3rd Annual Lay Summaries Summit

Advanced Methods for Medical Writing, Lay Summary Implementation and Improving Communication with Patients

September 24-25, 2018 • DoubleTree by Hilton Center City • Philadelphia, PA

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Return of Individual Results to Participants — From Theory to Practice

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Disclaimer

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• We are committed to autonomy in our research and to transparency in our relationships. The MRCT Center—and its directors—retain responsibility and final control of the content of any products, results and deliverables.
Learning Objectives and Outline

• Review the MRCT Center’s guidelines for returning individual results to participants
• Discuss the special case of genetic/genomic results that illuminate the complexity
• Consider challenges to effective communication in this setting
Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.
The various audiences of clinical trials data sharing

The sharing of research results from clinical trials with study participants, including aggregate results of the trial and individual results (e.g. results of and assignment to study arm, incidental findings, clinical and research results)

Sharing of
- Aggregate Research Results to participants
- Individual Research Results to participants
- Individual Participant level data (IPD)

Sharing clinical trial results on a website enables public transparency and trust
Participant journey

New Idea

Study Design
Protocol Development

Identify and Recruit

Last Patient
Last Visit

Close-out

IRB &
Other Regulatory
Requirements

Collect Data

Analyze Data
Interpret Results

Communicate Results

Patient-Facing Materials and Resources

25 Sept 2018
Available in

- English
- Albanian
- Portuguese
- Arabic
- Italian
- Russian
- Cape Verdean
- Khmer/Cambodian
- Spanish
- French
- Korean
- Chinese
- Greek
- Polish
- Vietnamese

https://catalyst.harvard.edu/services/rsa/
Projects advancing global directives

Why Volunteer in Clinical Research?

- The development of new medical treatments and appropriate participation of research volunteers is essential.
- By volunteering in a study, you are contributing to medical research in a meaningful way.
- You could also help researchers understand the natural course of a disease or condition.
- In some cases, you can try a new therapy before it is available outside of research trials.

10 Questions to Ask Before Participating in a Study:

- Why is the research being done?
- What is expected of me if I agree to participate in the research?
- How will I benefit from the research?
- Could the research hurt me?
- What will the researcher do with the information collected from me?
- Will the research cost me anything?
- Who pays if I'm unexpectedly injured or made ill?
- How long will the study last?
- What happens if I decide to leave the study?
- Who should I call if I have a question about the study or the research?
Projects advancing global directives

- **Informational Materials for Prospective Participants:**
  - 23 brochures developed
  - 15 languages available
  - 173,627+ downloads (as of June 2018)

- **Process**
<table>
<thead>
<tr>
<th>Brochure (Publication Year)</th>
<th># of Downloads</th>
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<tbody>
<tr>
<td>Should I Be a Research Subject? (2011)</td>
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<td>Bill of Rights (2012)</td>
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<tr>
<td>Social and Behavioral Research (2014)</td>
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<tr>
<td>Blood Draw for Research (2014)</td>
<td>3,444</td>
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<td>CT Scans for Research (2014)</td>
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<tr>
<td>PET Scans for Research (2014)</td>
<td>1,595</td>
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<tr>
<td>Genetics Research (2014)</td>
<td>5,133</td>
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<td>Incidental Findings (2014)</td>
<td>1,346</td>
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<td>Surrogate Decision Making (2014)</td>
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<td>Stem Cell Research (2015)</td>
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<tr>
<td>Research Data (2016)</td>
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<tr>
<th>Brochure (Publication Year)</th>
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<td>Meet the Research Team (2016)</td>
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<td>Using Telemedicine in a Research Study (2016)</td>
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<td>tES for Research (2017)</td>
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<td>TMS for Research (2017)</td>
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<td>What is a Clinical Trial? (2017)</td>
<td>2,121</td>
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<tr>
<td>COI in Research (2017)</td>
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</table>

Total Downloads thru June 2018: 41,598
Total Downloads 2011-2018: 173,627
Phasing of return of results: Aggregate study results

- Address whether, what, when and how to return results
- IRB review and approval
- Introduce PLS
- Manage expectations
- Engage and communicate
- Prepare summary, aligned with IC, CSR, Manuscript
- Web site or individual outreach through PIs/sites
- Follow up
Return of Aggregate Results Guidance Document
(Version 3.1, November 2017)

Return of Aggregate Results Toolkit
(Version 3.1, November 2017)

Return of Aggregate Results to Participants Principles
(November 2017)
MRCT Center current project:

- **Health Literacy in Clinical Research**
  - Dynamic tools
  - Clinical research terms (“non-inferiority”)
  - Informed consent tools

 ➢ Collective development of:
   ➢ Preferred terms (e.g. MedDRA terms)
   ➢ Common research procedures (e.g. IV infusion)

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      mrct@bwh.harvard.edu
Return of individual results to participants

- The plan for the return of individual results should be described in the study protocol and reviewed and approved by the IRB/REC.

- Protocol should describe each type of anticipated and unanticipated result, analysis plan (for medical significance, analytical validity and personal utility), method and form of communication and documentation, and responsibility grid.

- IRB/REC should pay particular attention to privacy, health, and well-being of participant.
The MRCT Center Tools for sharing individual results

- **Return of Individual Results Recommendations Document**
  (Version 1.2, November 2017)

- **Return of Individual Results to Participants Toolkit**
  (Version 1.2, November 2017)

- **Return of Individual Results to Participants Principles**
  (November 2017)
<table>
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<tr>
<th>Planning and Design Phase</th>
<th>Protocol and IC Development Phase</th>
<th>Active Trial Phase</th>
<th>Post-Trial Analysis Phase</th>
<th>Post-Trial Publication Phase</th>
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<tbody>
<tr>
<td>• Rationale Matrix for returning various types of data (Tool 1)</td>
<td>• Informed Consent language for return of individual results (Tool 4)</td>
<td>• Designation of third party (Tool 6)</td>
<td>• Communication of study results at the end of a trial (including study arm) (Tool 8)</td>
<td>• MRCT Center Return of Aggregate Results Toolkit</td>
</tr>
<tr>
<td>• Points to Consider along the clinical trial timeline (Tool 2)</td>
<td>• Checklist for IRB and Ethics Committees (Tool 5)</td>
<td>• End of study form (Tool 7)</td>
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<tr>
<td>• Selected return of results regulations and resources (Tool 3)</td>
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</tbody>
</table>
Principles for returning individual results

1. Providing individual research results responds to the expressed interests and expectations of many clinical trial participants that their results be communicated to them.

2. Considerations pertaining to the return of individual research results to clinical trial participants should be integrated into the clinical trial and proactively planned.

3. The informed consent process should include information about the sponsor’s intention regarding the return of research results and allow for discussion of participants’ preferences to receive these results.

4. The plan for the return of individual research results should be reviewed by an independent ethics body overseeing the research to ensure the rights and welfare of research participants are protected.
Principles for returning individual results

5. If results are offered, participants should be able to choose whether or not to receive their individual research results.

6. Sponsors and investigators have an obligation to act responsibly when returning individual results, taking into account medical significance, analytical validity and personal utility.

7. Individual research results should be returned in ways and at times that maintain the integrity of the research, insofar as the safety and welfare of the research participants are not at risk.

8. The purpose of research is not clinical care, and return of individual research results cannot substitute for appropriate clinical care and advice.

9. Return of individual research results should be planned and executed in compliance with institutional policies and local, regional, and national laws and regulations.
Data types for return to the research participant

A: Urgent Results & Urgent Incidental Findings

B: Routine Results & Non-Urgent Incidental Findings

C: End of study Individual Results
- Study Group Assignment
- 1° Endpoints
- 2° Endpoints
- Safety endpoints

D: Exploratory Results
- Includes exploratory endpoints
- During or after close of study
- May lead to future research

E: Aggregate Results
- 1° Endpoint
- 2° Endpoints
- Summary of Conclusions

Data types recommended for return, at a minimum, are highlighted in yellow
**What** should be shared? Recommendations:

- **Urgent Results & Urgent Incidental Findings:**
  - Always return as soon as interpreted and confirmed as valid

- **Routine Results & Non-Urgent Findings:**
  - Balance potential benefits against resource requirements: Case-by-case deliberation

- **End of Study Individual Results:**
  - At a minimum, offer information about study arm assignment and primary endpoints, after study concludes (unless it would compromise the integrity of ongoing studies)

- **Exploratory Results:**
  - Handle on a case-by-case basis

- **Aggregate Results:**
  - Return summary of primary endpoints and safety data, in accordance with applicable law and guidance
What should results be shared? Considerations:

- Has the participant opted in to receive results? (P1, 5)
- Are the results analytically valid? (P6)
- Does the result have clinical validity? (P6)
- Are the results urgent, actionable? (P7)
- Does sharing the result impact the integrity of the study? (P7)
- Does returning the result comply with institutional policies, legal and national laws, and regulations? (P9)
How to share results with participants?

• Considerations
  – Privacy of participant
  – Types of data
  – Access of participants to health care professional
  – Need for interpretation
  – Pros and cons of modalities

• Modalities
  – In-person meeting
  – Telephone/video-conference
  – Online patient communities or portal
  – Confidential letter
Template for Communication of Individual Study Results including Study Arm Unblinding

**Which group you were assigned to**

[Participants] in the study were put into [+] groups by chance. [If not randomized, list how many patients/people were in each group, and how this was determined.]

- **Group A** received [*simple explanation of study regimen for first arm, i.e., 100 mg of drug once per day*]

- **Group B** received [*simple explanation of study regimen for second arm, i.e., 50 mg of drug once per day*]

- **Group C** received a placebo treatment (a sugar pill) once per day.

You were assigned to the Group checked above.
**Summary of individual results**

**Individual Results**

The following table describes your results compared to all the participants in the study. [The specific population that was studied, including age and gender breakdown. Include eligibility criteria, including specific genetic mutations (when appropriate).]

[Research Institution]

[Study Name]

Sample Study Participant Summary Report

Summary report for all participants in the same group you were assigned

<table>
<thead>
<tr>
<th></th>
<th>YOUR INDIVIDUAL RESULTS</th>
<th>RANGE [the lowest and highest “normal” value]</th>
<th>MEAN [the average value for all participants in the group]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Name] Participants For Ages [X – XX] Years [Total =xx patients]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Endpoint 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Secondary Endpoint)*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Special Considerations: Returning Genomic Results

Overall principles and considerations for returning individual results to participants apply.
Returning Genomic Results

Orientation to technology essential to communicating complexities effectively

- Incidental vs. secondary findings
  - Analytical validity, clinical validity and medical actionability

- Duty to “hunt”?

- Right to refuse results
Additional considerations for returning genomic results

- To whom one can release genetic information
- International regulations and policies
- Specific guidance on considerations for informed consent
Informed consent and other considerations:

- Confidentiality and Privacy
- Access to Genetic Information/ Results of Incidental Findings
- Secondary Use/ Re-use of Samples or Data
- Potential Risks to Consider
- Benefits
- Alternatives
- Costs to Participant
- Duration
- Control of the Specimens/ Materials
- Significant new findings
- Withdrawal from research study

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### Case Study: Return of Genetic/Genomic Findings in research

1. **Confidentiality and Privacy**
   - Explain the level of certainty with which the data has been de-identified or anonymized, or whether there will be identifiers linked to genetic/genomic data or material.
   - If applicable, indicate if a US-HHS Certificate of Confidentiality has been obtained.
   - Address limits to confidentiality (e.g., who will have access and under what circumstances).
   - Indicate which third parties (e.g., family, third party payers, participant’s physician, outside researchers) will have access to samples/data.

2. **Access to Genetic Information/Results and Incidental Findings**
   - Define incidental/secondary findings.
   - Inform participants what information/results they can expect to receive.
   - Inform participants if results or incidental findings will or will not be provided and explain why.
   - If findings are to be disclosed, describe specific disclosure procedures (e.g., genetic counseling).
   - If findings are to be disclosed, explain implications of making primary results or incidental findings available to participants.
   - Provide the participant with the opportunity to choose whether he/she wants to receive primary or incidental results.
   - Inform participants of country-specific genetic discrimination law.

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Returning Data

• How to return?
  – Put in context: generally probabilistic rather than deterministic
  – If an individual possesses a genetic variant, inform what is known and what is uncertain, and the significance of “variant”

• Who will return?
  – Decided in advance or just in time; may require a team approach
  – Genetic expertise may be needed to interpret complex findings
National Laws, Regulations, Ethics Guidance

• United States:
  – CLIA and HIPAA
  – FDA Regulatory Considerations

• Outside the U.S.: Variations in legal treatment of genetic/genomic results

• Research Ethics Committee requirements and advice
Who should receive results? Who should share results?

Axes of Communication for return of individual results

- Sponsor (if applicable)
- Principal Investigator
- Website
- Study participant
- Primary Care Physician / Personal Physician
Return of Results – Current and Future state of Communications

1. Urgent & Urgent incidental
2. Routine & Non-urgent findings
3. Study Group Assignment
4. Individual Primary Endpoints Results
5. Aggregate Results

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We designed and conducted a study

| Study objectives:                                      | • Identify current practices for sharing results among investigators and treating physicians  
|                                                      | • Understand which results investigators and treating physicians believe should be dissemination and to whom (ideally)  
|                                                      | • Identify existing barriers to sharing results and potential solutions  |
| Questionnaire development:                           | Questionnaire developed by MRCT Center workgroup and CenterWatch using data from pilot of telephone interviews of investigators and referring physicians  |
| Dissemination method:                                 | Online survey  |
| Data collection period:                               | June - September 2017  |
| Response size (out of 20,000 surveys sent)            | n=160; survey disseminated to CenterWatch’s global investigative site and physician list of 20,000  |
Respondent Profile

- Both investigator and treating physician for many of my patients: 48%
- Investigator for clinical trials: 25%
- Treating physician (primary care provider or specialist) not actively involved in clinical trials: 4%
- None of the above: 23%

Sample size = 208, Base: All respondents

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### Respondent Profile

#### Site Type (n=160)

<table>
<thead>
<tr>
<th>Site Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic</td>
<td>70%</td>
</tr>
<tr>
<td>Hospital-based (non-academic)</td>
<td>19%</td>
</tr>
<tr>
<td>Practice-based</td>
<td>7%</td>
</tr>
<tr>
<td>Free-standing (no clinical care)</td>
<td>3%</td>
</tr>
</tbody>
</table>

#### Region (n=160)

<table>
<thead>
<tr>
<th>Region</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>31%</td>
</tr>
<tr>
<td>Europe</td>
<td>43%</td>
</tr>
<tr>
<td>Other</td>
<td>26%</td>
</tr>
</tbody>
</table>

#### Years involved in Clinical Research (n=150)

<table>
<thead>
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<th>Years Involved</th>
<th>%</th>
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<tr>
<td>4 years or less</td>
<td>8%</td>
</tr>
<tr>
<td>5 to 10 years</td>
<td>21%</td>
</tr>
<tr>
<td>11 to 20 years</td>
<td>36%</td>
</tr>
<tr>
<td>21 years or more</td>
<td>35%</td>
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</table>
Do investigators and treating physicians believe that investigators should receive results (ideally) - whether or not they are shared with patients or treating physicians?

**Ideally? * **
- Aggregate Results
- Study Group Assignment
- Individual Primary Endpoint Result

88%-95% agree/strongly agree

**Current state? **
- Aggregate Results
- Study Group Assignment
- Individual Primary Endpoint Result

Approximately half *never* receive these results from Sponsors
Do investigators and treating physicians believe the results should be further shared (ideally)?

**Should results be shared with treating physicians?**
- 69%-91% agree/strongly agree

**Should results be shared with patients?**
- 63%-91% agree/strongly agree

**Current State?**
- 40%-83% have *never* shared Results (across each of the result categories)

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Who do investigators and treating physicians believe should share results with study participants?

- Approximately **half** think **Investigators** should share the results

- A **third** think **either investigator or treating physicians** should share the results
Return of Results –overcoming barriers

• Sponsors should consistently provide results
• Investigator and treating physician **exchange contact information at beginning of trial**
• **Knowing the patient’s preference** regarding desire to receive results
• Participant **consent for investigator to contact treating physician**
• **Provision of a guidance sheet** for how and when to communicate results
• **Provision of a summary document** that gives an overview and context
• **A line of communication** between investigator and treating physician
• Guidance on mitigation of **legal and privacy risks**
Key survey findings

• A majority of investigators and treating physicians surveyed believe that **investigators should be receiving results** across each of the categories and yet this is not consistently done.

• A majority of investigators and treating physicians surveyed believe these results **should be further shared** with both treating physicians and **study participants**.

• **Treating physicians could help** share results with patients.

• **Barriers to sharing were identified** and potential **pragmatic solutions could be implemented** with relative ease.
National Academies of Medicine (NAM)
Returning of Individual Research Results to Participants

NAM Guidance concurs with all substantive MRCT Center recommendations:
• Respect for Persons/Autonomy
• Promote and safeguard the well-being of research participants
• Return clinically actionable results
• Maintain the integrity of the research
• Decisions vary on study-by-study basis
• Parallel decision-making framework with feasibility and value dimensions
• Planning for return of individual results
• Setting participant expectations in the informed consent process
• Identify appropriate communication modality

• Released July 10, 2018
• Refers to MRCT Center recommendations more than a dozen times
NAM Guidance differs from MRCT Center recommendations:

- No reference to or recommendations by types of data
- Need for quality management system
- Need to harmonize federal regulations by reshaping legal and regulatory landscape (CMS and HIPAA regulations)
Summary

- Most study participants do not receive results, but wish to
- Decision as to what results to share, how and when to share
- Participant autonomy and privacy paramount
- Study-by-study, result-by-result analysis
  - Medical significance
  - Analytical validity
  - Personal utility
  - Study integrity
  - Local, regional, and national laws and regulations
- Utilize available resources
Thank you

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