as part of process
MRCT Center endorses the use of health literacy practices when developing clinical research information for patients and participants.

Clinical Trial Life Cycle Overview

Health literacy supports the participant through these 5 steps of the clinical trial journey:

- **Discovery**: Public awareness of, education about, and access to clinical research
- **Recruitment**: Targeted, relevant, written and verbal invitations to join research
- **Consent**: Clear written and verbal conversations about informed consent to research participation
- **On Study**: Clear information about ongoing research procedures, data collection and reporting
- **End of Study**: Plain language summaries, results reports, and research publications
These principles of health literacy provide a basis from which to adopt and integrate health literacy practices into clinical research. They are intended to support clinical research stakeholders, including sponsors and funders, investigators and study teams, and institutional Review Boards in their communications with potential, enrolled, and past participants. Additional information on how to take action can be found here.

**Principles of Health Literacy in Clinical Research**

1. Create clear clinical research communications for the target audience.

   Clinical research and medical concepts can be difficult to understand regardless of a person’s educational background. Yet, individuals can only benefit from and use information that they understand. In order to communicate in ways that promote participant autonomy stakeholders must allow sufficient time to develop, test, modify, and confirm understanding of health-literate research communications.

2. Recognize that applying health literacy principles is a shared responsibility of all clinical research stakeholders.

**Recruitment**

Targeted, relevant, written and verbal invitations to join research

At “Recruitment”, specific information about one or more clinical trials is shared, with the intent of recruiting an individual to a particular research study.

- The focus is on developing relationships between research stakeholders and the study population, sharing accurate information, and laying the foundation for a positive research experience.
- All recruitment materials and scripts should go through usability testing with members of the population of interest.

**Plain Language**

At “Recruitment”, plain language explanations are needed to provide more details about the individual study that is recruiting participants:

- flyers, pamphlets, newspaper ads, billboard-type ads for subways and buses, radio ads and social media posts all need to use terms that are understandable to the target
Plain language is essential but not sufficient

And no need to reinvent the wheel
How to give yourself the study medicine
Panel A (Days 1-5) and Panel B (Days 6-10)

Study medicine
Each bottle holds 1 mL of active drug or placebo.
The study staff will tell you how much medicine to use each time (this is called your dose). Only give yourself the dose the study staff told you. Do not use all the medicine in the bottle.
The study staff will tell you how much to inject from each bottle.

Important safety information
- Refrigerate the kit box – Do not freeze.
- Only use each bottle 1 time.
- Use a new syringe and needle each time.
- Only uncap the bottles when you use them.

Steps to give yourself the study medicine

Get ready

1. Gather your supplies:
   - 2 syringes
   - 2 bottles of medicine
   - 2 alcohol swabs

2. Take out 2 bottles from the kit box and put the kit box back in the refrigerator.
   - Let the bottles sit on the counter for at least 15 minutes to get to room temperature.
   - Turn the bottles upside down and then right side up at least 3 times.

3. Wash your hands with soap and water.
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.
EU Clinical Trials Regulation 536/2014


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 trials;
8. Comments on the outcome of the clinical trial;
9. Indication if follow up clinical trials are foreseen;
10. Where where additional information could be found.

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Fair and balanced
Not biased nor promotional
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 the 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

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

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<table>
<thead>
<tr>
<th>Content</th>
<th>Example</th>
</tr>
</thead>
</table>
| Why the study was done (cont.)                                          | **For clinical trials that stop early:**  
This study was stopped earlier than planned. This can happen for many reasons.  

This study stopped early because *[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.]*  
... too many participants had side effects (see below).  
... *[drug generic name]* did not improve patient results.  
... *[drug generic name]* was not as effective as expected *[comparator]*.  
... *[drug generic name]* was much more effective than expected. *[if applicable, add]* The study was stopped so all participants had a chance to take *[drug generic name]*.  
... not enough people joined the study.  

*[Include a statement about what will happen next. ...]*  
• For side effects ..  
• For efficacy ...  
• For futility ...  
• Low accrual: ....]*
## 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;\text{drug A})&gt; to</td>
<td>This study found that people with (&lt;\text{disease/condition})&gt; who got (&lt;\text{drug A})&gt; had (&lt;\text{primary endpoint}&gt;).</td>
</tr>
<tr>
<td>prevent (&lt;\text{disease/condition})&gt; is effective.</td>
<td></td>
</tr>
<tr>
<td>This means that (&lt;\text{Drug A})&gt; is better than</td>
<td>In this study, people who got (&lt;\text{drug A})&gt; had more (&lt;\text{study endpoint})&gt; than some people who got (&lt;\text{Drug B})&gt; with the same health conditions.</td>
</tr>
<tr>
<td>(&lt;\text{Drug B})&gt;</td>
<td></td>
</tr>
<tr>
<td>(&lt;\text{Drug A})&gt; is better tolerated than (&lt;\text{Drug B}&gt;).</td>
<td>In this study, fewer patients who took (&lt;\text{Drug A})&gt; had (&lt;\text{list specific adverse events})&gt; than patients who took (&lt;\text{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](#)
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
  • Dose Escalation
  • Exploratory Biomarker
  • Mortality / Overall Survival
  • Morbidity

  • Non-Inferiority
  • Patient-Reported Outcomes
  • Prevention / Incidence
  • Progression-Free Survival
  • Surrogate Endpoint
Special Considerations

- **Timing**
- **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**
- **Assent for Return of Results to Children**
- **Complexities of the Global Context**
Role of IRB / REC

- There is currently no international agreement on the obligations and level of involvement of IRBs/RECs with respect to return of aggregate results.

- Results communicated after study closed: no requirement of IRB to review.
- If planned return described in study protocol, IRB/REC should review and approve overall plan to return, but not specific content.
- If plans change, or communicate during study, IRB/REC should review
Return of aggregate results

• Incorporated into the HRA (UK)
• Incorporated into the EMA guidelines
• Drafted FDA guidance
• Would be honored to work with other regulatory agencies, sponsors, and DIA

Harmonization
Global regulatory convergence
Comments, questions and discussion
Thank you

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