Considerations in and Value of
Return of Individual Research Results

Barbara E. Bierer, MD
Professor of Medicine, Harvard Medical School
Faculty Director, MRCT Center of BWH & Harvard
bbierer@bwh.harvard.edu
The views and findings expressed are my own and do not imply endorsement or reflect the views or policies of any of the affiliated organizations or entities of any member who contributed to the work of the MRCT Center. Individuals serve in their individual capacity.

The MRCT Center is supported by voluntary contributions (www.MRCTCenter.org) and grants. I have no personal conflicts of interest to disclose relevant to this work.

And thank you for inviting me.
Session Agenda

- MRCT Center Introduction
- Importance of Returning Individual Research Results (IRR)
- Evolution of this work
- Review of project update
- Website Demo
- Q&A
The MRCT Center is a research and policy center focused on addressing the conduct, oversight, ethics and regulatory environment for clinical trials.
Our Vision

Improve the integrity, safety, and rigor of global clinical trials.

Our Mission

We engage diverse stakeholders in the research enterprise to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.
Decision to return aggregate and individual results begin with commitment at study design, requires planning, and embodies respect.
### Rationale for returning aggregate results to participants: US Patient/Participant Perspectives

<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(^1)</td>
<td>• 98% of study staff would like to provide results to their volunteers(^4)</td>
</tr>
<tr>
<td>• 91% never hear back from study staff or sponsor(^2)</td>
<td>• 95% of research ethics board chairs strongly support (Canadian survey)(^5)</td>
</tr>
<tr>
<td>• If not informed, 68% would not participate in future trials(^3)</td>
<td></td>
</tr>
</tbody>
</table>

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.


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. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of that summary is set out in Annex V.

EU Annex V – Content of Layperson Summary

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 additional information could be found.

• Fair and balanced
• Not biased nor promotional

Target audience is the public, not only trial participants

4. General Principles

• Develop the summary for a general public audience and do not assume any prior knowledge of the trial.

• Develop the layout and content for each section in terms of style, language and literacy level to meet the needs of the general public.

• Keep the document as short as possible.

• Focus on unambiguous, factual information.

• Ensure that no promotional content is included.

• Follow health literacy and numeracy principles.

• Consider involving patients, patient representatives, advocates—and medical writers—in the development and review of the summary to ensure that it meets their needs.

Return of Aggregate Results Guidance Document

  - Process flow of returning results
  - Methods for returning results
  - Content of results summaries
  - Health and numerical literacy

Return of Aggregate Results Toolkit

  - Templates for communicating study results
  - Neutral language guidance
  - Endpoint table
  - Useful checklists
What about me?
Decision to return aggregate and individual results begin with commitment at study design, requires planning, and embodies respect.
Defining Individual Research Results (IRR)

**IRR is:**

Any data or test result from a research study that is specific to an individual, such as study arm assignment, lab results, or genetic sequencing data.

**IRR is not:**

Aggregate results, plain language summaries, or lay summaries that provide study participants with overall findings of a research study.
Research participants consistently desire and expect to receive both individual and aggregate research data from the research studies in which they have participated.

Expectations about data transparency and ownership are evolving in society; returning IRR anticipates and responds to those expectations.

Foundational ethical principles in research can and should be applied to the return of IRR to participants.
Version 1, Released in 2017

• Strong case was made for the ethical imperative of returning IRR
• Introduced classification of result types based on timing, actionability, etc.
• Robust set of considerations for returning genetic information
• Presented as a starting point for external stakeholders to build upon
Spectrum of results to return to participants:

- Aggregate research results (plain language summaries)
- Assignment to and results of study arm
- Routine clinical results performed in the course of research
  - Urgent
  - Actionable
  - Personally valuable
  - No known implications
- Incidental findings discovered in the course of a clinical trial
  - Of potential clinical significance or actionable
  - Of uncertain significance
- Research results
  - Of likely or uncertain significance
  - Of potential proprietary importance
  - Genetic/genomic results
- Other results
Launching the Return of Individual Research Results (IRR) Project & Website

Updated and released March 22, 2022

Contributing taskforce members:

- Sylvia Baedorf Kassis
- Barbara Bierer
- Linda Coleman
- Anna Kang Liu
- David Leventhal
- Megan McBride
- Lisa Murray
- Nancy Levitan Poorvu
- Sandra Prucka
- Kate Robins
- Jessica Scott
- Jamie Tyrone
- Carol Weil
- Sarah White
What should results be shared? Considerations:

• Has the participant opted in to receive results?
• Are the results analytically valid?
• Does the result have clinical validity?
• Are the results urgent, actionable?
• Are the results of personal utility?
• Does sharing the result impact the integrity of the study?
• Does returning the result comply with institutional policies, legal and national laws, and regulations?
Need for an update:

- Identified the need for practical, implementation-based resources
- Update/expansion of certain recommendations

IRR Taskforce:

- Convened 10-person taskforce to update the original materials and overall project
  - Included representation from industry, academia, IRB/HRPP, government, and patient advocates
- Objectives:
  - Find common problems and barriers throughout the process of returning IRR
  - Provide guidance/resources to help organizations address and overcome barriers
  - Promote the value of organizations to prepare for and prioritize returning IRR
Challenges Identified

- Perception of a high barrier to entry
- Concerns around liability/fear of the unknown
- Unclear differentiation of responsibilities between and among stakeholders
- Absence of regulatory requirements or guidance on what to return, when, and how
- Difficulty in achieving buy-in throughout the organization

Solutions Created for Version 2 Release

- Guidance on getting started with plan for gradual progression
- Roadmaps to clarify stakeholder roles and responsibilities
- Re-classification of result types to frame the return of IRR
- Guidance on how to create a return of IRR plan
- Specific tools for implementing the return of IRR
- Topics to review common concerns with or complexities of returning IRR
Intended Audience

**Research Sponsors**
Those developing treatments and financing clinical trials.

**IRBs & HRPPs**
Those providing ethical reviews of research or managing human research protections programs.

**Study Staff & Investigators**
Principal Investigators, study team members, and staff at research sites.

**Patients & Participants**
Those participating in or considering clinical trials, and their family members/caregivers.

The MRCT Center invites review, comment, and suggestions for revision from all stakeholders to MRCT@bwh.harvard.edu
How to get started
Why to get started
How to Get Started

- Proposed progression of return
- Designing a pilot
- Who to involve
- Methods for returning IRR

PROPOSED PROGRESSION

- SECONDARY OUTCOMES
- ROUTINE RESULTS
- PRIMARY OUTCOMES
- STUDY ARM ASSIGNMENT
-_plain_language_summaries
- URGENT FINDINGS
RETURN OF INDIVIDUAL RESEARCH RESULTS

- Stakeholder Roadmaps
- Determining what to return
- How to return
  (who/when/how/etc.)
- Result-specific guidance

Return of Individual Research Results

The MRCT Center is proud to release these updated resources. The guidance, recommendations, and tools on this website can further enable researchers to return individual research results (IRR) to participants.
New Result Type Classifications

URGENT

ACTIONABLE

PERSONALLY VALUABLE

NO KNOWN IMPLICATIONS
Determining what to return

Steps in a clinical trial

Types of data that may be generated in the trial

Classification of result
Stakeholder Roadmaps

- Roadmap for each stakeholder
- Provides a basic overview of each role’s responsibility/task during a given time period
- Links to additional guidance or tools relating to each responsibility/task

## Stakeholder Roadmaps

### Responsibilities/Tasks
- Organizational buy in
- Establishing a Policy
- Protocol Review
- Regulations

### Time Period

### Preparation

**Organizational Buy-In**
IRBs and HRPPs are important stakeholders and advisors throughout IRR, particularly during initiation of an IRR pilot or program, at any organization or institution.

Make sure to stay involved in both guide practices towards those that are beneficial to participants and to establish appropriate expectations for what should be included to enable appropriate IRB review.

**Establishing a Policy**

**Protocol Review**

**Regulations**

### On Study

**Informed Consent**

- Plans for IRR should be made during protocol development to enable all relevant details around IRR to be given to the participant during the informed consent process. The IRB should determine which details need to be included in the Informed Consent Form, and which can be communicated in other ways.

- [Click here for more on informed consent](#)

---

31 March 2022

©MRCT Center. All Rights Reserved.
How to Return IRR

Who should return result
When it should be returned
How it should be returned
Choice for participant as to whether to receive

Guidance separated by result type

Recommendations for who should return results of different data types:

- **Urgent**
  - PIs should generally give urgent results to the participant contextualized with appropriate medical information, connect with the healthcare provider, and document the handoff.
  
  Documentation should include the result, referral, and verification of the transfer of responsibility.
  
  It may be necessary to inform the healthcare provider first, and then inform the participant with recommended next steps. These situations include concerns around requisite psychological support systems (e.g., information indicating suicidality), or in settings wherein the nature of the problem might inhibit the ability of the participant to respond.
  
  If the participant is unreachable in an urgent situation and no alternative person has been designated by the participant, the PI and study staff should revert to procedures deployed in clinical settings and submit a report to the IRB as soon as reasonably possible. The medically responsible person affiliated with the trial should be contacted and tasked with this responsibility whether or not that person is the principal or site investigator of the trial.

- **Actionable but not urgent**
  - Click here for more about returning this data type.

- **Personally Valuable**

- **No known Implications**

Points to consider regarding who will communicate result to participant:

- **PI or Institution (or Research Site Staff):**
  - May require training regarding how to communicate and explain results
  - Should allow for the study context to be explained with results

- **Healthcare Provider (HCP):**
  - May require training on how to interpret and explain results
  - Research results can be communicated during medical care

- **Website Portal:**
  - Avoids scheduling a specific appointment
  - Allows data to be made available at any time, both during and after the study

More specific considerations on these topics and other important points to consider can be found on the respective Results pages: **Urgent, Actionable, Personally Valuable, and Have No Known Implications.**
Data-Type Pages

For each result/data type:

- Definition & examples
- Links to basic considerations (who, when, how, choice)
- Informed consent (IC) guidance
- IC sample language
- Regulatory requirements
- Gathering the participant’s healthcare provider contact info
- Accessing appropriate expertise to interpret results or advise in other capacities

HOW WE DEFINE ACTIONABLE RESULTS
An actionable result is one that has medical or personal decision-making utility, notably when additional diagnostic or preventive measures are needed or when alternative treatment is available.

Examples:
- A hemoglobin A1c (HbA1c) blood test, a measure of average blood sugar, is above normal, and may indicate diabetes or pre-diabetes.
- Genetic screening of an individual who has been personally unaffected by cancer returns the presence of BRCA1, a breast cancer susceptibility gene.

Reviewing the Basics for Returning Actionable Results:

How to Prepare and Additional Points to Consider

Informed Consent

It is likely that any study returning actionable results may also need to be prepared to return urgent results. Therefore, review the urgent result ICF requirements.

Many details specifically around returning urgent results (e.g., the necessity of obtaining and retaining information about the HCP) will need to be in an ICF, while other details can often be communicated outside of an ICF. Separating these details will reduce the length and complexity of the ICF without compromising accessibility of the information. It will depend study-by-study which details need to be in the ICF, and which do not.

The ICF may state that the participant will receive a separate information sheet (see an example here) that explains other...
RETURN OF INDIVIDUAL RESEARCH RESULTS

ABOUT  |  GETTING STARTED  |  HOW TO RETURN IRR  |  RESOURCES  |  TOPICS

• Tools and Templates
• Resources for participants
• 2017 Guidance Documents
• Health Literacy
• Aggregate Results
• Coming soon: Case Studies

(return of individual research results)

(return of individual research results)

(return of individual research results)

(return of individual research results)
Simple, downloadable tools supporting the adoption of returning IRR in a compliant and respectful way

RETURN OF RESULTS INFORMATION SHEET

Template Instructions (delete after filling in template):
This sheet is intended to support the decision and discussion around a participants’ choice to receive results. It should be adapted and/or adopted for the individual study and the choices that the participant may have.
The “red type in brackets” below should be changed to reflect the plan of the study and the types of results that a participant has the option to receive below.
Add and explain as many different types of results as necessary.
Record participants’ choices in your study documents and/or the informed consent form. In addition, check the boxes on this form for participants to take home as a reminder of their decisions.

<table>
<thead>
<tr>
<th>study name</th>
<th>insert I/R study contact</th>
</tr>
</thead>
</table>

What is this sheet?
This sheet describes the types of research results that you may choose to share with a participant in a decision study.
You can choose whether or not to receive these results.
Note, however, that we must return urgent results that require medical attention with you and/or your doctor. You do not have a choice with respect to urgent results. We will explain the reasons why below.

Can I change my mind about getting my results?
Yes, if you decide to receive results and change your mind later, you can contact us at any time by:

- Insert mode of contact

no matter what you decide, we will give you another choice to whether to receive results on:

- Insert pre-specified review time if applicable

Result 1: Urgent results that require medical attention
If any result like this must be returned:

Description: If an urgent result arises, we must return it to you in order for you to receive additional evaluation and/or care. Examples of this study could be:

- insert any plausible example from your type of study, such as:

  - A negative scan for this study found a tumor.

We might also need to share this information with your doctor or healthcare provider. Additional evaluation and/or care unrelated to this research, if you need it, will not be paid for by the study. You will need to follow up with your doctor.

Who would return this form and how? When would it be returned to me?
- Insert your return plan for urgent results
- Example: This would happen as soon as possible, as the result is confirmed by another test/s.

Who would return this form and how? When would it be returned to me?
- Insert your return plan for urgent results
- Example: This would happen as soon as possible, as the result is confirmed by another test/s.

What is this form?
In the insert plan language study title study there may be results about you that would be important for your healthcare provider or doctor to know. This form gives permission to contact your healthcare provider or doctor if necessary. We also ask you for your contact information.

When we would be required to contact your healthcare provider (where you don’t have a choice):
We must contact your healthcare provider if there is a result or medical finding that requires immediate attention, such as:

- insert any plausible example from your type of study, e.g. A routine scan findings a lump.

If you take part in this study, you agree that we can contact your healthcare provider when your study team decides it is necessary, generally for your safety and/or wellbeing.
Please know that medical care unrelated to the research will not be provided or paid for by the study, and you will need to follow up with your doctor.

Reasons you can choose to let us contact your healthcare provider:

- During and/or at the end of the study
- We will offer you some personal personal results
- You may want to share these results with your healthcare provider

Please provide your healthcare provider’s name, address, and contact information.
If you do not have a healthcare provider, please provide that last time you were seen for medical care.

Name of provider: ________________________
Clinic/hospital office phone number: ________________________

Appropriate professionals are included for urgent results or urgent medical findings that may occur during the study, and must be returned.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

Appropriate professionals are included for urgent results or urgent medical findings that may occur during the study, and must be returned.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.

In the case of non-urgent findings, the participant or their legally authorized representative is able to

- Insert an informed choice

- Whether to receive their individual results or not.
• **IRB Approval Checklist for Returning IRR**
  o A checklist to assist IRB members and Ethics Committees in reviewing return of IRR plans, based around the U.S. regulatory criteria for IRB approval.

• **Healthcare Provider Contact Form Template**
  o A template for obtaining permission to contact a participant’s healthcare provider or doctor about individual research results, along with their contact information.

• **IRR Information Sheet for Participants Template**
  o A template for supporting the decision and discussion around a participants’ choice to receive results, which should be adapted to reflect the plan of the study and the types of results that a participant has the option to receive, along with their decisions to receive them.

• **Informed Consent Sample Language**
  o Sample language to use in informed consent forms when explaining the different types of individual results that will be generated/returned to participants in a study.

• **Resources for Participants**
Resources for participants

Deciding whether or not to receive results

Considering genetic results

Questions to ask about individual results

Remember, joining a research study is an important personal decision, and participating in a study is your choice. Be informed. Ask questions. Get answers.

- What kinds of results will you share with me? If you are not sharing any results with me, can you tell me why?
- What happens if you find out something serious or other information about my health?
- Do I have a choice about which findings you share with me? What if I don’t want to know?
- Can I change my mind later about receiving these results?
- How can these results help me?
- Will you tell me about results that might affect my health or a member of my family’s health?
- Could results/findings affect my family planning decisions?
- Could you learn something new about my family history?
- Will you be able to make sure any findings are correct?
- Who can I talk to about these findings?
- Are my research data placed in my regular medical records?
- How will you protect my privacy?
- Who will pay for my follow-up care and treatment if a new medical issue is uncovered as part of the study?
- Will there be future research on any of my samples? Will I learn any of those results?
RETURN OF INDIVIDUAL RESEARCH RESULTS

Return of individual research results

- Informed Consent
- Regulations
- Liability
- Study Integrity
- Funders
- Genetics

The guidance, recommendations, and tools on this website can further enable researchers to return individual research results (IRR) to participants.
Coming Soon: Identified Areas for Continued Work

- Further review of returning genetic information
- Guidance for biobanks
- Returning IRR to parents, guardians, representatives
- Additional case studies
- And more!

Please reach out to us if you would like to collaborate or have suggestions
Website

mrctcenter.org/return-of-individual-results/
Thank you Discussion

Barbara E. Bierer, MD
bbierer@bwh.harvard.edu