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Patient Participation in Clinical Trials

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MRCT Multi-Regional Clinical Trials

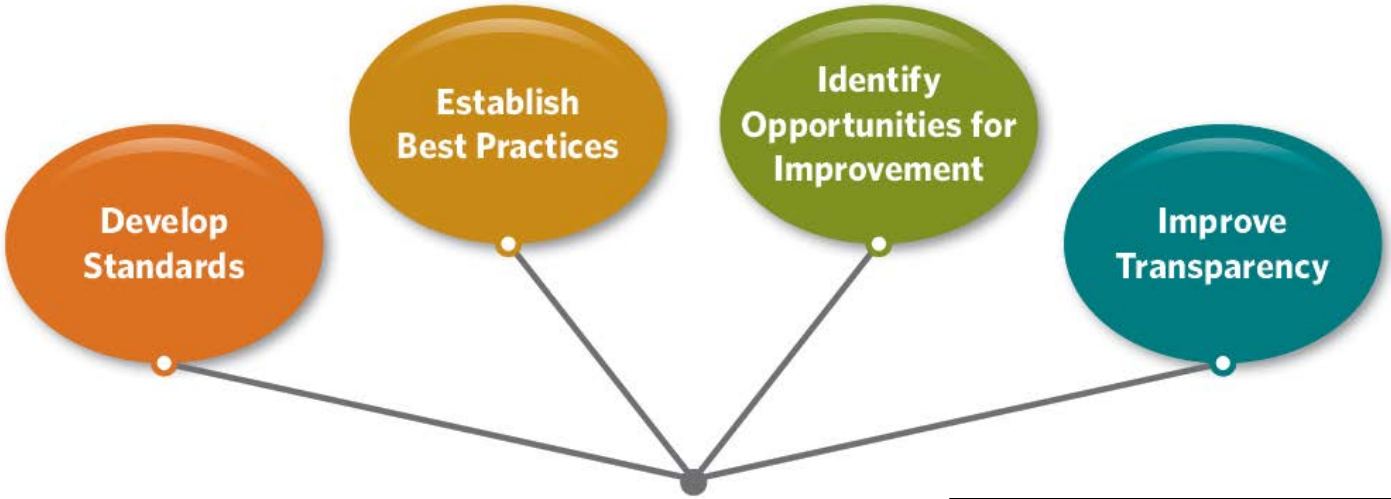
The MRCT Center at Harvard

Harvard MRCT Return of Results Initiative

DIA October 16, 2014 Barbara Bierer, MD

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.*



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

Returning Results and the MRCT Mission

Goals: Returning Clinical Trial Results (to trial 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.

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

Why Now?

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:

4. 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.

PhRMA/EFPIA

"…biopharmaceutical companies will work with regulators to adopt mechanisms for providing a factual summary of clinical trial results and make the summaries available to research participants."

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

- **Our work furthers these efforts by:**
  - Creating a guidance document that can function as a standard for groups wishing to return results.
  - Including input from multiple stakeholder groups:
    - Academics
    - Industry
    - Regulators
    - Patient-Advocates and patients
    - CROs
    - IRBs

Summary

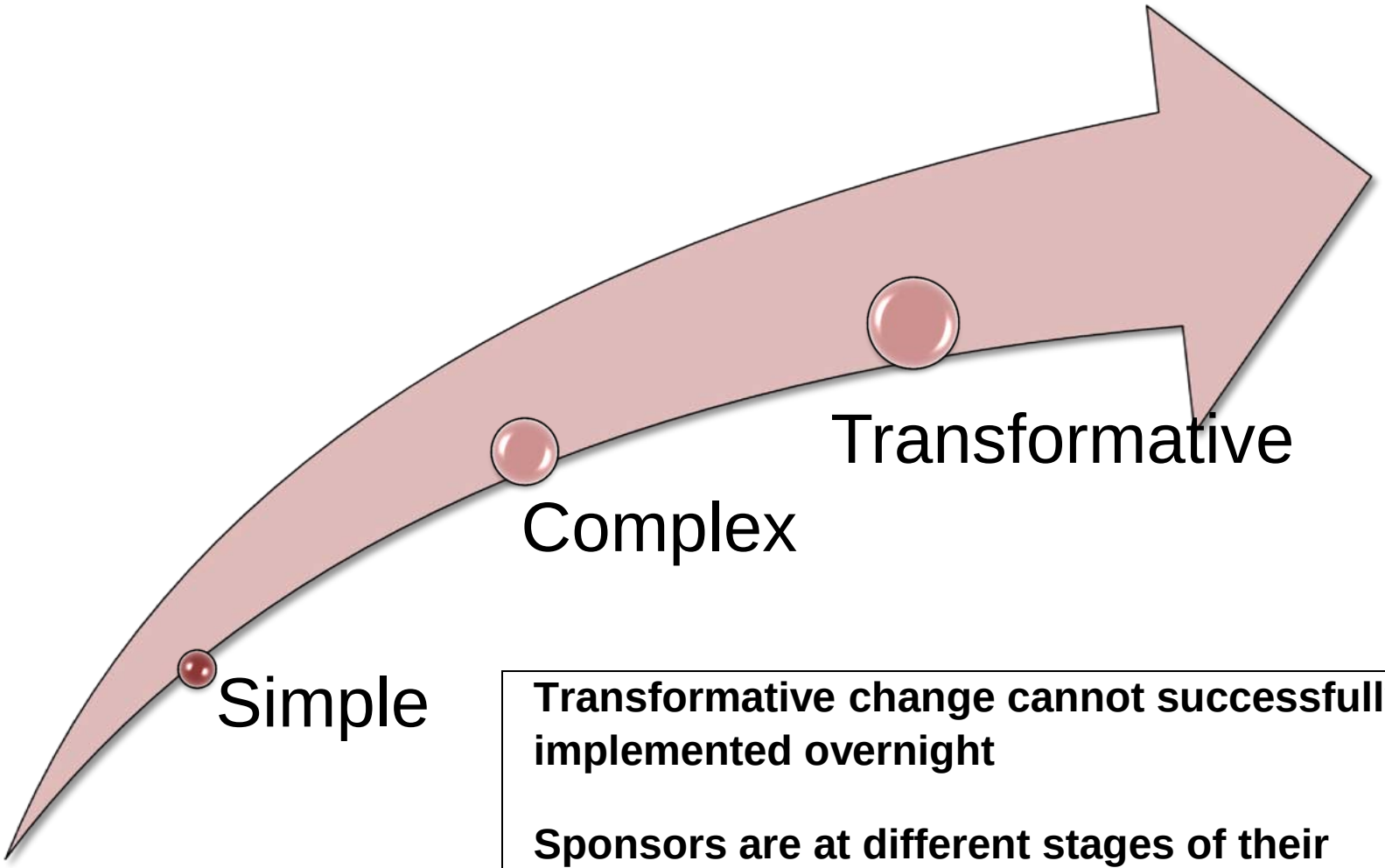
Return of results should become the expectation and practice in human subjects research. The practice demonstrates:

- 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 their own information) and understand the results.
- Participant has a right to choose whether to (and who may) have that information.

Standard methodologies and approaches should be developed so that roles and responsibilities are clear, and expectations are set and met.

Funding should be provided as an anticipated component of human subjects research.

Transforming the Participant Experience



Transformative change cannot successfully be implemented overnight

Sponsors are at different stages of their commitment to returning results – our pathway can assist sponsors regardless of the maturity of their program

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)
- Oversight of IRBs/Research Ethics Committee

Comprehension

- What do patients/participants want to know? And do they understand implications?
- Language in letter may be too scientific for non-scientists to understand.

Misinterpreting intent

- FDA and other regulators might view returning results as a promotional activity

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

*follow-on projects (out of scope currently)

Health Literacy

Emphasis on health literacy

- Health Literacy is not the same as literacy level or ability to read.
  - Health Literacy: “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.”[1]
  - Attention to numeracy principles as well

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

- The guidance template applies principles of health literacy.

- Required information on how to integrate health literacy into clinical trial processes to assure understanding, including information on numeracy; testing for readability; visuals; and writing style.

1. U.S. Department of Health and Human Services (HHS). Healthy People 2010. Washington, DC: U.S. Government Printing Office. 2000.

Incorporation of Numeracy

Definitions:

- "The ability to use probability and basic mathematical concepts" [1]
- "A constellation of skills necessary to function effectively in the health care environment and act appropriately on health care information." [2]

Best practices include:

- Consider when to include numbers to clarify information; use whole numbers
- Less may be more – include the most important numbers to make decisions; too many can be overwhelming
- Do the math (i.e. 5% of your body weight – for a 200 pound person, this would be 10 pounds)
- Give labels meaning – this can help in decision making
- Use visuals
- Present numbers in the expected direction (i.e. 0-100, 100 as best)
- Consider framing of risk

1. Peters, E., Västfjäll, D., Gärling, T., & Slovic, P. (2006). Affect and decision making: A "hot" topic. Journal of Behavioral Decision Making, 19(2), 79-85.
2. Berkman, N. D., Sheridan, S. L., Donahue, K. E., Halpern, D. J., Viera, A., Crotty, K., . . .Viswanathan, M. (2011). Health literacy interventions and outcomes: An updated systematic review. Evidence Report/Technology Assessment No. 199. (Prepared by RTI International–University of North Carolina Evidence-based Practice Center under contract No. 290-2007-10056-I. AHRQ Publication Number 11-E006. Rockville, MD. Agency for Healthcare Research and Quality.

Protocol and Study Details

Pre-Study preparation

- Organizational preparation, policies, processes
- Establish level/timing/delivery
- Resource planning

Protocol Development

- Describes return of study results as voluntary process, including who what where when and due diligence
- Include ICF section description

During study conduct

- Letter of appreciation
- Intermittent engagement

When study ends

- Content (and health literacy)
- Adherence to global regulatory framework

Participant End-of-Study Visit

- What participants can anticipate after their participation ends and advice regarding monitoring for adverse events, both anticipated and unanticipated, if appropriate.
- In the event of questions, or adverse events, whom to contact and contact information.
- A reminder, if appropriate, that the participant 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, should be explained.
- Advice as to where to obtain further treatment and/or clinical care, particularly in the event that the participant does not have a health-care provider.
- Any information regarding the participant's personal data developed during the study
- Whether the participant would or would not like to receive aggregated study results at end of study. If opt-in, then when and how to access the information.
- Contact information for the participant, if appropriate.
- Whether the participant would like to designate a third party to receive results in the event of their incapacity or death.

Aggregate Study Results: Suggestions

To Whom:

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

Method of Return:

- Interactive methods (e.g., face-to-face meeting(s), telephone call(s), two-way online meeting(s), dynamic email exchange, etc.,)
- Internet based methods (flexible, cost-effective, current, security important)
- One-way communications (video summary, automated phone message, printed materials)

Participant Clinical Trial Results Summaries

Creation of Summary

- To ensure that the summary is unbiased and not promotional, an independent and objective editor or editorial panel 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
- 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

Timing of Return of Results: Suggestions

Trial Type	Timing	Source Document	Action
Regulated trials (typically industry sponsored interventional studies)	Within 1 year of database lock	Clinical study report (CSR)	• Post non-technical summary on EudraCT • Return RRS to trial participants
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

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 drug studies with healthy subjects that establish pharmacokinetics
  - Tissue and blood studies that are exploratory or identifying clinical correlations
  - Pilot studies that are intended to determine whether further investigation is warranted.
- 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

Regulatory Compliance

- Regulatory requirements prohibit any type of promotional communication prior to FDA/EU/other regulatory agency marketing approval
- What constitutes “promotional language” in describing results?
- Will the FDA/EMA/other regulatory agency provide guidance in a timely fashion to delineate what the agency considers “promotional”?
- If not, does the FDA/EMA/other regulatory agency 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 (Phase1 vs Phase III, etc)?
- How will investigator-initiated trials be reviewed?

Neutral Language

Language to avoid	Language to consider
This study proved…	This study found that... This does not mean everyone in that group had these results.
This study proved that using <*Drug A*> to prevent <*disease*> is effective.	This study found that people with <*disease*> who got <*Drug A*> had <*primary endpoint*>.
The combination treatment of <*Drug A and B*> may also help alleviate <*a different disease/condition than what was studied*>	When <*Drug A and B*> are used together, people in this study had <*study endpoint*> .
This means that <*Drug A*> is better than <*Drug B*>.	In this study, people who got <*Drug A*> had more <*study endpoint*> than some people who got <*Drug B*> if they had the same health conditions.
<*Drug A*> works better than <*Drug B*>, but some people didn't tolerate it as well.	In this study, more people got <*study endpoint*> with <*Drug A*>. They also had more adverse events that interfered with their daily lives, like <*specific adverse events*>.
<*Drug A*> is better tolerated than Drug B	In this study, fewer patients who took <*Drug A*> had <*list adverse events*> than patients who took

Neutral Language (2)

Language to avoid	Language to consider
People taking <*drug A*> lived longer after they had <*therapy*> for <*disease/condition*>, even with more adverse effects.	People who took <*drug*> had more time before their <*disease/condition*> came back and they lived longer. These patients also had worse adverse events and got more <*diseases/conditions*>.
While the combined treatment of <Drug A and B> did not extend life over <Drug A> alone, people felt better and lived longer with the combined treatment.	People in both groups had the same kind of results (outcomes), but people who took the combined treatment had milder adverse events like *<list specific adverse events>*. The amount of time they lived depended on how they felt when they started either treatment.
All groups had the same results . More studies are needed.	There was no effect in the treatment arms. All groups still had pain and numbness in their fingers or toes (called neuropathy).
People in group <*1*> were able to tolerate the highest dose of <*Drug A*> so more studies will be done.	This study found dose levels that patients can take without too many adverse events. These doses will now be used to learn if <*Drug A*> works in certain patients.

Future Directions

- **Collaboration among parties**
- **Iterative process improvement with experience**
- **The necessity of empirical research**
- **A call for global harmonization**

Return of results – current workgroup

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Yann LeCam – EURODIS
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Thank you

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