MRCT Center

Return of Individual Results to Participants

Toolkit

Framework

MULTI-REGIONAL CLINICAL TRIALS

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

Version 1.2

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INTRODUCTION

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) Return of Individual Results workgroup is a multi-stakeholder group comprised of 45 international members from academic and medical centers, industry, clinical research organizations, regulatory agencies, institutional review boards, non-profit agencies, and patient advocacy organizations.

The workgroup developed this Toolkit to accompany the *MRCT Center Return of Individual Results to Participants: Recommendations Document*. The *Recommendations Document* addresses the basic principles, processes, content and data types (urgent results, routine results, end of study individual results, exploratory results) for returning individual results to study participants. This Toolkit provides practical tools, forms, checklists, sample letters and case studies. It is meant to include hands-on instruments for implementing the basic principles of the *Recommendations Document*.

This Toolkit includes tools for the study team that plans the study, for the Ethics Committee/Institutional Review Board and for site staff who return results. The Toolkit also contains practical implementation tips and case studies of scenarios for prospective trials, ongoing trials and retrospective/closed trials as well as cases in which the informed consent does not explicitly plan for return of results. The case studies are accompanied by analyses that reflect considerations for returning individual results.

The MRCT Center encourages broad dissemination of the Toolkit along with the *Recommendations Document*. The MRCT Center appreciates feedback and additional contributions (addressed to MRCT@bwh.harvard.edu) so that we can continuously improve this Toolkit. If these materials are used in their entirety or in part, attribution should be made to the "MRCT Center Return of Individual Results to Participants Toolkit, Version 1.2 (accessed at www.mrctcenter.org/……)."

The toolkit is based on the Principles from the *MRCT Center Return of Individual Results to Participants Recommendations Document*.

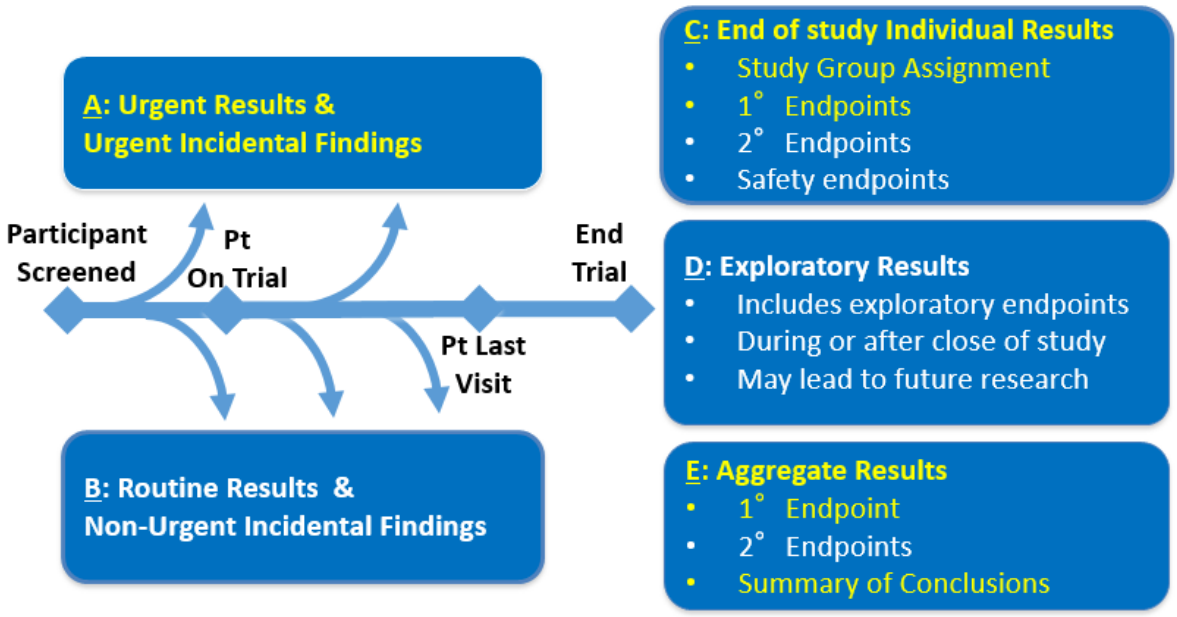
Principles: Return of Individual Results to Participants

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.
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 return individual research results responsibly, 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.

Figure 1 summarizes the high-level return of individual results tasks by phase, and suggests when specific Data Types might be considered for return. Figure 2 mentions the tasks and lists the Tools presented in this Toolkit and demonstrates how each Tool fits into the clinical trial timeline.

Figure 1: Clinical Trial Data Types That May be Returned



Data types recommended for return, at a minimum, are highlighted in yellow

Figure 2: Return of Individual Results Tasks and Tools by Trial Phase for Clinical Teams

	Planning and Design Phase	Protocol and IC Development Phase	Active Trial Phase	Post-Trial Analysis Phase	Post-Trial Publication Phase
Data Type to be returned			• Urgent, medically actionable findings (Data Type A) • Individual incidental and routine findings, including screening results (Data Type B)		• Individual Study Results (Data Type C) • Aggregate Study Results (Plain Language Summary; Data Type E) • Exploratory Results (Data Type D), in some cases
Return of Individual Results Tasks	• Choose which data types and identify what data will be returned. • Understand the global context for and legal constraints of Return of Individual Results in all study sites.	• Develop ICF including participant option to receive results and modality for return • Train site staff in Return of Individual Results processes	• Select designee(s) if any to receive results • Confirm opt-in/opt-out decision made in ICF • Return Data Types A and B, as appropriate • Track and maintain updated contact information • Support MD/PCP[1] understanding of individual data & its interpretation (Data Types A or B)	• Sponsor - Prepare Return of Individual Results Materials (Data Type C) • MD or PCP confirm the designee(s), if any, who are eligible to receive study results after the trial is complete • MD or PCP provide summary of individual data & interpretation (for Data Types A or B).	• Prepare and release Return of Individual Results materials • Prepare and release Aggregate Study Results (Plain Language Summaries) • Respond to questions from providers and participants
Return of Individual Results Tools	Tool 1: Rationale Matrix for returning various types of data Tool 2: Points to Consider along the Clinical Trial Timeline Tool 3: Selected Return of Individual Results Regulations and Resources	Tool 4: Informed Consent Language for Return of Individual Results Tool 5: Checklist for IRB and Ethics Committees	Tool 6: Designation of Third Party Tool 7: End of Study Form		Tool 8: Communication of study results at the end of a trial (including study arm) MRCT Return of Aggregate Results Toolkit[2]

[1] PCP = primary care provider

[2] "MRCT Return of Aggregate Results Toolkit, Version 3.0". Accessed November 1, 2017. http://mrctcenter.org/wp-content/uploads/2017/03/2017-03-13-MRCT-Return-of-Aggregate-Results-Toolkit-3.0.pdf

1. TOOLS FOR THE TEAM PLANNING THE STUDY

Aimed at assisting the study team, this section includes a checklist of points to consider for return of individual research results when planning the clinical trial; links to selected regulations and resources regarding returning individual results; and template informed consent language. In addition to these tools, clinical trial developers should also prepare templates for the documents listed in Section 4 of this Toolkit, "Tools for site staff who return results."

Tool 1: Rationale Matrix for Returning Various Data Types

This tool depicts the justification for returning various data types and is related to **Principle 1**: Providing individual research results responds to the expressed interests and expectations of many clinical trial participants that their results be communicated to them.

Summary of Justification for Return of Results:

There is a strong ethical obligation to return Urgent results and Urgent incidental Findings (Data Type A) in a timely manner. We also recognize a strong ethical justification for return of Individual Study Results (Data Type C - Primary Endpoints, Secondary Endpoints and Study Arm) at the end of the study unless returning these data would compromise the integrity of the current study or ongoing studies or there are significant feasibility issues. There is a counterbalancing ethical duty to respect the expressed preferences of study participants who do not wish to receive research results.

Practical Implementation for Sponsors:

Planned, prospective trials: There is an obligations to return Individual Study Results (Data Type C-Primary Endpoints and Study Arm) if feasible and such return will not compromise study integrity. The consent form should include language to allow participants to opt in/opt out of receiving results. Resources to implement return of results should be prospectively planned and financed. Data Type A – Urgent Results and Urgent Incidental findings should always be returned due to the medical signficiance (and actionable nature) of these results; if such results may be obtained, and the return to either the participant or the primary care provider will not be elective, this fact and the return process should be included in the consent form

Ongoing trials (that have not planned for return of individual results in the consent form or budgeted resources for return of individual results): If participants are still in contact with investigators, or the investigators in contact with participants' heathcare providers and the study is ongoing, the sponsor or study team may revise the consent form to include a section on return of results. If the consent form

explicitly did not allow for return of results, and because Data Type A – Urgent Results and Urgent Incidental findings should always be returned due to the medical signficiance (and actionable nature) of these results, the IRB should be consulted prior to return of these findings.

Completed or Closed studies (that have not planned for return of individual results in the consent form or budgeted resources for return of individual results): The impracticality of finding and re-contacting participants renders the option of returning individual results impractical. In some rare instances researchers may consider returning Data Type A – Urgent Results and Urgent Incidental findings if the results have medical signficiance and/or are actionable; the IRB should be consulted prior to return of these findings.

Part 1A: Completed, Closed or Ongoing Studies (studies commenced or completed)

	Urgent results and Urgent Incidental Findings	**Routine Results and Non-urgent incidental findings**	**Individual Research Study Results (study arm, primary endpoints)**	**Exploratory Results**
Return of results is included in the Informed Consent Form (ICF)	**Strongest** Justification for returning results.	**Strong** Justification for returning results if feasible, study/data integrity will be maintained, and opt-in selected. As highlighted above, the justification is tightly linked to the length of time between results generation and the result it can be made available to research participants.	**Strongest** Justification for returning results, if feasible and study/data integrity can be protected, and opt-in selected.	**Weak** Justification for returning results. Unless the ICF specifically states exploratory results will be returned, there is little justification for return as the significance of these results significance is uncertain.
ICF is silent on returning results	**Strongest** It is not ethically justifiable to wait until after the trial concludes to return urgent information that can impact medical management	**Moderate** Justification for returning results. Ideally the research participant should be prepared for receiving results and have had the opportunity to express whether or not they were interested in receiving this information.	**Moderate** Justification for returning results. Ideally the research participant should be prepared for receiving results and have had the opportunity to express whether or not they were interested in receiving this information.	**Weak** Justification for returning results.

ICF affirmatively states that results will not be returned	**Strong** Justification for returning results to ensure patient safety is protected. In this case, IRB/REC should be consulted and engaged in the decision and process to recontact participant(s) and the disclosure plan.	**Weak** Justification for returning results.	**Weak** Justification for returning results.	**Weak** Justification for returning results.
Return of results is not consistent with laws, regulations and/or policies	**Strong** Justification for returning results may be necessary (urgent, consistent with GCP). In these situations both legal counsel and IRB/REC involvement should be sought.	**Weak** Justification for returning results.	**Weak** Justification for returning results.	**Weak** Justification for returning results.

Part 1B: Planned and Prospective

	Urgent results and Urgent Incidental Findings	**Routine Results and Non-urgent incidental findings**	**Individual Research Study Results (study arm, primary endpoints)**	**Exploratory Results**
Results can be provided in real time[1]	**Strongest** Justification for returning results. Consistent with GCP guidance.	**Strong** Justification for returning results, if feasible, and should be planned	**Weak** Disclosure of results may compromise integrity of study data.	**Weak - Moderate** Justification for returning results. However there may be instances (e.g. whole genome sequencing) where exploratory results may contain information with clinical validity and utility causing moderate justification, if participants knowingly consent to receipt of exploratory results

Result return cannot occur until the trial concludes[1]	**Strongest** It is not ethically justifiable to wait until after the trial concludes to return urgent information that can impact medical management	**Weak - Moderate** Justification for returning results if feasible, and should be planned. Note, results may have different utility if returned long after they were generated. For instance, a hematocrit value may change in time and be less useful at the time it is returned.	**Strong** Justification for returning results, if feasible and study/data integrity can be protected	**Weak - Moderate** Justification for returning results. However there may be instances (e.g. whole genome sequencing) where exploratory results may contain information with clinical validity and utility leading to moderate justification.

[1]The assumption here is that data have been generated in a lab that is certified or accredited according to national and local requirements (in the U.S.: CLIA-certified), that the test itself is clinically and analytically valid, and that provision of the result to the participant will not compromise scientific integrity.

Tool 2: Points to Consider Along the Clinical Trial Timeline

This tool is related to **Principle 2**: Considerations pertaining to the return of individual research results to clinical trial participants should be integrated into the clinical trial and proactively planned.

Concordant with Principles of the *Recommendations for Returning Individual Results* document, these Points to Consider offer a checklist for the study team to use during the planning, recruitment /active trial and post-trial phases for return of individual results activities. All items should be considered, and decisions should be made that take into consideration the context of the specific study.

Checklist for Study Team

	Planning and Design Phase	Checkmark / Comment
	Type of Laboratory	
1.	Is the research procedure performed in a setting and in ways that are equivalent to or different from that of the clinical setting?	
2.	Where and by whom will the research procedure be performed?	
3.	If the research test or procedure is performed in the United States, is the research test or procedure performed in a laboratory that has been certified by under the Clinical Laboratory Improvements Amendment (CLIA) and is using CLIA laboratory procedures to conduct testing? Is the research test or procedure covered under the Health Insurance Portability and Accountability Act (HIPAA)? (Centers for Medicare and Medicaid Services)	
4.	For procedures performed outside of the United States, is there a national standard for validation of laboratory practices?	
5.	Is there documentation of chain of custody of the sample and or other quality control measures in the laboratory/medical setting?	
	Polices and Regulations:	
6.	Do institutional policies, local, regional and national regulations allow and/or require return of individual research results? (Principle 9)	
7.	Are there specific legal and/or regulatory requirements that apply (note many will be silent on this issue)? (see "Tool 3: Selected Return of Individual Results Regulations and Resources")	

8.	Is any institutional review or sign-off required? Does the IRB/REC require consultation, or review and approval? Is an informed consent form required?	
	Resources: **Are appropriate resources for returning individual results available?** Considerations include:	
9.	Are resources available for costs for legal counsel (to analyze applicable country-specific regulations for countries where study sites are located)?	
10.	Are resources available to interpret results to ensure physician and patients can put the result(s) into context? Note, in some instances (e.g. genetic counseling), specialists may be necessary.	
11.	Are resources available for local healthcare and additional diagnostic testing, if necessary?	
12.	Are resources available for site staff training for delivering results and responding to questions?	
13.	Are resources available for preparation, QC and distribution of individual results?	
14.	Are resources available for website development and maintenance (depending on modality of results return)?	
15.	Are resources available for translation costs for results return?	
16.	Are resources available for tracking of participant preferences for return of results opt in/out?	
	Considerations for each anticipated research result **(Principles 2 & 3)**	
17.	**What** individual results will be shared? See Tool 1 and Fig. 2 for data types and justification	
18.	Are results to be returned valid and useful? (Principle 6) What is known regarding the clinical validity (i.e., specificity and sensitivity) of the test and the result?	
19.	Given what is known about the test/procedure, will the results be interpretable?	

20.	Will the result(s) be reviewed and interpretedt the results before being shared with participants? Is the person interpreting the results appropriately licensed? If not, is there access to a professional who is appropriately licensed to interpret the result and, as appropriate, communicate this information to the research participant?	
21.	**When** will individual results be shared relative to when the procedure was performed? Consider the urgency of the findings, when results will be available, and when they can or must be acted upon -- during or after the trial.	
22.	Will the results be available while the participant is enrolled in the trial and/or the trial is still ongoing?	
23.	If the participant is no longer enrolled, is the trial still ongoing? If not, is there a plan in place to allow for the return of results after the trial has concluded? Has the participant been made aware of this plan and agreed to it during the consent process?	
24.	How soon can results be made available without jeopardizing the trial or the safety and welfare of the participant? (Principle 7) Consider preparation time.	
25.	Could communication of the result impact the integrity or bias the outcome of the trial? If so, would results return provided at a later time mitigate this risk? What would be compromised if results were provided at a later time?	
26.	**How** will the results be shared? Consider processes for electronic, paper and interactive means (including phone calls or face-to-face meetings) for sharing results and the unique context of each study's results, each study site, and each participant; consider what will be provided and how; opt in/opt out in informed consent form; and/or sharing results upon request.	
27.	If the appropriate method of communication is through the participant's health care provider, does the informed consent secure permission for such contact?	

28.	**Who** will communicate the result – and with what interpretation if any – to the participant, guardian or legally authorized representative? Consider the role of principal investigator, research nurse and study team, study coordinator, sponsor and/or designee, and healthcare provider. If results are shared after the conclusion of the trial it will be important to plan in advance how results will be communicated so that the research participant is informed of the disclosure plan during the informed consent process.	
29.	What training will be offered to site staff and sponsor staff to prepare them for sharing individual research results? Are there appropriate skills/information/tools for facilitating this process at the site?	
30.	Regardless of the timing of follow up (e.g., urgent, routine), if the result is one that demands referral for clinical care, who will be responsible for such referral? Have the costs of referral been considered?	
31.	Will counseling or other support be offered to the participant?	
	Protocol and Informed Consent Development Phase	
32.	Has the return of results disclosure plan been established and communicated as part of the informed consent process? The plan is necessary to ensure research participants are aware of what results may be returned (and which will not and why), have the opportunity to communicate their interest in receiving information, are prepared for how the information will be delivered/communicated to them, and understand the approximate timing that results may be returned (Principle 3). To plan accordingly consider the following:	
	Tracking participant contact information:	
33.	How will participant contact information be tracked, accessed and utilized?	
34.	Is there a tracking process for return of results preferences and who will manage this?	
35.	How will individual results (study arm assignment and individual endpoint data) be returned after study sites are closed? (Principle 6)	

	Informed Consent document:	
36.	Does the return of individual research results plan comply with GCP In all circumstances and at all times, to protect the safety of participants?	
37.	Does the informed consent document give the participant the option to receive individual results? (Principle 3) Consider: Potential participants should be informed of their right to request and/or to decline receiving results and if the choice is not available (e.g. urgent results will be returned). Potential participants should be informed whether and what results will be returned, and under what conditions. This information should include the fact that, in addition to anticipated results from clinical and research tests and procedures, some results are unpredictable, and some are incidental findings.	
38.	Does the informed consent document include--if results will be offered to be returned--the anticipated timeframe for when the results will be available should be included? Consider: A reminder should be provided at participant's last visit.	
39.	Does the informed consent document inform potential participants whenever results will *not* be returned, or will be returned only in specified circumstances? Consider: It is helpful to explain the reasoning behind any intent not to return. The participant will then be in a position to agree or decline to be in the trial with full knowledge of these limitations.	
40.	If opt-in/opt-out, how will this be tracked, communicated and implemented?	
41.	If opt-in/opt-out, who will have access to the opt in/opt out decisions and permissions?	
42.	Does the informed consent document delineate the role, involvement, and communication plan with the participant's healthcare provider?	
43.	Does the informed consent document make the research participant aware of any results that may need to be disclosed to a participant's health care provider (whether intended or due to unforeseen circumstances)? There may be times when such permission is a condition of trial participation.	

44.	Will potential participants be informed if and when results will be entered into the clinical record and/or in any data-sharing repository? Consider: Occasionally such entry is mandatory and is therefore a condition of trial participation. The participant should be informed of any possibility that the result might affect his or her insurability (e.g. health insurance, long term disability, life insurance, etc.) since the disclosure might impact the decision to participate.	
45.	Do the participants have the opportunity to name a designee (or designees) to receive the results? (Principle 1)	
46.	If a designee is named, how will this be documented, tracked and implemented? Are there legal requirements for who may serve as designee for the receipt of research results, and how this must be documented in the jurisdiction in which the research participant resides? Consider: All country specific regulations should be known and followed. (See sample, Tool 6 in this Toolkit)	
47.	Does the research participant have a clear understanding of what information will be shared with: them directly, their family member, primary care physician, others?	
	Active Trial Phase	
48.	Has appropriate training for the investigative site and sponsor been developed, helping to enable the data disclosure plan to be successfully carried forward?	
49.	Do the investigator and study staff understand what results will be shared and the method for tracking participant interest? Are expectations for documentation clear and communicated (e.g. designee designation, participant receipt of information, length of time, etc.)?	
50.	Does the sponsor understand which individual results will be made available, how and when the information can be communicated, how and to whom information is communicated, how to document results sharing, and how long this documentation should be retained? If results will be disclosed after the trial has concluded, are appropriate processes and SOPs in place and responsible parties aware?	

51.	If the participant receives results directly, does the principal investigator and site staff (and healthcare provider) have access to the same participant data such that they can respond to questions)? Do they have the required expertise to address questions about the results?	
52.	How will patient expectations be managed (e.g. what results will be received and the significance thereof, whom to contact with questions; confirmatory testing and future diagnostic or therapeutic actions)?	
	Post-Trial Analysis Phase	
53.	What and when will data be shared?	
54.	Will any interpretation—but not medical advice—of individual results be provided? (Principle 8)	
55.	Has access to third-party medical interpretation, outside of the trial, been considered?	
	Post-Trial Publication Phase [Public disclosure; after the study site is closed]	
56.	Who will prepare results to be shared with participants?	
57.	Will participants have the opportunity to select from among the results available to receive, and is selection logistically feasible?	
58.	How will participants be contacted when results are available? Will results be returned upon request or automatically?	
59.	Will there be an opportunity for participants to ask questions?	
60.	How will the results be communicated (e.g. internet portal, written communication, in-person meeting) and who will communicate?	
61.	Will exploratory results be shared that become available at different times after the trial?	

Tool 3: Selected Return of Individual Results Regulations and Resources

This tool is related to **Principle 9**: Return of individual research results should be planned and executed in compliance with institutional policies and local, regional, and national laws and regulations.

The links below are current as of the date when this document was issued. Please check for the most current version of the regulations.

Region	Regulations and Resources
	Points to Consider • Identify local individuals, resident in the country ("on the ground") who know and can represent the laws and regulations and their interpretation • Laws and regulations are not static but constantly evolving
International Resources	**Regulations** • U.S. Department of Health and Human Services - Office of Human Research Protection: International Compilation of Human Research Standards (enumerates over 1,000 laws, regulations, and guidelines that govern human subjects research in 130 countries) http://www.hhs.gov/ohrp/international/compilation-human-research-standards/ • McGill and Centre of Genomics and Policy: GenBiblio – Database of Laws and Policies (searchable database of international laws and policies) www.humgen.org
United States of America	**Regulations:** • Clinical Laboratory Improvement Amendments of 1988 ("CLIA") – require that clinical laboratories meet certain quality standards, to ensure reliability of the lab test results https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/ • 42 CFR 493 – Laboratory requirements – require that prior to releasing test results, a lab must demonstrate the analytical validity of a specific test, etc. https://www.gpo.gov/fdsys/granule/CFR-2011-title42-vol5/CFR-2011-title42-vol5-part493/content-detail.html • Health Insurance Portability and Accountability Act of 1996 (HIPAA) – Covered entities are required to give individuals access to the patient information held in a designated record set http://www.hhs.gov/hipaa/

- The Genetic Information Nondiscrimination Act of 2008
  https://www.eeoc.gov/laws/statutes/gina.cfm
  This act prohibits discrimination on the basis of genetic information. This act affects health insurance and employment.

- Genetic Privacy Laws – 50 State survey
  This resource provides a 50-state guide to genetic privacy law, referencing and summarizing the state statutes.

  https://www.healthlawyers.org/hlresources/Public%20Documents/50state_chart_final.pdf

Resources:

- Consortium of Independent Review Boards (CIRB) -
  http://www.consortiumofirb.org/
  Non-profit organization of independent institutional review boards

- Center for Information & Study on Clinical Research Participation (CISCRP) –
  https://www.ciscrp.org/
  Non-profit organization dedicated to engaging the public and patients as partners in clinical research. Provides resources that assist clinical trial stakeholders, including preparation of non-technical, lay-language clinical trial results to study volunteers

- Secretary's Advisory Committee on Human Research Protections (SACHRP) of U.S. Department of Health and Human Resources
  http://www.hhs.gov/ohrp/sachrp-committee/
  Provides expert advice and recommendations to the Secretary of Health and Human Services on issues pertaining to the protection of human subjects in research.
  On return of aggregate summary research results:
  - https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2015-april-24-attachment-d/index.html

  On return of individual research results:
  - https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2015-september-28-attachment-c/index.html

  On return of incidental findings:
  - https://www.hhs.gov/ohrp/sachrp-committee/recommendations/%20attachment-f-august-2-2017/index.html

- Consortium on Law and Values in Health, Environment & the Life Sciences (at University of Minnesota)
  https://consortium.umn.edu/publications

	Publications include articles debating the return of incidental findings in genomics research: On managing incidental findings in human subjects research: ➢ https://consortium.umn.edu/publications/managing-incidental-findings-human-subjects-research-analysis-and-recommendations On managing incidental findings and research results in genomic biobanks and archives: ➢ https://consortium.umn.edu/research/managing-incidental-findings-and-research-results-genomic-biobanks-and-archives ➢ https://consortium.umn.edu/symposia/returning-incidental-findings-and-research-results-genomic-research-biobanks-archives • U.S. Food and Drug Administration (FDA) Public Workshop – Patient and Medical Professional Perspectives on the Return of Genetic Test Results – March 2, 2016 http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm478841.htm "The purpose of this workshop was to understand patient and provider perspectives on receiving genetic test results. The topic(s) discussed focused on better defining the specific information patients and providers prefer to receive, how those results should be returned, and what information is needed to understand the results so that they may effectively aid in medical decision making."

Return of Results implications Under HIPAA / CLIA

(excerpted from Ropes & Gray presentation "Legal Issues in Return of Results to Research Subjects" from Mark Barnes, David Peloquin, March 24, 2017, with permission)

Participants have increasingly requested their research records that have been generated during and as part of clinical research. Research data may in some cases be generated by testing in in non-accredited (e.g., CLIA non-certified) labs:

1. Joint HIPAA/CLIA Rule (2014):

With intent to harmonize CLIA and HIPAA on individuals' access rights, a joint CMS/OCR rule was issued on Feb. 6, 2014, with a compliance deadline of Oct. 6, 2014.

- Rule amended CLIA to permit CLIA-certified laboratories to give completed test results directly to a patient or patient's representative
- Rule amended HIPAA to require laboratories that are "covered entities" subject to HIPAA to provide patients access rights to their protected health information (PHI) held

in a designated record set (DRS). The DRS includes a covered entity's medical record, billing record, and other records that are used in whole or part by the covered entity to make decisions about the individual.

2. A regulatory conflict exists between HIPAA and CLIA

- CLIA prohibits returning results to individuals for the "diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of, human beings" if results not generated in a CLIA-certified laboratory *See* 42 C.F.R. § 493.2; Centers for Medicare and Medicaid Services (CMS), Research Testing and CLIA Regulations. CMS representatives have in public presentations interpreted this provision as prohibiting the use of results from a research laboratory to refer an individual for re-testing (even if a potentially actionable result is found) at a CLIA-certified laboratory. In contrast, HIPAA requires providing access to information held in the DRS, which may include research test results, depending on whether the test results are included in the covered entity's medical record, billing record, or otherwise used to make decisions about the individual, such as determining whether to offer the individual enrollment in a research study.

3. A clinical laboratory has no obligation under HIPAA to create explanatory materials, but it has the option to do so.

> There is no requirement under the HIPAA Privacy Rule for the clinical laboratory to interpret the test results for an individual if the laboratory does not ordinarily perform interpretation. The laboratory may include a disclaimer, caveat, or other statement explaining the limitations of the laboratory data for diagnosis or treatment or other purposes. The laboratory may also provide educational or explanatory materials.

See Tool 4 for related informed consent language.

Tool 4: Informed Consent Language for Return of Individual Results

This tool is related to **Principle 3:** The informed consent process should include information about the sponsor's intention regarding the return of research results and allow for discussion of participant's preferences to receive these results. It is also related to **Principle 5**: If results are offered, participants should be able to choose whether or not to receive their individual research results.

This tool is intended to provide an overview of what to include in the informed consent document in regard to returning individual results as well as sample language that can be used in informed consent forms in order to describe to participants how their individual results may be returned.

1. Key Questions to Consider for Informed Consent Document

- Is the result an urgent, actionable finding? (Principle 7)
- Has the participant expressed a desire (e.g., opted in) to receive results? (Principles 1 and 5)
- Is the result analytically valid? (Principle 6)
- Does the result have clinical validity? (Principle 6)
- Does returning the result at a given time impact the integrity of the study? (Principle 7)
- Does returning the result comply with institutional policies, legal and national laws and regulations? (Principle 9)
- Is the Informed Consent Form explicit as to whether individual research results will be returned?
- Does the participant have a choice to request access to results or decline receiving results?
- Will some individual results (e.g. exploratory) not be returned? Is a rationale given for this decision?
- Will some individual results (e.g., urgent findings) be returned in any case?
- What is the timeframe for returning what kind of results?
- Will raw data be returned if requested by participant?
- What level of interpretation, if any, will be provided?
- What is the appropriate means of communication (e.g., participant's health care provider)?

Additional considerations:

- The participant's health, understanding, and well-being
- What data elements become available at which time during the clinical trial
- How to balance returning small amounts of data with limited benefit potential versus waiting for more complete individualized data sets that can be interpreted in the context of aggregate results
- Whether providing information in real-time is beneficial for the participant versus providing data after the trial has ended.

2. Considerations for Informed Consent Document and Process in Genetic/Genomic Research[3]

Purpose of Study: Participants should be informed of the purpose for the genetic/genomic portion of the study and that samples will be used for genomic/genetic research.

- Define genomic/genetic research in general and how it fits in with the overall study purpose/objective (what is being studied, why and how)
- Explain primary as opposed to secondary or exploratory objectives, if applicable

Confidentiality and Privacy: Address procedures for maintaining confidentiality

- Explain the level of certainty with which the data has been deidentified or anonymized, or whether there will be identifiers linked to genetic/genomic data or material
- Describe plans for security of genetic/genomic data/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

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.

Secondary Use/Re-use of Samples or Data

- Inform participants if other researchers may be given access to samples or genetic/genomic data (with or without direct or indirect identifiers)

[3] The considerations for genetic/genomic research informed consent were adapted from Selwitz, 2014, "Issues to be Addressed in Obtaining Informed Consent Involving DNA Banking and Genetic Research." Available at: https://www.research.uky.edu/ori/ORIForms/D57-Issues-to-Address-Informed-Consent-in-DNA-Genetic-Research.pdf, accessed November 1. 2017

- Give participants option of consenting or refusal to future/secondary use
- Inform participants if/how they may be re-contacted (and by whom)
  or
- Give participants option to indicate if willing to be re-contacted
- Participants may want to limit use of sample and associated data

Potential Risks to Consider

- Social Risks: Breach of confidentiality could impact insurability, employability, reproduction plans, family relationships, immigration status, paternity suits, stigmatization
- Psychological Risks: If information is disclosed, impact of learning results; impact if no effective therapy exists; psychological stress for family members
- Physical Risks: Physical risks associated with collecting samples for research purposes
- Unknown Risks: Participants should be informed that there may be risks of which we are currently unaware

Examples of Variables Potentially Impacting Risks

- What is currently known with respect to the gene and disease being studied?
- Will identifiers be linked directly or indirectly to the samples? (define how)
- Are safeguards for maintaining confidentiality adequate?
- Will participants be informed of test results?
- Does an effective intervention/therapy exist?
- Will the investigator collect more tissue than needed for clinical purposes?
- Are family members included in the study?

Benefits

- Inform participant of no direct benefit, if applicable
- Inform participants of uncertainties regarding benefits
- Include other potential benefits as appropriate: advancement of knowledge; clinical relevance to individual, family, or society as a whole; long term benefit if investigator plans to re-contact participants to disclose clinically relevant information

Alternatives

- Explain if the genomic/genetic component of the study is optional or required
- If required, the alternative is not to participate in the study

Costs to Participant (if not already part of the main consent): Inform participant of any costs not covered in study such as the costs of genetic counseling

Duration: Participants should be informed of sample storage and destruction timelines/logistics

Control of the Specimens/Materials (if not already part of the main consent)

- Explain who controls the specimen/materials (e.g., custodian)
- Participants should be informed if research could lead to commercially valuable product and whether participants will receive a portion of any profits

Significant New Findings: Discuss policy regarding willingness to inform participants if later tests have clinical relevance and whether participant wishes to know

Withdrawal from Research Study (if not already part of the main consent)

- Inform participants of rights to withdraw without penalty and include procedures for doing so
- Inform participants of procedures for subsequently requesting that samples/materials be destroyed, or
- Inform participants of procedures for subsequently requesting that identifiers be removed from materials
- Describe any limitations on ability of participants to withdraw data or genetic samples

3. Sample Language

The following model language can be used or amended for the "return of results" section of an informed consent document. Section headings are *Elements of the Consent* for consideration by teams as they develop the processes for returning individual results.

Introduction:

You will have the opportunity to receive results that emerge from the trial *[define the types of data expected; e.g. screening results, individual end of study results]*. Some results will be available during the trial and some will be available at the conclusion of the trial or after the results are analyzed (and some will be available after the trial in cases of sharing exploratory results). Please know that the delay in receiving results may be long.

Opt-In to Receiving Results **Sample Text**

Results listed below will be available to you during or after the trial

- Xxxx
- Xxxx
- Xxxx

The results listed below will not be available to you at any time during or after the trial:

- Xxxx
- Xxxx
- Xxxx

Please indicate by signing below if you would be interested in receiving these results.

_____

SIGNATURE OF PARTICIPANT INDICATING INTEREST IN RECEIVING RESULTS

The study team will offer to return certain results to you after the trial is completed (estimated on or about xxx date). You will be asked again (or, during your last study visit) if you would like to receive these results. Of course, under some conditions, the study team may not be able to do so.

Results Returned to Primary Care Physician **Sample Text**

Your doctor in this study has [describe procedure, e.g., removed some tissue, taken blood and urine samples] to do some tests. The results of these tests will be given to your primary care doctor and might be used to plan your care. Your primary care doctor may discuss the results with you.

Results Returned to Participant

Screening Results **Sample Text**

You will receive the results of the screening tests even if you are not eligible to join the [Study name] study.

(For some tests, such as HIV or pregnancy tests that were performed, include list here…)

You will be told your results as soon as they are available. You may talk with the study staff about the meaning of your results and if you have further questions.

***Primary Endpoint, Study Arm and Aggregate Results* Sample Text**

When the results of the [Study Name] are available to share we will inform you of the overall summary results of the study. We will also share your individual results with you if you requested that, approximately at *[add number]* months after we made the summary results available, via *[add means by which results will be shared, e.g., letter, phone call, visit in our office, on our website for overall results etc.]* Your individual results will include which study group you were in (e.g., what treatment you received) and may include the measurements that we took from you (e.g. blood results, images, survey results) and, if appropriate, how they compare with other participants in the trial.

***Exploratory Results / Genomic Data* Sample Text**

In the course of the research, we may generate results that could be of medical significance or personal use to you. In those cases, we reserve the right to contact you and provide the option of receiving those results. If you do not hear from us, this does not mean you should not continue with regular medical care.

The researchers do not plan to contact you or your regular doctor with any results from tests done on your stored blood, fluid or tissue samples or DNA results from your sample of blood. This is because research tests are often done using ways that are experimental, so the results do not usually help doctors manage your health. Neither your doctor nor you will receive results of these tests and we will take measures to protect your results to the extent possible. If you have any questions, you should contact [Principal Investigator] at ___-___-____.

Nevertheless, sometimes researchers decide that a test result is so important for your health that they will notify your study doctor; your study doctor may then try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your contact information. If you want your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name and contact information.

If anticipating that a positive result generated in a non-CLIA lab may have future implications for a participant's health, language may be inserted such as the following to ensure that CLIA regulations are followed (see Tool 3 above).

If a result is obtained in the xxx test for yyy that the institution believes is important for your health, your doctor may order a validated test from a laboratory certified to perform this type of test.

Note: Refer to GINA – Genetic information nondiscrimination act of 2008 if relevant, see Tool 3

***If Providing an Option to Receive Genomic Data* Sample Text**

Define genomic results (refer to footnote [4] for useful language)

Your genetic test result will be provided if you choose to receive it.

Please initial whether or not you wish to receive your genetic test result

_____ I wish to receive my genetic test result

_____ I do not wish to receive my genetic test result

If you choose to receive your genome sequence data, please note you may wish to consult with a genetic counselor regarding the results.

***Biospecimen Storage and Future Research* Sample Text**

As part of this study, we are obtaining samples of your blood *[specify other fluid type, e.g., CSF, urine]* and tissue [*specify tissue type (e.g. skin, tumor)* from you. If you agree, the researchers would like to store your leftover samples for future research.

You will not receive any direct benefit from donating your samples. Research performed on these samples may provide additional information that will be helpful in understanding [Condition], as well as similar and other conditions and may benefit other patients in the future.

It is possible that your samples might be used to develop products or tests that could help future patients. You and your family will not receive any financial benefits or compensation from, or have rights in any developments, inventions, or other discoveries that might come from this information.

If a rare situation comes up in which the researchers decide that a test result may be important for your health, the researchers will notify your study doctor and your study doctor will try to contact you. If you have any questions, you should contact [Principal Investigator] at ___-___-____.

As an example of an additional resource for model consent, see:

*"***Model Consent Content for Genome, Exome and Other Genomic-Related Analysis**"

NIH National Cancer Institute, download from: https://cdp.cancer.gov/resources/elsi/ethical_informed_consent.htm, scroll down to: "Model Consent Content for Whole Genome, Exome and Other Whole Genomic-Related Analysis" (accessed November 1, 2017)

[4] https://cdp.cancer.gov/resources/elsi/ethical_informed_consent.htm;
Exploratory result or specific test defined in trial primary or secondary objectives. In the latter case you may be able to specify the actual test while in the case of exploratory you cannot.

2. TOOLS FOR INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEES

This section includes a checklist for the Institutional Review Board/Ethics Committee ensuring that the study protocol and informed consent form include pertinent sections for return of individual results to study participants.

Tool 5: Checklist for Institutional Review Board (IRB) and Ethics Committees [5]

This tool is related to **Principle 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 humans participating as subjects in a research study have been protected.

There are three different time frames in which investigators or sponsors may plan to return individual study results to participants: 1) the plan may be introduced in the initial protocol; 2) investigators or sponsors may choose to incorporate the return of individual study results into ongoing trials--a change that would require approval by the IRB/REC; and 3) investigators or sponsors may decide to provide a summary of individual research results to participants for studies that are already completed and closed. If the study is closed, the decision may not need to be reviewed or approved by the IRB/REC as the IRB/REC no longer has oversight responsibilities. Some exceptions may apply (e.g. if the decision to return results contradicts what was stated in the informed consent), then consultation with the reviewing IRB/REC is recommended.

This worksheet aims to assist IRB members and Ethics Committees in their role to support the return of individual results to study participants. The U.S. regulatory criteria for IRB approval at 45 CFR 46.111(a)(1-7)(b) and 21 CFR 56.111(a)(1-7)(b) are used here. The worksheet may need to be adapted for other agency and governmental regulatory requirements, including those with oversight in international and transnational settings.

[5] This tool is modified from *MRCT Return of Results Toolkit Version 3.0*, "Ethics Committee Checklist for Aggregate Research Results Summaries," http://mrctcenter.org/resources/2017-03-13-template-mrct-return-of-aggregate-results-toolkit-version-3-0/ (accessed 12 November 2017)

Regulatory Criteria for IRB Approval			
Determine whether the plan for return of results meets criteria for approval. If YES, note protocol-specific information that supports your determination. If NO, note specific changes the investigator must make to meet this criterion. If UNKNOWN, note additional information needed to help you decide whether the criterion is met.			
(1) Study protocol and/or Informed Consent Form describes whether and which results will be returned, and timing for results to be returned. If yes: • Is the protocol clear in distinguishing between data types: routine results, urgent results, incidental findings, and exploratory/genetic results?	☐ YES	☐ NO	☐ UNKNOWN
• Is there an opt-in or opt-out option?	☐ YES	☐ NO	☐ UNKNOWN
(2) (if Yes to #1) Templates are provided to aid in the communication of results to participants. • Have template documents and pre-planned information letters been submitted for IRB approval? or	☐ YES	☐ NO	☐ UNKNOWN
• Has a website been prepared to communicate results to participants and language submitted for IRB approval? Will participant privacy be protected?	☐ YES	☐ NO	☐ UNKNOWN
• Has the plan for how results will be returned been reviewed?	☐ YES	☐ NO	☐ UNKNOWN
(3) Risks to participants are minimized by using procedures that are consistent with sound research design. • Are results going to be validated if the plan includes assurances that only validated results will returned (taking into account medical significance, analytical validity and medical actionability) to prevent ambiguous or incorrect information from being returned to participants?	☐ YES	☐ NO	☐ UNKNOWN

• Are there adequate provisions in place in the local healthcare setting for confirmatory testing if necessary, clinical follow up, and counseling. Is it clear to the participant how to access these resources and how costs and charges will be paid?	☐ YES	☐ NO	☐ UNKNOWN
• Have risks been adequately addressed and minimized? Particular attention should be paid to privacy concerns and potential psychological stress, as well as the nature and mode of communication with participants (including genetic counseling).	☐ YES	☐ NO	☐ UNKNOWN
(4) Risks to participants from returning results are reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result. Risks include any physical, psychological, social, legal, and economic risks to participants. • Are these risks clearly communicated in the informed consent form to research participants? Are benefits appropriate and not overly stated?	☐ YES	☐ NO	☐ UNKNOWN
• Are procedures and/or safeguards in place to insure that benefits can be realized (i.e. that participants have the ability (in terms of funding as well as their stage of illness) to act on "actionable" information?	☐ YES	☐ NO	☐ UNKNOWN
• Do the possible benefits of the information (e.g. clinical action, knowledge) outweigh the risks of disclosure (e.g. false positive results, psychological stress)?	☐ YES	☐ NO	☐ UNKNOWN
(5) Selection of participants for receipt of individual results is equitable. • Are all appropriate participants (e.g. consented and/or randomized) offered the information?	☐ YES	☐ NO	☐ UNKNOWN
• Are any participants excluded from access to information without appropriate justification?	☐ YES	☐ NO	☐ UNKNOWN

(6) The participant has the ability to access the individual results or to decline access to the information. Each prospective participant or their legally authorized representative may make an informed choice as to whether to receive the information. • Are all participants able to opt-in or opt-out of receiving the information?	☐ YES	☐ NO	☐ UNKNOWN
• Is there a plan for tracking these decisions? Consider if re-consent is needed based on the time between when consent is obtained and results are made available.	☐ YES	☐ NO	☐ UNKNOWN
• Are procedures for communicating results respectful of the wishes of the participants?	☐ YES	☐ NO	☐ UNKNOWN
(7) If returning the research results could involve more than minimal risk to participants, the communication plan includes adequate provisions for how the participants will be monitored to ensure participant safety.	☐ YES	☐ NO	☐ UNKNOWN
(8) Is there a provision in the consent that will cover who will receive results in the event the participant is unable / deceased and a plan in place to assign a designee?	☐ YES	☐ NO	☐ UNKNOWN
(9) There are adequate provisions to protect the privacy of participants and to maintain the confidentiality of individual participant data.	☐ YES	☐ NO	☐ UNKNOWN
REVIEWER'S COMMENTS			

3. TOOLS FOR SITE STAFF WHO RETURN RESULTS

This section includes:

- Sample authorization form for designation of a third party
- Helpful forms for: use at end of study, and returning individual results in the context of aggregate results
- Sample notification letter for returning individual results after unblinding

Templates for these forms and letters will be prepared by the study team that plans the study. Once approved by the IRB/REC, these forms and letters will be used by the site staff who return results.

Tool 6: Sample Authorization Form: Designation of Third Party

This tool is related to **Principle 1**: Providing individual research results responds to the expressed interests and expectations of many clinical trial participants that their results be communicated to them.

The following example can be used if the trial participant wishes to designate a third party to receive individual research results. Note that this form can be used at the beginning of the trial or, with some modification, during the trial if the participant so wishes.

[Trial Title] (include simple title and identifying numbers)

Authorization for Third Party to Receive Research Results

During this trial, I may not be in a position to receive research results about me. As I instruct here, I would like those results to be shared with the person(s) below.

Participant, patient, parent/Legal Guardian Name: _____

Participant's Name (if different): _____

Street Address, City State :

_____

Phone: _____ Date of Birth: _____

I request that information about me that you obtain during or after this trial, be released to:

Designee Name:

_____

Street Address, City, State:

_____

Phone: _____ Relationship: _____

My signature below indicates that I understand what information will be released.

I further understand that the information to be released may include information regarding *[mention specific potentially sensitive information, e.g. drug and alcohol use or AIDS/HIV]. [If applicable]*

I understand that I may revoke this consent in writing at any time, but that it will remain valid to the extent that action has already occurred based on this authorization.

Signature: *Participant, Patient, Parent/Legal Guardian* _____

Relationship _____ Date _____

Tool 7: End of Study Form

This tool is related to **Principle 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.

Background

The participant's last study visit is not necessarily a visit at which specific information will be available or communicated. That said, study participants often anticipate that, at the close of their participation, results will be returned. Indeed it is common for participants to believe that they will hear "how they have done" and even the results of the study contemporaneous with their final visit, only to learn that the study has not ended and it may be some time before results are available. Therefore, the participant's last study visit is an opportune time to—again—express appreciation for the participant's volunteerism and set expectations for the future including the timing and process for return of results. It is recommended that site study staff be provided with a prepared document that will enable them to communicate expectations regarding follow-on interactions as well as whether, which and when individual and/or aggregate summary results will be available to be returned. The National Health Service (NHS) in the United Kingdom has developed a detailed information sheet to guide communications with participants during their last study visit. [6] Their guidance recommends that, at a minimum, this information should include:

- How those that have participated in the research can access the study results. As a rule, all participants should be routinely informed as to how they can access the study findings.
- How those who would rather not see the findings can opt out of the process, if this has not been communicated already.
- An acknowledgement of the contribution they have made to research and the improvement of healthcare." [7]

The Study Team should prepare the "End of Study Form" in advance. The Site Teams can adapt the form for their use. The Patient Information Sheet may require translation that should be completed in advance.

[6] NHS "End of Study Guidance." Accessed November 1, 2016. http://www.hra.nhs.uk/documents/2014/09/information-participants-end-study-guidance-researchers.pdf

[7] NHS "End of Study Guidance." Accessed November 1, 2016. http://www.hra.nhs.uk/documents/2014/09/information-participants-end-study-guidance-researchers.pdf

Headings and guidance in the Sample "End of Study Form" below are adapted from the NHS Guidance; this content has also been adapted from the MRCT Return of Aggregate Results Summary Guidance Document (version 3.0). [8,9]

Sample End of Study Form:

[Trial Title]

Include simple title and identifying numbers.

Introduction

Explain to participants that their involvement in the study is coming to an end. This form will establish expectations for the information that they can expect to receive, if they opt-in to receive it. Include a comment thanking the participant for their contribution to this research.

How will the results of the research/my individual results be made available to me?

Explain the various communication options that are available to participants, based upon what options were offered in the informed consent form. If necessary, study reference numbers should be provided to request results of the study from a website, mail, or telephone system.

Explain to the participant if certain results will not be provided or will be provided at an unspecified future date. E.g.,

- It will take some time until information is gathered from all participants in this study. We expect to complete data gathering around (month/year).
- It will take us about (e.g. one year) to analyze and interpret the results of the study. You can expect to hear from us around (month/year). At that point, we hope to provide you with your individual results (define what type of results will be returned) and how they fit into the overall results of the study and (if blinded study) which treatment you were assigned to. We cannot promise that this information will be available at that point, but we will try. Please keep us informed if your contact information changes, since it will be difficult for us to provide you with the results generated after the study if we cannot reach you.
- *For a longitudinal study:* This study will gather data over many years. We hope to give you occasional updates, approximately every (#) years; the next update is scheduled for (month/year). At that time, we hope to provide you with your individual results and how they fit

[8] Ibid.

[9] "MRCT Return of Results Research Results Summary Guidance Document, Version 2.1". Accessed November 1, 2016. http://mrctcenter.org/wp-content/uploads/2017/03/2017-03-13-MRCT-Return-of-Aggregate-Results-Toolkit-3.0.pdf

into the overall results of the study. We cannot promise that this information will be available at that point, but we will make our best efforts.

Keep in mind that while participants may have elected to or not to receive results at the start of the trial, their preferences may have changed during the trial. Study staff should confirm the participant's choice and contact information. If their preference has changed, study staff should record the participant's current preference on this form. This information should be tracked and documented; e.g., in study site files. Participants may also wish to indicate a designee to receive results.

When results from your research study are available, you have the option to receive these results. They can be communicated to you in the following method:

On your informed consent form [Dated:_____] you indicated that you [did / did not] wish to receive these results. If you wish to change your response, please indicate this choice below:

I do wish to be contacted to receive my individual research results:_____

I do NOT wish to be contacted to receive my individual research results:_____

I wish to assign a designee to receive my individual research results on my behalf:_____

Name of Designee(s):_____

Contact Information for Designee: _____

Mailing Address for Designee:_____

Signature:_____ Date:_____

Study Staff:_____ Date:_____

Will I be given any results about me as an individual?

Describe clearly which results will be communicated: routine results, research results, incidental findings, and/or genomic findings.

When study information is typically provided but will not be for this particular study, describe to the participant why this is the case (for example, if the IRB/REC has recommended not to return results that are either experimental in nature or indicative of a genetic diagnosis for which there is no available treatment).

Which arm of the study was I in?

If a significant amount time is required before this information can be released, inform the participant of the expected timeline. Only on very rare occasions for urgent medical management is it necessary to break the code and tell the study participant which treatment arm they were on.

Who may contact me in the future? Who will have access to my personal data?

In some cases, participants may be contacted if adverse events are uncovered that may impact their health. Every effort will be made to contact the participant using the contact information available.

A reminder of the privacy policy can be provided to the participant to answer any questions about who will have access to their personal contact information after the study is complete. Participants can be given an opportunity to review and amend their contact information, which will be stored in case the study team must contact the participant in the future.

Participant Contact Phone Number: _____

Participant Contact Email Address: _____

Participant Contact Visiting Address: _____

Participant Designee, in unable to reach using the above details: _____

If I have any questions who should I contact?

If participants, designees, or family members have additional questions (if designees or family members have been given permission in the consent form), provide them with adequate contact information that will remain active even if the study site is expected to be closed at the conclusion of the study.

Contact Phone Number: _____ Contact Email Address:_____

Contact Visiting Address: _____

Permanent Contact Mailing Address (Study Sponsor or CRO): _____

Additional Content

- These results were collected as part of a research study that gathered information about groups of people. This study does not and cannot substitute for appropriate clinical care and advice for individual participants. You should continue to receive your medical care from your healthcare provider.
- It is important that you get information from a medical professional (either your primary care physician or the study investigator) to help you make sense of your individual results.
- Some of these results may not be acted upon right away but might become useful in the future.

Tool 8: Sample Form: Communication of Study Arm and Individual Study Results at the End of Trial

This tool is related to **Principle 6**: Sponsors and investigators have an obligation to return individual research results responsibly, taking into account medical significance, analytical validity and personal utility. It is also related to **Principle 8**: The purpose of research is not clinical care, and return of individual research results cannot substitute for appropriate clinical care and advice.

This letter and template for unblinding study arm and communication of individual study results at the end of study is intended as an example of how a team might consider sharing these results in the context of aggregate findings. This form is intended to accompany the release of aggregate results.

Workflow:

While the study sponsor will prepare the release of aggregate study results, the study site will fill out the forms for releasing individual level results. Study design needs to include time and resources for investigator or site staff to share results with study participants.

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

		[Study Name] Participants For Ages [X – XX] Years [Total =xx patients]	
	YOUR INDIVIDUAL RESULTS	**RANGE [the lowest and highest "normal" value]**	**MEAN [the average value for all participants in the group]**
Primary Endpoint 1			
(Secondary Endpoint)*			

* While the primary endpoint(s) may be communicated, there is no agreement on whether secondary endpoints should or need to be communicated. It is reasonable to consider significant safety or other events that would impact the interpretation of primary endpoint(s). Notably, any intended selection of secondary endpoints should be determined in advance, and generally included in the informed consent for clarity. Finally, if secondary endpoints are selected, such selection should be fair and balanced.

Note that some investigator teams and sponsors will communicate the results not only of the group to which the participant was assigned but the range and mean of each of the study groups (in this example, Group A, B, C). Presentation of more complete information may be helpful for participants to understand the relative significance of their own result.

4. CASE STUDIES

This section includes case studies of individual results from the Return of Individual Results Workgroup and analyzes them through the lens of the "Considerations for returning individual results" from the *MRCT Center Return of Individual Results to Participants: Recommendations Document*. These case studies are for illustration purposes only to assist the reader to grasp the complexity of returning results.

Case Study 1: HER2 Negative Metastatic Breast Cancer

Sponsor conducted a large, disease-based, observational study of more than 1,200 women with HER2-negative metastatic breast cancer. Sixty-five percent (*n=~780*) of enrolled participants also participated in a sub-study for future exploratory research and donated tissue samples. Tissue samples from the substudy were centrally retested for HER2 status and compared to the results reported by the enrolling center. Sixty-four percent (*n=~500*) of these samples were suitable and included for centralized HER2 testing using IHC and FISH assays.

Retesting through centralized labs and confirmatory testing found that 22 samples were determined to be HER2-positive and had been incorrectly classified as HER2–negative. Of these 22 samples, 18 had been tested by a local lab using only one testing method.

Accurately determining HER2 expression is critical in breast cancer because the results have significant impact on treatment decisions regarding HER2 targeted therapies and possibly clinical outcomes.

The tissue sub-study informed consent form stated that individual research results would not be given to the study site investigators, patients, or treating physicians. However, because the results significantly impact patient care, the sponsor and the Study Steering Committee decided that study investigators whose patients' tumors were determined to be HER2-positive upon retesting by central labs and confirmatory testing be informed. This decision was made after seeking both legal and ethical advice. It was then up to the study investigator, exercising independent professional medical judgment, whether to inform the patient.

Return of Individual Results Framework Analysis

Challenges	• Informed consent form stated that research results would not be given to the patient, investigator, or any of patient's doctors • No direction given regarding communication of results to patient
What?	• HER2-positive results were shared with investigator • Results were generated in CLIA certified lab using FDA approved assays with confirmatory retesting • Results were actionable

When?	• Sub-study started May 2008 • Discordance in results first observed & testing ongoing – Sept 2010 • Letter and results to investigators – March 2011 • Sub-study completed in 2013 • Aggregate results published in peer-reviewed journal in June 2014
How?	• Letter and lab report sent to investigator • Investigator communicated to the patient directly
Who?	• Sponsor does not collect individual identifiable information from patients to contact them • Results were returned to investigator who is also the patient's treating physician • Investigator/treating physician role to exercise professional medical judgment regarding sharing results with patients and impact on treatment decisions

Points to Consider:

It is challenging to anticipate return of individual research results to patients when drafting informed consent forms for rather broad future research purposes.

Notwithstanding the informed consent language, the fact that the results were 1) actionable for treatment decisions and clinical outcomes, 2) the study design was intended to include only HER-2 negative patients and 3) performed in CLIA-certified labs using FDA approved tests, favored the ethical decision to return the discordant research results.

Case Study 2: Clinical Trial of Asthma Inhalers with Incidental Findings

In a clinical trial for an asthma inhaler, a 66-year old woman was screened for inclusion in the trial. The screening laboratory result returned an ionized calcium level of 8.6 ng/dl (normal for age: 4.8-5.7 mg/dl). The potential participant was not yet enrolled in a trial.

This laboratory value was not included as an inclusion or exclusion criteria, and the informed consent was silent on how to approach screening results and specifically a calcium value. Nevertheless the investigators felt that this was an "urgent" result requiring immediate action. Even though there was no clarity in the informed consent document as to whether these results should be returned to the patient, it was a medically actionable, urgent result, and the investigators immediately told not only the potential participant but asked her for the contact information of her healthcare provider. In the US, returning results would require that the tests were conducted in a CLIA-certified laboratory; the investigators did not think it would be medically responsible to repeat the test before taking action.

Analysis

Challenges	• Informed consent was silent on whether to return screening results • The result was urgent and actionable • Clarify whether to return to participant or health care provider and conditions for each • Calcium value was not included as inclusion or exclusion criteria • Need clinical guidance on the severity and urgency related to returning incidental findings • In US, results must be from CLIA-approved lab; elsewhere less clear
What?	• Abnormal lab values
When?	• Depending on severity, results should be returned ASAP
How?	• Prepare patients such that they could receive information that is related to their health care
Who?	• Investigator was not the participant's treating physician in this case • Investigator informed the potential participant immediately because it was an "urgent" result requiring action • Documentation of "handoff" was needed

Points to Consider:

This case demonstrates that the planning of any study should include consideration of results obtained from screening procedures and communication plans at the very outset of participant engagement, before the processes outlined in an informed consent document are operative. These plans should ideally be detailed in the study protocol, and reviewed and approved by the institutional review board/research ethics committee.

Case Study 3: Biomarkers for Early Prostate Cancer

Investigators are uncovering potentially sensitive and specific new biomarkers for early prostate cancer. De-identified excess blood bank products (i.e., samples that have been stripped of identifiers and replaced by a code) are used as a source material. The investigators routinely measure Prostate Specific Antigen (PSA) as a control for comparison to any novel biomarkers. From the first batch of 160 samples, 12 samples have baseline PSA levels >1.0 ng/ml, four samples >3.0 ng/ml, and two samples are >20.0 ng/ml.

For reference, a PSA level of 1.0 to 1.5 ng/ml, correlates with a likelihood of prostate cancer being diagnosed over the next 5-years of approximately 15%. A baseline PSA level of 3 to 10 ng/ml correlates

with a likelihood of prostate cancer being diagnosed over the next 10-years of approximately 40%[10]. For PSA levels of 20-29.99 ng/ml, the predictive value of PSA is more than 70%.[11]

The investigators inform the blood bank of the result and learn that the director of the blood bank has retained the code linking the sample to the identified donor. Investigators approached IRB for guidance, since the informed consent document executed for blood bank donation permitted secondary research on donated blood, but the return of research results was not specifically addressed at the time.

In brief, the investigators were concerned that they were now in possession of information that may be considered "actionable" to participants. The investigators considered the results neither "urgent" nor "routine." As mentioned, the informed consent document did not consider nor mention return or research results (and therefore neither opt in nor opt out). The PSA values were obtained from a research laboratory, not a laboratory that was CLIA-approved or equivalent certification. Therefore the validity and quality of the result is questioned, but nevertheless, potentially medically, socially, and/or personally useful to the participant. The investigators thought it important that the results be returned in a "timely" fashion. There were no institutional policies applicable to this situation. However, in the US the applicable regulations (CLIA and CMS) are not aligned and give conflicting advice.

The investigators felt uncomfortable not acting upon the results that they had obtained. Because the blood bank samples were de-identified (the director of the Blood Bank retained the code allowing re-identification of the donors) and not anonymized, and because the informed consent document had not considered the return of results, the investigators queried the institutional review board (IRB) for advice. The IRB recommended that researchers should contact all the participants with higher test values, not just those with highest test values and return their data.

Analysis

Challenges	• CLIA-approved diagnostic in a non-CLIA lab • Results not requested by patients nor did they know of study • Research was to be done on de-identified samples, though blood bank maintained code • Whether to return at all not clear (ICF silent)
What?	• PSA value tests performed on discarded blood bank specimen
When?	• In a timely fashion
How?	• Informed Consent stated (1 line) that blood could be used for research but otherwise silent on return of results • IRB consulted

[10] http://prostatecancerinfolink.net/2015/04/10/correlating-baseline-psa-levels-to-future-10-year-risk-of-prostate-cancer-diagnosis/ (accessed 11/16/2016)

[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2574301/ (accessed 11/16/2016)

Who?	• IRB, recommended that researchers should contact all the participants with higher test values, not just those with highest test values and return their data.

Points to Consider:

This case illustrates how critical it is to address the potential for the return of results in the planning stage of every study, including biomedical specimen repositories and when considering sample distribution.

Case Study 4: Discovering Sexually Transmitted Infections in a Cohort Study in SE Asian Country

A research collaboration in a Southeast Asian country conducted a research study for adolescents and young adults who were recruited as healthy volunteers. The study followed these patients over a period of time to study factors related to infection of human papillomavirus (HPV) infection. Study patients were from two populations: an HIV-positive group and an HIV-negative group of healthy volunteers. The study focused on identifying factors related to infection with HPV. As a part of the study, participants (females and males) in both groups routinely had a panel of lab tests to screen for a number of sexually transmitted infections (STI). The laboratory tests used to screen for STI in the study is based on nucleic acid amplification assay which provide higher sensitivity than the conventional Gram's stain and culture used to diagnose STI among symptomatic clients. It was observed that about 10% of participants had a positive result for at least one STI; the majority were asymptomatic. While the follow-up for study patients was scheduled every six months, a more rapid intervention was required for those who were discovered to have a positive STI result.

During the screening, participants were informed that their HIV test results would be returned if they were HIV-Positive, so that treatment could be initiated at a local hospital, but it was not written in the ICF or protocol. This disclosure and counseling is common in this country's practice setting and is in the national treatment guideline. The disclosure to the individual's sexual partners was not explained in the ICF.

Participants who received a positive laboratory result were contacted by study staff and asked to return to their primary care hospital as soon as possible for STI treatment. In cases where the patient was in the HIV-positive arm of the study, the site Principal Investigator (PI) could contact the participant's primary HIV care provider (PCP). The PCPs were informed of the STI testing results and were responsible to follow-up with the patient. In the group of healthy volunteers, participants often did not have a PCP, and some were not able to easily return to the tertiary hospital for further care. In these cases, the site PI was consequently not able to contact a PCP to ensure that the proper education and follow-up would take place, and so attempts were made to notify the participants directly.

A concern that was raised by investigators and community advisory board was how to counsel and inform the patient's sexual partner(s) that there was a reason for them to be tested for STIs. Although

this was not explained in the Informed Consent Form (ICF) or in the study protocol, it is a part of the Thai national treatment guideline for treating patients with STIs.

Analysis

Challenges	• Many participants did not have a PCP to ensure proper follow-up • Sensitivity surrounding test results and impact on partners • ICF was silent on the disclosure / return of results to partners (who would may impacted by the results) • Standardly available tests may be less sensitive than the nucleic acid tests used in the context of biomedical research.
What?	• STI findings during the course of the study of HPV and in screening (STI screening test including blood test for VDRL, chlamydia trachomatis test, and physical examination (pelvic and male sexual organ area examination)
When?	• During study visits (lab test every 6 months)
How?	• Contacted by study staff and communication in person by PI if PCP not available
Who?	• HIV-negative arm of study: Study participants with positive lab results were contacted by study staff and asked to return to their primary hospital for STI treatment • HIV-positive arm of study: PI contacted participant's primary HIV care provider

Points to Consider:

This case study highlights the potential differences between a clinical research protocol and common medical practice in a study country. Typically, providers in this country only test for an STI when symptoms are present. Moreover, the standardly available tests may be less sensitive than the nucleic acid tests used in the context of biomedical research. As many research projects involving STIs include regular testing for a broad range of multiple STIs, this may result in the discovery of STIs in asymptomatic patients who did not expect to have an STI. The lack of a PCP can also complicate the further clinical management of study patients who are identified to have medical issues that need urgent attention.

Case Study 5: Incidental Findings in the Context of Universal Health Coverage in SE Asian Country

In this Southeast Asian health system, all people in the country are covered by universal health coverage (UHC). In practice, this means that everyone has a Primary Care Center to visit for their basic needs. From experience in clinical research, there are some incidental findings from research studies which need further treatment and care according to the UHC. This scenario is a HPV study in adolescents and young adults in an HIV-positive group and an HIV-negative group of healthy volunteers. The study focused on identifying factors related to infection with HPV but also offered a pregnancy test before performing a pap smear in females. Sometimes the participants will find they are pregnant which they did not know before the test. In other cases, a pap smear was conducted and found abnormal results which should be further investigated to determine the degree of disease progression. Further investigation including tissue biopsy will be provided according to the national guideline which indicates that sponsors are responsible for the cost that occurred. If tissue abnormality is confirmed (either precancerous or cancerous lesions), participants will be informed about the results, as stated in the Informed Consent Form, and will be referred to a large referral hospital for further treatment and care according to the national guideline.

Analysis

Challenges	• Informed Consent stated that sponsor is responsible for follow-up costs of abnormal results (in this country with universal health care coverage)
What?	• Abnormal pap smear results were found in some study participants • Consider whether a positive pregnancy test is an "Incidental finding"
When?	• Tests performed during the study visits (every 6 months)
How?	• If positive results are found, participant is referred for further investigation through tissue biopsy • If abnormality is confirmed, participants will be informed and referred to large hospital for further treatment and care
Who?	• Participants are informed about the results, as stated in the Informed Consent Form, referred to a large tertiary care hospital for further treatment according to the national guideline.

In other studies, such as when MRI studies are performed to study gray and white matter, small tumors can be discovered. When this occurs, the PI reports the incidental findings to the sponsor, and the sponsor is responsible to pay for the cost of the work-up to confirm the diagnosis. After this, patients are referred to a referral hospital for continuing treatment.

Analysis

What?	• Incidental finding of brain tumor
When?	• During the study visit (yearly MRI)
How?	• PI reports incidental finding to sponsor • Sponsor is responsible for work-up to confirm diagnosis
Who?	• After diagnosis is confirmed, patients are referred to hospital for continuing treatment

Points to Consider:

When a sponsor is responsible for follow-up care for incidental findings, a system needs to be in place for where to refer participant to receive continuing treatment.

These scenarios highlight a transition between the sponsor's responsibility and the health system's responsibility when investigating and providing long-term care for findings that are discovered during a clinical trial.

Case Study 6: Discovering HIV Status in Healthy Clinical Trial Participants in India

In a Phase I clinical trial study, healthy volunteers were consented and screened. In this process, a healthy volunteer was identified to have an HIV infection. This was an unexpected result for the participant who had been involved in multiple clinical trials/research projects in the past as a healthy volunteer.

The ICF did not have any specific conditions to govern the return of results to the participant. It only indicated that healthy volunteers would be screened and enrolled only if they met the eligibility criteria. The PI involved a counselor to communicate with the participant and ask him to be re-tested on the basis that the results of the test were equivocal. The repeated lab test was also positive for HIV, and clinical history determined that the participant was recently married but also had sexual partners outside of the marriage. The wife was contacted and counseled to be screened for HIV and both individuals were referred to the general medicine department of the hospital for follow up.

In India, it is typical for incidental findings or results to be communicated directly from the PI to the participant. The PCP who referred the patient to the study is also informed, because the participant may not be able to communicate the details of the findings or results clearly to their provider. The communication is documented in a case report form and filed for review by the sponsor during the next routine monitoring visit. If incidental findings occur after enrollment or after randomization, the sponsor is also informed as this a medically important event and participant is discontinued from the study.

Research protocols indicate that the treatment resulting from incidental findings must be in line with the typical care pathway that would be followed outside of a research study. In cases where there is no PCP, the participant is referred to the appropriate specialist, and if there are multiple physicians who could provide this service, the patient is allowed to choose which physician will receive the results.

Analysis

Challenges	• Informed Consent did not have specific conditions to govern return of results to participants
What?	• HIV test results in a clinical trial were positive for a "healthy volunteer" who was believed to be HIV negative.
When?	• Test results were collected prior to enrolling healthy volunteers.
How?	• In India, findings are communicated directly from PI to participant and partner; the PCP is also informed in cases where they were responsible for referring the patient into the trial. It is the usual practice to inform the concerned person regarding unexpected or unusual findings. Further, it is common practice to inform participants who are a screen failure why they were not enrolled. • Communication is documented in a case report form.
Who?	• Typically in this country incidental findings are communicated directly from PI to participant. • Participant, PI, and PCP are all involved. • In cases where there is no PCP, the participant is referred to an appropriate specialist, but the results are only shared when the participant selects a specialist and gives his/her approval to share the results.

Points to Consider:

This case demonstrates the unique scenarios that can occur when selecting healthy volunteers for a clinical trial, emphasizing the importance of clear and proactive communication and informed consent. These principles are important for all participants, even for healthy volunteers who are believed to be at minimal risk as a result of their participation.

In the case of laboratory findings for sexually transmitted infections, it is important to understand local regulations and standard of care regarding informing, counseling, and treating sexual partners of individuals who test positive for an STI. In such situations we need to remember the ethical principles of research including autonomy, beneficence and justice.

Case Study 7: Retrospective Pharmacogenomics Research Using Exploratory Techniques

An international Phase III trial of an investigational medication was conducted in patients with advanced-stage ovarian cancer. Currently in most clinical trials, individual exploratory genetic results are generally not returned to study participants, and this was the case at the time the protocol and ICF were developed for this study. As a result of emerging scientific evidence during the trial, the team was directed to conduct an exploratory retrospective pharmacogenomic study to look for correlations with a particular genetic variant and differential response to therapy.

The exploratory retrospective genotyping was conducted in research laboratories using next-generation sequencing (NGS) technologies intended to screen for single nucleotide variants, and small insertions and deletions. However, quality systems and associated credentials for reporting exploratory research results which could be used for clinical decision making were not in place. The exploratory pharmacogenomic analysis showed that participants with specific germ-line variants had an improved progression-free survival prognosis.[12]

There were diverse opinions amongst the sponsor, investigators and ethics on the importance and relevance of the genetic findings and substantial debate as to whether providing this type of information would be actionable in patients with advanced disease. Notable variations between country regulations, guidance and clinical practice regarding the communication of this type of information to study participants was identified. In the end, a decision to communicate the aggregate results provided a mechanism to disseminate the overall study finding. Individual participants could request their results if desired.[13]

Analysis

Challenges	• Informed Consent and study protocol did not foresee returning individual genetic results • Diverging opinions amongst the sponsor, investigators and ethics committees and regional differences in regulations, guidance and clinical practice • Genotyping was performed in research labs Quality systems and associated credentials for reporting exploratory research results which could be used for clinical decision making were not in place.

[12] Harter, P., et al. "BRCA1/2 mutations associated with progression-free survival in ovarian cancer patients in the AGO-OVAR 16 study." Gynecol. Oncol. 140.3 (2016): 443-9. http://www.sciencedirect.com/science/article/pii/S0090825815302304?via%3Dihub

[13] Pulford, DJ., et al. "Communicating BRCA research results to patients enrolled in international clinical trials: lessons learnt from the AGO-OVAR 16 study." BMC Medical Ethics 17.1 (2016): 63. http://bmcmedethics.biomedcentral.com/articles/10.1186/s12910-016-0144-y

What?	• After the conclusion of an international advanced-stage cancer trial a retrospective exploratory pharmacogenomic analysis found patients with clinically important genetic variants had improved PFS. .
Why?	• Because the findings may be useful to patients, mechanisms to communicate the results were evaluated.
Who and How?	• Sponsor, investigator and ethics committee discussed the importance and relevance of returning genetic findings to patients with advanced disease and decided to communicate aggregate results. • Notable differences between regulations, guidance and clinical practice in various countries were identified. • Aggregate result communicated via clinical site investigators. • Investigators were encouraged to discuss the overall findings with participants and depending on local guidelines, test availability and individual circumstances, to discuss whether it would be appropriate to seek genetic counselling and a diagnostic quality test. Participants could request their individual research result via their clinical site investigator.

Points to Consider:

This case demonstrates the need to consider in advance the potential challenges of returning individual results when conducting exploratory and retrospective genomic research. Consideration should be given on how to handle genetic results in the study protocol and informed consent. For example, the need for clarity of informed consent and for patient engagement to ensure clinical trial participants can indicate their preference and understand the circumstances under which their genetic research results would be returned.

In addition, the importance of communicating genetic research results was recognized. However, returning individual results was challenging due to unforeseen differences in local requirements, clinical practice, and ethical opinion. Furthermore, there was a diversity of opinion about the benefits of communicating exploratory retrospective genetic findings where their interpretation and relevance in advanced disease was unclear.

The principle of autonomy supports creating conditions to enable study participants to choose if they wish to receive these types of individual results. The principle of non-maleficence, which requires physicians to do no harm, may conflict with any principle which supports the sharing of results, as these results could potentially cause further distress to participants without providing additional actionable information to guide their clinical treatment for this end-stage disease. There is the additional consideration that the test was conducted in a research setting, which gave rise to the recommendation to share aggregate results. Study investigators were encouraged to discuss the overall findings with surviving participants and based on local guidelines, test availability and individual circumstances, to discuss whether it would be appropriate to seek genetic counselling and a diagnostic quality test. In this

way participants would benefit from understanding the research and the implications to them and their family, and would be in a better position to make a more informed decision regarding follow-up.

The case highlights the tension that may exist between ethical principles and operating in an international setting where the local requirements and practices may differ. It is important to carefully weigh all ethical perspectives together with regulatory and healthcare practice and to ensure clarity of informed consent and appropriate patient engagement, before coming to a decision about returning exploratory retrospective pharmacogenomics results.

Case Study 8: The Role of CLIA Regulations and *A Priori* Informed Consent in Releasing Genetic Data to Family Members

A research participant with a known clinical diagnosis of a genetic condition elected to participate in a clinical trial for a new beta blocker. As part of participation in this trial a whole blood sample was obtained for exploratory pharmacogenomic (PGx) research, the scope of which included studying genetic factors that may contribute to differences in drug efficacy and safety. During the course of research, a panel of genes was examined which included the fibrillin-1 gene known to be associated with Marfan syndrome. While a mutation in this gene was identified during the course of the exploratory PGx research, results were not immediately returned. The decision not to communicate the results of genomic research was driven by the fact that the informed consent document indicated that results would not be returned and also because research grade analyses were utilized.

After the patient passed away from other causes, family members subsequently contacted the investigators due to their interest in understanding their relative's treatment assignment and to learn if any results associated with genetic analyses performed were available. After consultation with an internal ethics committee, it was decided that the genomic results could have a significant healthcare impact on family members who are genetically related to this research participant making it ethically permissible, but not an ethical obligation, to provide this information to the family even though the consent stated results would not be provided. If results were to be provided to this research participant's family, according to the maxim of justice that "like cases should be treated in a like manner", it was felt that other research participants who desire them should also be provided with results of genotyping the fibrillin-1 gene (via communication with the research investigators).

In parallel to seeking bioethics guidance, the research laboratory that conducted the genomic testing was consulted. This laboratory is located in the United States where it holds Clinical Laboratory Improvement Amendments (CLIA) status. However, since the original agreement involved analyzing the gene panel using research grade analyses CLIA processes were not utilized. Sharing a result could thus put the laboratory in jeopardy of losing their CLIA status.

As a result, the family requesting information was provided with their relative's treatment assignment but the results of genomic research were not provided.

Analysis

Challenges	• Informed Consent specifically stated that study results would not be shared with participants. • Results were generated in a CLIA certified lab, but CLIA certified processes were not utilized as this was not in the study protocol.
What?	• Genetic results and treatment assignment for an investigational product of a new beta blocker to treat a symptom of a rare disease.
When?	• Results were requested by family members after the patient had already passed away from unrelated medical causes.
How?	• The investigator was provided with the treatment assignment for this research participant so that he/she could disclose this result to family members. • Results of genomic research were not provided.
Who?	• Internal ethics committee decided that genomic results could have a significant healthcare impact on family members genetically related to participant, making it ethically permissible, but not an ethical obligation to share results with family members.

Points to Consider:

This case contained several complicating variables. One major variable is the US-specific regulation requiring that samples which are returned to individuals must be from a CLIA-certified laboratory, collected and analyzed using CLIA-certified methods. In this study, it was never intended that results would be returned, so research grade analyses (and not CLIA certified analyses) were utilized.

Additionally, this case was based on a request for results disclosure from a research participant's family members and not from the research participant themselves. Since the informed consent document stated that individual research results would not be shared it is difficult to know what the research participant's views may have been about receiving this information or about having it communicated to family members directly. Adding further layers of complexity to the decision to disclose, we know this research participant already carried a clinical diagnosis of Marfan syndrome making disclosure of the mutation of limited value to the participant if they were still living. While disclosing the result could have some impact for family members, this impact again would be limited (mainly useful for reproductive decision making) since the diagnosis of Marfan syndrome can be made based off of clinical criteria.

Due to the unique impact that genomic results can have for a research participants' immediate and extended family members it is essential that one includes in the consent discussion provisions for

sharing the outcome of research with a third party in the event that the participant themselves is not able to receive the information directly when it becomes available.

Case Study 9: A Patient Engagement Pilot Initiative to Provide Patients with Access to Data During a Clinical Trial

An industry sponsor conducted an iterative pilot study to demonstrate the feasibility of providing participants with select routine laboratory results during an ongoing clinical trial. This pilot was an element of a larger patient engagement initiative, conducted in US locations, subject to Federal and State HIPPA review. Participants enrolled at sites in the US were provided with access to their individual laboratory results following routine study visits so that they could manage and coordinate their care and share this information with their health care provider. This was an open-label, global rheumatoid arthritis (RA) safety study among adults suffering from RA.

For the pilot study, the process for sharing results was added to the existing clinical trial protocol and ICF. Study patients were offered the opportunity to participate and consented to data-sharing via the Data Sharing Authorization form. Essentially, they were required to opt-in for their information to be available on the site. Participants could then easily access their data via a secure website where their individual laboratory results collected at study visits were shared directly with them. The website enables easy, real-time access to their individual results and participants can save these data to their own medical record or electronically share it with caregivers. The system enables one-way communication, without interpretation of results. Investigators and study coordinators at study sites can view the same data as the participants, which is helpful when participants ask for assistance in interpreting the data that was provided.

Analysis

Challenges	• Returning laboratory results to participants during an ongoing trial via web portal
What?	• Routine safety laboratory results conducted in CLIA laboratory: hematology, chemistry, lipid profile. • Results were presented without interpretation, with disclaimer regarding interpretation and questions. • Access to routine lab data during a trial is feasible for specific data
When?	• Data were shared via the website with individual participants approximately 2-4 weeks after data collection. This provides PI adequate time to recognize and respond to abnormal data through physician follow-up so as not to interrupt standard protocol procedure. • Patients can access, save, share data during and after the trial. • Patients may save data during this period to their own medical record or as a report. • Data available delivered upon authorization within 24 hours

How?	• Patients agree to and provide authorization via ICF or electronically to share data with a third party to be shared with them. • Opt-out option always available. • Permission to be contacted sought. • Disclaimer regarding result interpretation and questions. • De-identification • 3rd party and external costs • English only • Private, secure web portal access • Maintenance of technology by 3rd party
Who?	• Accessible only by patient and designated site staff • Long term communication as long as patient agrees • Patient has choice to share data with HCP or trusted caregivers.

Points to Consider:

This case study shows the benefit of proactive planning and integration of the return of individual results into a larger clinical trial. One of the factors that contributed to the successful uptake of this initiative by clinical trial participants is that study site staff were trained to counsel participants in how to use the portal, and they have been given the same level of access to the online portal as participants. This enables staff to understand and explain the data that participants are viewing in case there are any questions or concerns.

It has also been beneficial to have a minimal delay between data collection and data access through the portal. This has allowed study coordinators and physicians to identify any urgent findings and address them in a timely manner. Ultimately, it decreases site burden by allowing patients access to data they wish to have rather than asking the sites to provide copies of their laboratory reports. Additionally, easy access to data may alleviate the burden of repeating laboratory tests for healthcare needs outside of the study setting. It also eliminates the site burden to print or make copies of lab data requested by study participants.

Case Study 10: Pfizer Link: Returning Clinical Data to Patients with Online Patient Community and Blue Button®

Blue Button is a feature developed by the US Department of Health and Human Services to make individual health data available for download to individual users. It was piloted at the Veterans Affairs and Centers for Medicare and Medicaid Services and is now available for other organizations to adapt for their IT infrastructure.

Data Holders can "Make personal health information, either complete health record and/or a subset such as a visit summary, available to individuals and their caregivers in a secure, timely, and usable

manner allowing them to: View, download, and transmit their health data from a secure portal in a format that is both machine and human readable (requirement for Stage 2 Meaningful Use) to a destination of their choice (for example, via **Direct** [http://wiki.directproject.org/], **Microsoft HealthVault** [https://www.healthvault.com/) or similar protocols."[14]

An industry sponsor built an "Online Patient Community" with Blue Button data download capability to communicate proactively with study participants and maintain post-clinical trial relationships. Through the Blue Button platform, study participants were able to access the following information at the end of the clinical trial: their individual study arm, start/stop date of treatment, concomitant drug info, full lab tests, including hemoglobin, ECG, heart rate, medical history, and interpretation of vital signs. The website was designed with security and privacy in mind. It required participants to opt-in and complete multi-factor authentication in order to access their results. Invitations to the website were fully integrated into the study close-out process. Once patients had access to their data, they could decide how to use it. They were encouraged to share with their physician or load into a Personal Health Record of their choosing.

Analysis

Challenges	• Returning individual study results to participants at the end of a trial via web portal
What?	• Study arm • Start and stop date of treatment drug • Concomitant drug info • Full lab tests, including hemoglobin, ECG, heart rate, significant medical history • Vitals Interpretations and Comments
When?	• Patient data are made available after participation in trial ended • Considering data return of labs, vitals, during Phase I studies with healthy volunteers
How?	• Clinical Trial Online Patient Community • Patient opt-out as default, opt-in requires registration, multi-factor authentication process • Fully integrated into study close-out process and operations

[14] Source: https://www.healthit.gov/patients-families/join-blue-button-movement (accessed 11/22/2016)

Who?	• Once patients access their data, they are free to use it however they want (Encouraged to share with their physician or load into a personal health record) • Surveying PIs to determine if they would like to play a greater role in data return

Points to Consider:

This case demonstrates the benefits of proactive and integrated planning in returning results. The opt-in procedures protect participants from receiving results that they do not wish to receive, and it provides an opportunity to ensure that participants are informed that these results do not constitute medical advice. Linking the online patient community program enrollment with the close-out procedure for the study enabled the industry sponsor to utilize resources that were available at the study site and provide participants an opportunity to ask questions.

Case Study 11: Hypothetical Case: Incidental Findings From a Clinical Research Study Involving The Generation of Exploratory Genetic Data

On the advice of his cardiologist Jake, aged 57, decided to participate in a large research study of an investigational drug for people like him with chronic coronary heart disease. Jake had his first heart attack at age 55 and was now on multiple medications for high blood pressure and cholesterol. He started to exercise some and eat better and wanted to do whatever he could to avoid another heart attack or even an early death, like his father. The study doctor explained that the investigational drug would be compared with placebo, or a sugar pill, but that everyone in the study was guaranteed to receive the current "standard of care" for chronic coronary heart disease. He was told the study would take a long time to complete, possibly even 5 years, because the primary goal was to compare the total number of people who had a heart attack, stroke or death in each of the groups (something he called MACE), and it would take a long time to accrue enough of these events to make a meaningful comparison. Other types of research were described in the 25-page informed consent form, but the study doctor explained that those were mainly "exploratory" objectives and would not contribute directly to answering the main study question.

Several months after the initial study visit, where he was given blinded study medication and many cardiac tests were conducted and various samples obtained, Jake was contacted by the study coordinator to come in to review some "findings" with the investigator. Jake was curious as he had been told that the study would take several years to enroll and complete. The study doctor explained that, while conducting the exploratory genomic analyses to identify genes potentially associated with cardiac disease, the large pharmaceutical company which sponsored the study identified a specific genetic variant called APOE4. He also explained that the APOE4 variant may be associated with an increased risk or susceptibility to Alzheimer's disease "later in life" and called the finding "incidental" because it was not anticipated in the research protocol or informed consent form and he had no clear

direction about what to do with the information. The study doctor said, as this was not his area of expertise, he could not advise Jake on the actual risk of developing Alzheimer's or potential timing (early or late onset) associated with the finding. He advised Jake to follow up on his own with a neurologist and a genetic counselor for additional information. Jake left the meeting with the investigator in total shock. He did not know how to describe to his wife what had happened or even if he should share the results with anyone in his family before he talked to someone who knew more about the risk associated with the "incidental" finding.

Framework Analysis

Challenges	For the exploratory genomic endpoint, genome-wide association (GWAS) microarray with imputation [1, 2] was used in this study to analyze genetic or chromosomal variants over large stretches of the genome. This technique can be expected to produce incidental findings based on: • If the chip used in a genomic microarray is not specifically targeted to the domains under study (and the software does not mask other results), incidental findings may increase. • Even if a chip is "targeted" or the software masks other results, unexpected patterns not under study in the genetic and chromosomal regions being examined may yield incidental findings, as may unexpected pleiotropy, such as in the case of APOE alleles. • Incidental findings may also appear in analysis of "boundary regions" • Commercially available chips and analysis software may not always be tailored to the research question at issue. • In discovery research it is difficult to identify what might be an incidental finding, as any genomic pattern correlating with pathology may potentially be captured and studied (present or future)
What?	• Many incidental findings from research may turn out to be false positives in "normal populations" • Informed consent form did not state anything about the possibility of incidental genomic findings • No direction established or given regarding communication of results to research participant • Results were deemed "actionable" by the investigator (but were they really?) • Subject's blood relatives could also be impacted by the incidental finding • Immediate follow-up consult and confirmatory testing (may or may not be available in a timely manner, who pays for confirmatory tests?)
When?	• WRT timing, the investigator could have delayed meeting with the subject and consulted with experts outside his area (in addition to the EC or IRB) to determine the most appropriate course of action
How?	• Site and investigator communicated to the patient directly rather than attempting to contact the referring physician or a genetic counselor

Who?	• Investigator/treating physician role to exercise professional medical judgment regarding sharing results with patients and impact on treatment decisions

Points to Consider:

The genomics analysis in this study was an exploratory endpoint. An incidental finding is a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study. This case demonstrates the importance of communicating the specific nature and target of genomic research, the potential for genomic incidental findings to research participants, and any known limitations of specific techniques used for genomic analysis. It also serves as a reminder for the need to include detailed information on how to handle incidental findings in the research study protocol and informed consent.

Medical literature has demonstrated the effectiveness of narrative writing in enhancing patient, family, and healthcare provider self-reflection and empathy [3]. This hypothetical case takes somewhat of a narrative-based approach to a hypothetical research participant's experience in a clinical trial. Similar to the personal illness narrative, by presenting the case from the perspective of the research participant, we attempt to elicit, interpret, and translate what it may be like to receive incidental genomics findings through his experience.

The principle of autonomy supports creating conditions to enable study participants to choose if they wish to receive incidental research results. The principle of non-maleficence, which requires physicians to do no harm, may just as easily support the opposite position, as these type of results could potentially cause harm or further distress to the subject without providing additional actionable information to guide their clinical treatment.

The investigator could argue that he has a duty to act in the best interest of the patient which would require that he take reasonable measures to "rescue" him from the danger posed by the genetic variant. However, given that research, even in a clinical setting, differs from clinical care in both its goals and its procedures, standards for return practices in the research setting should not be driven purely by clinical standards. The distinction between research, an activity focused on the acquisition of generalizable knowledge, and clinical care, an activity focused on the treatment and decision making for the patient, is important in determining an appropriate practice for the return of genomic research results. [4, 5, 6]

The case highlights the tension between ethical approaches and demonstrates the importance of carefully weighing all ethical perspectives before coming to a decision about returning individual genomic results directly to a research participant.

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