MRCT Center
Return of Individual Results to Participants
Recommendations Document

October 20, 2017
Version 1.1
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1. Executive Summary

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 internationally diverse members from academic and medical centers, industry, clinical research organizations, regulatory agencies, institutional review boards, non-profit agencies, and patient advocacy organizations (Appendix 1). After reviewing multiple case studies and considering the ethical foundations and relevant issues, we have formulated key principles and recommendations regarding the return to participants of their individual results from clinical trials in which they were enrolled. We have relied on foundational contributions from many stakeholders. Note however, that what follows is aspirational: we are well aware that most academic- and industry-sponsored protocols do not envision or provide for return of individual research results. Greater transparency in general, and returning results in particular, are growing areas of interest and provide for greater engagement of participants. These guidelines are not prescriptive and are proposed guidelines as a starting point, a beginning from which we, as a community committed to transparency and trust, will learn. We anticipate that the guidelines, the principles, and the accompanying toolkit that follow will improve iteratively with greater experience, interaction, and feedback.

The generation of individual results that can be returned to research participants can occur as early as pre-screening for study eligibility and extend past the end of the clinical trial (Figure 1). This includes urgent results and urgent incidental findings (Type A), routine laboratory results and non-urgent incidental findings (Type B), individual end of study results, including about assignment to treatment or study arm and primary study endpoints (Type C), exploratory results that may be ancillary to the endpoint(s) of the trial (Type D), and aggregate results (Type E). Notably, there is a compelling ethical (and medical) obligation to return urgent results and urgent incidental findings (Data Type A) in a timely manner. As appropriate, the protocol and informed consent document should anticipate these eventualities.

While there is a diversity of opinions about the ethical obligation to return individual’s findings, we recommend that:

- **Data Type A** results (urgent results and urgent incidental findings) should always be returned to the medical caregiver or the participant as soon as they are confirmed to be valid and both outside of normal ranges and associated with an urgent need to return due to the potential consequence for diagnosis, treatment, or care of the individual.

- For **Data Type B** results (routine results and non-urgent incidental findings) the balance of potential benefits to the individual participant should be weighed against resource requirements and feasibility of implementing return of routine results. Other considerations also apply (see below).
• For **Data Type C** (end of study individual results), at a minimum and if feasible, research participants should be offered information regarding their study arm assignment in which they participated after the study concludes. In addition, communication of primary endpoints should be offered at the end of the study, unless returning these data would compromise the integrity of the study or ongoing studies. Communication of secondary endpoints should be consistent with the European Union (EU) Guidelines for aggregate results (European Commission, 2017; Health Research Authority, 2017; and see Data Type E below).

• **Data Type D** (exploratory results) should be handled on a case-by-case basis.

• For **Data Type E** results (aggregate results), a summary of primary endpoints and safety data important to the overall results of the trials should be returned, in accordance with applicable law and guidance, e.g., European Union (EU) Guidelines (European Commission, 2017; Health Research Authority, 2017) and MRCT Center Return of Results guidance document for aggregate results. (Multi-Regional Clinical Trials Center of Brigham and Women’s Hospital and Harvard (MRCT Center), 2017a).

The determination of whether, when, and how to return individual results will be based at least in part on the nature of the results and their significance as discussed further below. Notably, the key principles and recommendations do not address return of aggregate results of the clinical trial (Type E), a set of separate but related issues that the MRCT Center has addressed elsewhere.¹

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¹ See Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) (2017a, 2017b).
The following principles, developed by the MRCT Center Return of Individual Results Workgroup, address the return of individual results collected during a clinical trial to research participants or their designees. These principles complement previous recommendations for the return of aggregate research results (see http://mrctcenter.org/projects/return-of-results-to-participants/). Individual results are generated in different contexts and at different times during a trial. Whenever a validated result is medically actionable, there is an ethical responsibility to return the relevant result either directly to the physician(s) with primary responsibility for care to the individual or to the participant, documenting the communication and transfer of responsibility.

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 act responsibly when returning individual results, taking into account medical significance, analytical validity and personal utility.

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

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

9. Return of individual research results should be planned and executed in compliance with institutional policies and local, regional, and national laws and regulations.

These principles are minimum “default recommendations” for returning individual research results to study participants who have indicated that they want to receive results. The principles and recommendations were designed for clinical intervention trials in well-resourced environments but might be applicable beyond that to other types of trials and other environments. They are intended to apply to all participants including normal volunteers. These recommendations are not prescriptive. The type of trial, type of data and timing need to be taken into consideration for each trial and decisions need to be made on a case-by-case basis.

The underlying ethical foundations for these principles and approaches are discussed in Section 4. Each of these principles is discussed in detail in Section 5. What results to return (considering different types of data in a research study), when to return them, who should be responsible, how results should be communicated are addressed in Section 6. Special considerations in the return of genetic and genomic results are discussed in Section 7, and conclusions in Section 8. A number of appendices are attached, and this Recommendations Document is accompanied by a Toolkit that provides practical tools and case studies for implementing the principles.
2. Introduction

This section describes the purpose and scope, target audience, approach, and health literacy principles.

2.1 Purpose and scope

Patients, and parents, guardians and legally authorized representatives, and patient advocates speaking on their behalf (hereinafter patients/patient advocates) often express the desire to receive both individual and aggregate research data from the clinical studies in which they have participated (Shalowitz, 2008). In addition, certain individual results have the potential to be useful to individuals if returned in context. The lack of guidelines and criteria for returning results has made it difficult to determine what data are to be returned and when and how these data should be communicated.

The MRCT Center has previously developed guidelines for the return of aggregate results to research study participants.\(^2\) Aggregate results (also referred to as plain language, non-technical, public, or “lay” summaries) provide study participants with overall findings of a clinical research study without providing any information about how individual participants responded during the trial. Additional guidelines have been needed for the return of individual results, as participants often would like to know their assignment to study or treatment arm (in blinded trials) and to have access to their individual data or research results.\(^3\)

The MRCT Center coordinated a diverse, multi-stakeholder workgroup of 45 members from seven countries—including academic and industry leaders, not-for-profit institutional and government representatives, health policymakers and patients/patient advocates. The objectives of this workgroup were: (1) to determine the principles that might guide the return of individual results, (2) to define methods to facilitate communication of results to individuals, and (3) to develop best practices and a framework to manage disclosure of individual results to individuals and follow-up for those disclosures.

The workgroup reviewed case studies,\(^4\) evaluated the case studies to identify and categorize ethical and practical issues, and agreed upon principles (see Section 5) to provide guidance on the return of individual results to study participants. These principles apply to all

\(^2\)See Multi-Regional Clinical Trials Center of Brigham and Women’s Hospital and Harvard (MRCT Center) (2017a, 2017b)

\(^3\) Generally, in the context of returning results, the terms data and results are used interchangeably. However, there is a distinction in large-scale genomic sequencing, such as whole genome sequencing, a methodology that generates raw data. There are no research “results” until the data is interrogated via a research query. In this Recommendations document, any important distinction will be annotated and clarified.

\(^4\) Case studies were contributed by workgroup members and are further described in the accompanying Return of Individual Results Toolkit.
interventional trials\textsuperscript{5} that anticipate the generation of new data, whether or not that trial is published. The principles build the foundation by addressing “what,” “who,” and “when” and “how” in Section 6 and specific issues with genetic and genomic data are considered in Section 7. An accompanying Toolkit provides additional tools and resources that focus specifically on “how.” Both the Guidance and the Toolkit allow for flexibility. The principles are anticipated to be applied only after consideration of case-specific information and adapted to the case and situation.

We realize that the return of individual results in the clinical trial is a complex issue that has resulted in inconsistencies in what and how information is communicated to research participants. We ask that those who use these recommendations and toolkit provide the MRCT Center with feedback and lessons learned by emailing MRCT@bwh.harvard.edu. Based on input and experience, the MRCT Center anticipates revisions to these recommendations.

2.2 Target audience

The target audience includes sponsors, principal investigators, and study coordinators who generate and/or maintain individual participant (patient) level data obtained in preparation for, during, or following the completion of clinical trials and for those who plan, design, and oversee clinical trials that gather individual participant-level data.\textsuperscript{6} This document was designed for clinical intervention trials, but we think is applicable to other types of trials as well. The target audience should consider the principles laid out in this document, as well as other available resources, when determining what results are feasible to return.

3. Terminology

Key terminology for discussions of returning individual results to participants is defined (in alphabetical order).

- **Accreditation**: A type of quality assurance process under which services and operations of institutions or programs are evaluated by an external body to determine whether applicable standards are met. If standards are met, **accredited** status is granted by the appropriate agency.

- **ACMG**: American College of Medical Genetics and Genomics

\textsuperscript{5} Indeed, these principles also apply to other types of trials as well, but the specific circumstances of interventional trials are discussed in detail in this document.

\textsuperscript{6} While this document was developed in collaboration with patients and patient advocates, it is not written specifically for them. Nevertheless, the MRCT Center invites review, comment, and suggestions for revision by participants, patients and the public at large (to MRCT@bwh.harvard.edu).

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4. **Actionability**: The degree to which a personal research result can be used to guide decision-making (American College of Medical Genetics and Genomics (ACMG) Board of Directors, 2015). Many further categorize actionability in terms of **medical or clinical actionability** (the degree to which a result may be used to guide medical and health decisions, see Section 5.6). A result is generally considered to be “clinically actionable” if there are established therapeutic or preventive interventions available, or other available actions that can be taken on the basis of the result that may change the course of disease. A result is generally considered to have **personal utility** if the result may be of value to an individual or for purposes to guide decision-making other than for diagnostic or therapeutic reasons, e.g. preparation for the future, etc.).

- **Analytical Validity**: the analytical specificity and sensitivity, accuracy and precision of the test. In the context of genetic testing, how well the test predicts the presence or absence of a particular gene or genetic change.

- **CLIA (Clinical Laboratory Improvement Amendments Act of 1988)**: U.S. federal regulations that establish standards applicable to U.S. facilities or sites that test human specimens for health assessment or to diagnose, prevent or treat disease.

- **Clinical Significance**: The extent to which a result or finding has medical implications for an individual or an individual’s offspring (reproductive significance).

- **ctDNA (Circulating Tumor DNA) TESTING**: The analysis to detect cancer biomarkers from small pieces of DNA released by dying tumor cells into the bloodstream.

- **Clinical Trial**: Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate safety and the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioral treatments, process-of-care changes, preventive care, etc. (Smith et al., 2015). A **randomized clinical trial** prospectively assigns human participants to one of two or more groups.

- **Clinical Utility**: Whether the test can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to the individual.

- **Clinical Validity**: The accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in an individual. In the context of genetic testing, how well the genetic variant being analyzed is related to the presence, absence or risk of a specific disease,
• **Exploratory Results**: Data collected for exploratory purposes or future research, rather than confirmatory analyses. This includes data collected during a trial that are not analyzed until after the trial has ended. These data include data pertaining to exploratory endpoints, for example, biomarker analyses of various mutations or gene expression. Exploratory results may be generated during the study, or years after the end of the study.

• **Genetic**: the study of specific genes.

• **Genetic Testing**: The analysis of DNA, RNA, chromosomes, proteins, or metabolites that detect genotypes, mutations, or chromosomal changes.

• **Genomic**: The study of an organism's entire genetic makeup (genome).

• **Germ-Line Mutations**: Hereditary mutations that are passed from parent to child and are present in every somatic cell in the body

• **Health Literacy (US)**: The degree to which individuals have the capacity to obtain, process and understand basic health information needed to make appropriate decisions. (Note: Low health literacy can affect people of all ages, races, incomes, and education levels). Although health literacy is commonly defined as an individual trait, it does not depend on the skills of individuals alone. Health literacy is the product of the interaction between individuals’ capacities and the health literacy-related demands and complexities of the health care system (U.S. Department of Health and Human Services (HHS), 2010).

• **Health Literacy (Europe)**: The capacity to make sound health decisions in the context of everyday life – at home, in the community, at the workplace, in the healthcare system, in the market place and in the political arena (Kickbusch et al., 2005).

• **Incidental Findings**: A finding discovered in the course of research concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting the research but is beyond the aims of the research (S. M. Wolf et al., 2008).

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7 Adapted from: International Conference on Harmonization (1998).
8 Note that data collected for confirmatory purposes during a trial may later be used secondarily used for exploratory research. In this document, we do not reach to comment on the responsibilities of a researcher engaged in secondary research. This document addresses the decision of whether and how to return results pertaining to the primary purpose for which they were generated and by the primary individuals.
9 The Presidential Commission refers to anticipatable incidental findings and unanticipatable incidental findings. The recommendations here apply to both findings equally (Presidential Commission for the Study of Bioethical Issues, 2013).
• **Individual Study Results**: Data recorded within a clinical trial database associated with individual participants. This may be in the form of data collected about an individual participant’s clinical outcome during the trial (for primary and key secondary endpoints). It can also include details of randomization and treatment received, and adverse event information.  

• **Next Generation Sequencing (NGS)**: High-throughput method used to determine a portion of the nucleotide sequence of an individual’s genome. This technique utilizes DNA sequencing technologies that are capable of processing multiple DNA sequences in parallel.

• **Personal Utility**: The value of the data or results outside of the direct medical context (e.g., to inform decision making about future life plans in the case of late-onset medical conditions, health-related choices related to well-being); and/or the value to the individual to have one’s own data or results. An overall measure of personal usefulness that indicates whether the information can “reasonably be used for decisions, actions or self-understanding which are personal in nature.” (Bunnik et al., 2012) To have personal utility, the information must be meaningful and be put to use in some reasonable way (Bunnik et al., 2012). “Reasonableness” varies among individuals depending on lifestyle, health awareness and behaviors, family dynamics, personal choice and interest, and psychological effects of disease risk perception.

• **Pharmacogenomics**: The study of how genes affect a person’s response to drugs.

• **Routine Results**: Laboratory and imaging results that are collected at baseline and regular clinical study visits, such as weight, blood pressure, heart rate, blood results, x-rays and which do not require immediate follow-up. These may be standard of care testing and procedures that are conducted under the study protocol.

• **Somatic Mutations**: Non-inheritable spontaneous mutations that form in the DNA of individual cells (e.g., tumor tissue) during a person’s life

• **Transparency**: Timely sharing of information in ways that are accessible and understandable to stakeholders, and openness to meaningful public input into the policy-making process.


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10 Adapted from: Smith et al. (2015).
• **Urgent Results:** Medical results or findings that are unexpected and pose an immediate threat for severe health consequences if not treated or addressed.\(^{13}\)

• **(Clinical) Utility:** The usefulness of a test for clinical practice. The impact of a test on patient outcomes, including speed to diagnosis, treatment decisions, patient management, and the potential for prognosis on the individual being tested, the individual's family members, and society in general (American College of Medical Genetics and Genomics (ACMG) Board of Directors, 2015).

• **Validity:** Analytic validity indicates how accurately and reliably the test measures a certain criterion, such as a genotype of interest.\(^{14}\) Clinical validity refers to the accuracy to predict a clinical outcome (Eckstein, Garrett, & Berkman, 2014).

• **(Genetic) Variant:** An alternation (mutation) in the most common DNA nucleotide sequence. The alteration may be benign, pathogenic, or of unknown significance.\(^{15}\)

• **Whole Exome Sequencing (WES):** The method used to determine the nucleotide sequence primarily of the protein-coding regions of an individual’s genome and related sequences, representing approximately 1.5 % of the complete DNA sequence.

• **Whole Genome Sequencing (WGS):** The method used to determine the complete DNA sequence (approximately 3.2 billion base pairs (nucleotides)) of an individual’s genome.

### 4. Ethical Foundations

No single foundational ethical value can provide a satisfactory justification for either an unrestricted duty to provide individual results to participants or for the complete absence thereof. Each situation must consider the facts of the specific case and attempt to balance a number of ethical values, many of which are inter-related and some of which may conflict with each other in a given situation. Ethical values are to be analyzed together as interwoven and interdependent concepts. In so doing, it is possible to identify circumstances in which there are compelling reasons to provide individual results to participants as well as reasons to limit and constrain returning results.

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This section briefly describes the ethical values of beneficence, non-maleficence, autonomy/respect for persons, favorable risk/benefit ratio, and transparency which are underlying foundational values for the Principles in Section 5.

4.1. Beneficence

Beneficence refers to the sponsors’ and researchers’ duty for securing participants’ well-being in research trials by maximizing the possible benefits to participants and minimizing risk of harm (UNESCO, 2005). A physician-investigator has a responsibility to provide medical care as it relates to the trial, and a treating physician or caregiver has an ongoing responsibility to the patient in the setting of medical care. According to the World Medical Association’s Declaration of Helsinki, “it is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research” (World Medical Association, 2013). At a minimum, and with regard to returning individual results, this statement can be interpreted to mean that there is a strong duty to provide and act upon urgent, actionable findings without delay for the study participant. It compels one further to question the extent of the duty to provide for a participant’s “well-being” in settings other than “urgent, actionable findings.” In this context, it is important to remember that the fiduciary duty of a physician to his or her patients differs fundamentally from the duty of a researcher to a participant; the researcher is engaged in activities that will (hopefully) contribute to generalizable knowledge and benefit society, that is, the focus of the research is to benefit future patients but not necessarily current participants. That is not to say that a biomedical investigator can abandon the care of a participant. It has been argued that a duty of ancillary care by researchers is grounded in beneficence since “an ethically acceptable approach would recognize a partial entrustment of participants’ health to researchers.”

4.2. Non-maleficence

Non-maleficence means that research participants should not be intentionally harmed; instead, adequate care should be provided to minimize the risks of research (Presidential Commission for Study of Bioethical Issues, 2011). The immediate health of participants should always have precedence over the interest of science. With regard to returning individual results, there is a strong duty to share results that have (immediate) relevance to the care that the participant is receiving and where there is a risk that the participant might be harmed if the results are not shared.

4.3. Respect for persons / Autonomy

Respect for persons, often operationalized as respect for autonomy, is based on the understanding that individuals have the right to make decisions about what happens to them independently, and cannot be a means to an end, even if that end is important and socially valuable research. Respect for persons is reflected in research through the informed consent

Consent is valid only when it is freely provided prior to any research intervention or activity and only after being presented with all the relevant information needed to make an informed decision. With regard to returning individual results, respect for persons dictates that participants should be given a choice as to whether they wish to receive individual results, and that, in the event that there is no intention to offer return of results, participants are advised of this in advance of agreeing to participate in the trial. In this latter case, the prospective participant is therefore free to make a decision as to whether to participate in the trial despite not being able to receive individual results. Respect for persons also dictates that confidentiality of results returned is maintained and that results returned only to the participant or his/her designee. Autonomy may be and is often in conflict with beneficence and non-maleficence, in that a participant who autonomously decided not to receive results could be hurt by not receiving urgent, actionable results, results that the physician is obligated to return based on the values of beneficence and non-maleficence. This ethical value of “respect for persons” demonstrates an awareness of the collaborative nature of clinical research.

The fact that participants may wish to have results does not automatically confer a duty on investigators or sponsors to provide those results; it does, however, imply that the intention, whether to return individual results or not, be transparent. In a discussion of autonomy as it relates to clinical trials, the concept of a donative contract must be considered. Countering the affirmative obligations of researchers to return results to the volunteer participants is the idea that the “subject-researcher relationship...should be viewed as a sort of arms-length donative contract: an agreement under which the donor-subject agrees to make a gift to the donor-researcher, who arguably holds the gift in trust for society... and does not promise anything directly in return” (Meyer, 2008).

4.4. Favorable Risk/Benefit Ratio

In the context of clinical research, the risk / benefit ratio is assessed comparing the risk of the project or trial to the benefit to the study population or society as a whole in gaining the generalization knowledge. In a successful collaborative partnership between sponsors, investigators and participants, the benefits to participants and society outweigh the foreseen risks (Emanuel, Wendler, & Grady, 2000). In some respects, returning results with utility or actionability for the patient and their caregiver may be considered a “benefit” if those data would not have been made readily available to the patient outside the context of a trial.

17 There may be limits to the concept of a donative contract in the event of medically actionable results. It is not our intent here to examine the limits of such a contract, as decisions for each situation will be based on the facts of the case, but rather to expose the underlying ethical framework that should inform those decisions.
4.5. Transparency

Transparency in the context of return of individual results implies that decisions will be made with all available information at the time, using processes for decision making that are as open as possible, and engaging the appropriate stakeholders (including, as appropriate, the participant or designee). While transparency has rarely been applied to research ethics, in the context of returning results to participants it is important to recognize that embracing transparency will promote trust and accountability, and ensure that all stakeholders are fulfilling their own responsibilities in a complete, objective, and clear fashion. A commitment to transparency will help to enhance trust and promote community engagement in research and in the research enterprise itself.

5. Principles and Recommendations

The principles and recommendations that follow are intended to assist decision-making in returning individual results to study participants who have indicated they wish to receive results. These principles are not prescriptive but serve as guideposts that allow researchers, sponsors, institutions, and institutional review boards (IRBs), and most particularly participants, to consider the practical and ethical impact of providing individual research results from clinical trial participation. Developing guideposts recognizes that, while decisions regarding individual results return may vary from one trial to the next, there is a set of principles that remains consistent and relevant to any situation as one develops a robust data return plan.

These principles will typically apply to interventional trials but are also applicable to other types of trials such as cohort and adaptive studies. As researchers develop a data return plan, they should consider whether and what information can be communicated to an individual, when that information can be provided, and by whom. These principles should aid in developing this plan regardless of the type of data being generated (Figure 1). One should recognize that these decisions need to be made on a case-by-case basis.

5.1 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.

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18 IRBs are also known as research ethics committees (RECs) or ethics committees (ECs). Here the term IRB(s) will be used throughout.

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The clinical research enterprise increasingly recognizes that participants can and should be engaged as partners who are actively involved in research and the generation of new scientific knowledge. Providing clinical trial participants with information about them generated through their participation in the trial is important as a matter of respect for individuals’ autonomy.

**Autonomy and the case for the return of individual research results**

The affirmative argument for returning individual clinical trial results is grounded in the principle of respect for persons and acknowledgment of individuals’ autonomy. As articulated in the Belmont Report, “To respect autonomy is to give weight to an autonomous person’s considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person’s considered judgments or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so” (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979).

In some countries, the law guarantees the ownership of one’s personal data. In other countries, the concepts of ownership and control are less clear. Whether an individual “owns” the data derived through voluntary participation in a clinical trial is a matter of ethical and policy debate. Some people assume that the individual is considered to have donated their data through the informed consent document and process, and that, fundamentally, data derived through research differs from that of clinical care. Some patients, patient advocates, ethicists, and others argue that all collected or generated data about a particular individual belong to the individual (Davis, 2016) and should be available upon request; others find this claim problematic (Contreras, 2016). We do not posit that either stance is correct and for purposes of this document, we do not engage in that debate. We do not need to reach to the issue of data ownership in order to find justification to return individual results. Respect for persons justifies the intent.

The focus here is on individuals’ ability to obtain their own information so that they can make considered judgments about how to carry this information forward. It is important to acknowledge and appreciate that participants may have reasons other than medical ones for wishing to receive this information, as it may help to inform other decisions that affect their life, family, health, and well-being. Genetic information, unlike many other data types, has significant implications beyond the individual and is discussed in detail below (Section 7).

In addition to respect for autonomy, the ethical goals of transparency and community engagement are advanced by returning research results. Transparency builds trust in the

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19 For instance, countries in Europe have highly regulated and actively enforced data privacy laws.

20 In some countries, the concepts are evolving. In the US, for instance, the US Precision Medicine Initiative (PMI) views research participants as “active collaborators” in the research; returning results is a key feature of the PMI governance structure (The Precision Medicine Initiative, 2015).

21 President Obama’s Remarks at the PMI Summit, as reported by DJ Hirschfeld.
research enterprise and is an essential component of treating patients as partners. Community engagement is furthered by reciprocity – people give their data and specimens to researchers and, in exchange, they receive information about themselves.

**Balancing autonomy with other values**

Respect for persons is one of a number of ethical principles (Section 4) that must be balanced when determining whether, and what, individual research results will be returned in any given trial.22

A countervailing argument to returning data reflects a concern for the welfare of the individual on the one hand and societal burden on the other. In the absence of clinical utility, the participant may be burdened by, even overwhelmed by, a wealth of data of uncertain significance. Consider an individual receiving every exploratory test and laboratory result without having an understanding of how to interpret those results or even if those results have analytic validity. Imagine giving a participant his or her whole genome sequence – the precise order of the four bases (adenine, guanine, cytosine, and thymine) without any interpretation or simply the dictum to find someone to help with interpretation. Not only could the individual be distressed, but clinical investigators and health care providers may be burdened with the communication and with the follow-up of research results despite the lack of clinical (or personal) utility they could provide. Unnecessary testing and procedures in response to spurious or ambiguous research results will place an economic burden on society. Finally, the promise of individual test results should not be used to induce participants to volunteer in a trial.

**Participant Perspectives**

Several studies have shown that the vast majority of participants in clinical trials are interested in receiving results from the studies in which they participated.23 Researchers should consider and appreciate the various reasons why participants may want access to their results. Clinical actionability (discussed in Principle 6) is only one reason individuals may value individual research results. Patient advocate representatives may provide valuable insights into patient attitudes toward the return of individual results, and into which types of results may be considered of value by research participants.

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22 The type of data and the context and details of the clinical study are important considerations, as is discussed further in this document.

5.2 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.

In the planning stage, consideration should be given as to whether and how much data to return, which results to return, and when, by whom, and how results will be provided. Resources for the return of individual results process should be allocated accordingly. The operational challenges, feasibility and burdens placed upon investigators, sites and sponsors should be considered at this time.

Preparation and forethought are essential in return of individual results. Return of individual results should be coordinated with any return of overall results, as appropriate. Throughout the planning of any prospective clinical trial, consideration should be given as to whether, what and when results will be obtained, and who will communicate them to whom. The likely clinical validity and potential significance of these data must also be considered. Further planning should involve any necessary “hand-offs” (e.g. from the individual in receipt of the result to the research team to the participant or their designated caregiver)—if it is decided to return the results. Notably, there are practical implications at each stage of planning. For instance, if results will only be available after the participant has completed the study, contact information for the participant will need to be maintained, and the participant, and potentially the IRB, will need to agree to such contact. Prospective planning and communication will also help to inform the participant to understand whether, what, and when results may be returned. Participants then have the opportunity to decide how and to whom this information is provided.

During study design
During trial planning, the study team should prospectively review each planned research procedure and the types of results (as well as the range of possible result values) they will generate. Protocol designers can use this information to develop an appropriate communication and action plan, ensuring the safety and welfare of participants. Towards this end, the following questions may be pertinent:

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24 Research “procedure” here is used to represent tests including blood or urine laboratory (e.g. hematology, chemistry, etc.) tests, radiography, pulmonary function or cardiac tests, microbiology, etc.; genomic and genetic determinations; as well as procedures (e.g. radiographic procedures, biopsies, endoscopy, etc.) and tests/procedures that are experimental in nature. One definition holds that “A medical procedure is a course of action intended to achieve a result in the delivery of healthcare” (Wikipedia contributors, 2016). A medical procedure with the intention of determining, measuring or diagnosing a patient condition or parameter is also called a medical test. Other common kinds of procedures are therapeutic (i.e., with the intention or treating, curing or restoring function or structure), including the large group of surgical procedures.

25 Note that we have replicated certain parts of the guidance documents in the MRCT Center Toolkit for convenience. This list of questions is included as Tool 2.

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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?

6. What is known regarding the clinical validity (i.e., specificity and sensitivity) of the test and the result?

7. Given what is known about the test/procedure, will the results be interpretable?

8. Who will receive and interpret the result? Is the person interpreting the results licensed appropriately? 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?

9. When will the results be available relative to when the procedure was performed?

10. Will the results be available while the participant is enrolled in the trial and/or the trial is still ongoing?

11. 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?

12. Could communication of the result impact the integrity or bias the outcome of the trial? If so, would this answer differ were the result provided at a different (later) time? What would be compromised if results were provided at a different (later) time?

13. Who will communicate the result – and with what interpretation – to the participant, guardian or legally authorized representative?

14. Regardless of the timing of follow up (e.g., urgent, routine), if the result is one that demands referral for clinical care, who will ensure such referral?

15. Will counseling or other support be offered to the participant?

16. Is the appropriate method of communication via the participant’s health care provider, and does the informed consent ask for permission for such contact?

Excluded from this discussion are results from medically-indicated clinical tests that are secondarily used for research—in these situations, the clinical setting and designated health care providers are responsible for follow-up decisions. Examples include results of a complete blood count, chemistry lab or radiography that is completed during a clinical visit, the results of which are used in the research record; or a PET scan, indicated for clinical care, the results
of which are also used for determination of response to an investigational therapeutic regimen.

Protocol drafters should methodically delineate and review each required research test and procedure, determine the validity of each potential result, identify each result that could be obtained at each time interval, determine what results would require immediate (urgent) or routine communication and the parameters for such return. Only then can the protocol drafters consider and recommend an appropriate communication and action plan, ensuring the safety and welfare of the participant.

We cannot recommend the threshold at which results “should” be communicated. These decisions are situation-dependent and case-specific. At a minimum, we believe that participants should be informed of their right to request the information, and that participants should be informed if, and which, results will not be returned, as discussed further below.

Access and Equity
Equity and access are not equivalent across international sites in a global trial, as there may be significant differences in individuals’ ability to act on individual research results depending upon their socioeconomic status and health system access. Information technology resources and internet connectivity can vary widely within and between countries in a multi-regional clinical trial (MRCT). Investigators who are accustomed to conducting research in technology-rich settings should be thoughtful about how information is returned, including potentially offering resources for providers. Technological approaches that match the resource setting should be chosen, and consideration given to methodologies that provide effective and equitable access.

In addition to differences in internet and telephone access and differences in the degree of health literacy, there are also significant barriers to disseminating information to participants who do not speak or write the predominant language in the region where the study is conducted. Health literacy principles should be employed in English and in each language that was used for the informed consent. Special accommodations should be considered for individuals who are not literate.

5.3 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 participants’ preferences to receive these results.

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26 Whether individuals in different locations, or existing under different circumstances, should be treated differently in any given location, is a separable ethical issue.
The informed consent process should be explicit as to whether individual research results will be returned to participants and what and when information will be returned. Participants should be informed that they also have the right to change their decision at the time information is made available. If results will not be returned, this should be stated clearly, preferably with an explanation of the rationale for the decision not to return.

Implications for the informed consent document and process

The results generated from research procedures are a foreseeable benefit (and risk) of the research, whether anticipated or incidental. Thus, mention must be made in the informed consent document, and explained during the informed consent process, of the possibility of such results, and the plan for handling them. At a minimum, the following areas should be addressed:

1. In all circumstances and at all times, the return of individual research results must comply with GCP to protect the safety of participants.
2. Potential participants should always be informed of their right to request and to decline results.
3. 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.
4. If results will be returned, the anticipated timeframe for when the results will be available should be included. A reminder should be provided at participant’s last visit.
5. Given that results may need to be disclosed to a participant’s caregiver (whether intended or due to unforeseen circumstances), the research participant should be made aware of this possibility and consequently plan for this possible disclosure. There may be times when such permission is a condition of trial participation.
6. Potential participants should be informed if and when results will be entered into the clinical record and in any data sharing repository. Occasionally such entry is mandatory and is therefore a condition of trial participation. If this could affect a participant’s insurability (whether applicable to health insurance, long term disability, life insurance, etc.) the patient should be informed of this since it could impact their interest in participation and/or receiving research results.
7. Potential participants should be informed whenever results will not be returned, or will be returned only in specified circumstances. 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.

The IRB should review the informed consent document to ensure that intentions and limitations of return of individual research results are clearly outlined, including the potential

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27 And aggregate research results, as discussed in a separate MRCT Center guidance.
benefits and risks of return. Specific recommendations regarding genetic and genomic data and informed consent documents are discussed in Section 7.4.

**Considerations in providing individual results to a designee**

There will be circumstances in which delivering results directly to the research participant is not possible and a designee will be involved in the disclosure process. In the case of pediatric patients, the parent or guardian is the designee. In cases of an individual who lacks capacity for decision-making, the Legally Authorized Representative may serve in that role. Occasionally, the adult/competent research participant may also wish to designate a third party to be the designee; this should be documented, and any restrictions to open communication with the designee noted. Further, researchers should anticipate other eventualities (e.g., future incapacity or death) and discuss them with the participants in advance of any unexpected event. In some countries (e.g., Sweden), it is illegal to contact family members with health-related information unless the participant has agreed in advance.

Appropriate return of individual results requires awareness of local and national regulations that govern information disclosure and consent (Principle 9). The output of this review should be incorporated into the informed consent and enrollment process at each study site. In addition to review of regulations, researchers in local study contexts will be an invaluable resource by providing anecdotal and practical advice that reflects current practices, many of which may not be enshrined in the legal framework or academic literature.

Cultural considerations are also fundamental. Local social customs regarding the discussion of conditions that may carry a stigma such as HIV infection or cancer, differing family structures that impact decision-making, and divergent cultural norms on familial (and community) decision-making all play a role in the deliberations about whom to inform, and may differ across countries and regions (Garrison, 2015). Again, local researchers and patient groups may be able to offer important insights.

Further complexities exist when considering the return of genetic data. These data are often, but not always, present as an exploratory objective in the clinical trial. Due to the implications of genetic results for immediate and extended family members, additional questions arise regarding what obligation, if any, exists to provide such results to individuals who are not participating in the study. Particularly when the participant is deceased, researchers may feel an ethical obligation to provide results to family members or may be approached by family members who are seeking this information. Again, it is essential to seek advice within the local jurisdiction, as the extent to which information can be provided to family members in the event the research participant is unable to give affirmative consent for this will vary. In the US, for example, the HIPAA privacy rule protects individually identifiable health information about a decedent for 50 years following the date of death of the individual (45 CFR 160.103 (definition of Protected Health Information (2)(iv)), (S.M. Wolf, 2015), although communication of personal medical information to family members and others who

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29 And for HIPAA-covered entities in the US.
participated in care is allowable. Anticipating and planning for situations that require affirmative consent by the participant, therefore, are advised.

Special considerations should be given to pediatric research participants who may reach the age of majority before results disclosure. Some genomic results generated during the study may not affect that participant’s health until adulthood. It may be important, in such cases, to protect children from learning risk information about adult-onset diseases before they have attained the developmental maturity to process such information.\(^3\) Further, information about the child may have immediate implications for adult family members. When and to whom such genetic information should be disclosed must be considered on a case-by-case basis, and optimally in the planning stages of the trial. Differing family dynamics, cultural views, and national laws and regulations should be taken into account when planning for results disclosure to minors participating in clinical trials. Importantly, whether the pediatric patient will be offered results upon attaining the age of majority should be considered optimally during the planning phases of the trial; in such cases, provisions for re-consent of the now adult participant may be needed.

It is also important to consider where a participant will feel most comfortable making decisions about whether or not, and how, to receive results. These discussions may be most appropriately held not at the clinical trial site, but at the venue where the individual routinely receives medical care (e.g., a primary care office). It may be helpful to ask participants to identify or nominate a designee or health care professional to be their primary point of contact during the study, and then opt-in or opt-out of specific data types that they wish to receive directly.

5.4 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 research participants are protected.

The overall plan for return of individual research results (whether, how, when and by whom results will be disseminated) should be reviewed and approved by an independent body, generally a research ethics committee (REC) or institutional review board (IRB) that is charged with the responsibility of protecting the participants’ rights and welfare. The REC/IRB should also review disclosures that were not planned but are deemed necessary for compelling clinical or ethical reasons (e.g., unexpected genetic findings with potential impact on a participant or their family).

Independent ethical review boards, such as RECs and IRBs, are country-specific and have the responsibility of protecting participants’ rights and welfare. They are guided by ethical foundations, such as those outlined in Section 4 of this document. They may also address other ethical issues that emerge and, since they have knowledge of laws and regulations that may impact a participant’s ability to access research data (Principle 9), they may make specific recommendations related to these patient rights when reviewing protocols and disclosure plans.

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

For most categories of results, individuals should have the opportunity to decide whether or not they wish to receive them. Results of critical and immediate clinical importance may represent exceptions to this presumption.

To respect an individual’s autonomy one must, “give weight to [their] considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others” (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). In the context of return of results, this includes giving individuals the opportunity to receive or not receive individual research results, and respecting the decisions they make in this regard. Individuals should be given the opportunity to decline results. For the categories of results in Figure 1 (including pre-study screening results, routine results and non-urgent incidental/secondary findings, urgent incidental/secondary findings, individual study results, and exploratory results) individuals should be told which results, will be returned and why. Individuals should also be informed that these results can sometimes signal temporary and easily remedied medical conditions (a low blood-glucose measurement, for example), but in rare cases can also have long-term consequences for participants and their family members, such as the finding of a malignant tumor or the prediction of a genetic

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31 A recent study concluded that “additional findings” was the preferred term by patients which was considered more neutral and accessible than other terms. See: Tan et al. (2016)
condition that has not yet been manifested and/or diagnosed. For findings which were not anticipated at the outset of the study (e.g. incidental findings and results from unspecified exploratory testing), the choice an individual made at that time may not be considered an informed choice. In this situation, re-consenting when additional information is available may be an appropriate approach. These conversations are delicate, however, as a participant’s autonomous decision to receive information should be independent of the specifics of that information. It is usually helpful, and may be required, to consult the IRB/REC in these situations.

If testing for potentially-significant results (e.g. a known genetic variant) in an accredited laboratory, researchers should provide participants with a structured opt-in or opt-out process. If, however, tests are performed in a research laboratory or are exploratory in nature, researchers should explain that results will not be returned and why. This process should allow patients and their designated representatives an opportunity to be educated about the data and their potential limitations (i.e., clinical validity and utility, which are discussed below in Principle 6).

Ideally, educational sessions and the return of individual research results should take place while the study is still ongoing, regardless of when the results will become available for disclosure. There are two reasons for this. First, it ensures that participants are informed as fully as possible of potential future events related to the study and understand the risks and benefits of receiving the information. Second, it is likely to be a more efficient use of resources to engage with participants during the study than to attempt to re-contact participants after a study site has closed, at which point the logistical challenges are greater and the site risks losing contact with participants.

Only in rare cases should an individual not be given the opportunity to opt out of receiving results. If an urgent result is obtained, the investigator may be compelled to return—and/or to act on—the result regardless of the participant’s preferences (e.g., malignant hypertension or a dangerous blood potassium level). This situation does not present a problem if the investigator is also the participant’s healthcare provider; in this case the fiduciary duty of the provider to the patient is operative and no permission is needed. But if there is an urgent result, the participant has chosen not to receive results, and the investigator is not the participant’s healthcare provider, the IRB/REC should be consulted if time permits. If it is not possible to obtain IRB/REC advice in time to avoid potential harm, the researcher should exercise his or her best judgment in returning results and consult with the IRB/REC afterwards in order to determine if further action is needed or if a different approach should be taken should the situation arise again. If critical results of immediate clinical importance are a possibility, and not informing the participant would put them at risk of injury, we recommend that the informed consent form state explicitly that this information will be

32 Unless the decision is made, concordant with GCP, that a result must be returned.
33 If the researcher is not a licensed health-care provider, a licensed professional—potentially the medically responsible physician associated with the trial—should be consulted.

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shared with the participant and/or directly with their health care provider, in accordance with
the non-maleficence principle (see section 4.2). This will allow researchers to take action
quickly to help ensure the safety of the trial participant—and provides clarity for the
researcher so that he/she may exercise his/her duty. It will also empower the participant,
given this knowledge, to choose whether or not to participate in the study at a time
appropriate to make the decision.

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

Participants should be provided access to as much of their data as possible; however,
consideration should be given to the validity of the test as well as to the medical,
social, and/or personal usefulness of the results to participants. Additionally,
communication should use plain language and follow health literacy principles.

While there are numerous arguments in favor of the return of individual research results to
clinical trial participants and many participants may be interested in receiving their individual
results, careful consideration should be given as to whether to return results. This is especially
ture in instances where there is uncertainty regarding the validity or medical actionability of
the result or if there is a risk of misinterpretation or therapeutic misconception\textsuperscript{34,35} that may
result in ill-informed decision-making.

Importantly, clinical research differs from clinical care both in terms of its goals and
procedures (Jarvik et al., 2014), and thus results that are communicated to individual
participants will likely differ between these settings (Principle 8). Further, researchers and
sponsors need to be aware that different locales may have different regulatory and legal
requirements for the return of individual results, and some jurisdictions may require
confirmatory diagnostic tests prior to disclosure. In addition, sponsors cannot interact directly
with trial participants, as per International Council for Harmonization/Good Clinical Practice
(ICH/GCP) guidance; thus they cannot return results directly but need to engage an
intermediary such as investigator, study site team, third party website or communications
team.

\textsuperscript{34} Therapeutic misconception is defined: “Therapeutic misconception exists when individuals do not
understand that the defining purpose of clinical research is to produce generalizable knowledge,
regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention
under study or from other aspects of the clinical trial.” See (Henderson et al., 2007).
\textsuperscript{35} Snowdon, Garcia, and Elbourne (1997); Featherstone and Donovan (2002); and Corrigan (2003)
quoted in Hallowell et al. (2009).
In a finite number of cases and consistent with GCP, return of results may be obligatory. This is supported in the Declaration of Helsinki: “While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects” (World Medical Association, 2013) (Principle 8). For instance, the identification of an imaging anomaly suggestive of the presence of a tumor requires informing the participant and making provisions for appropriate clinical follow up. If a result is uncovered that has a significant impact on the research participant’s health and well-being, it is paramount that the result be returned in a timely manner. Resource requirements may be challenging; it is exactly for this reason that planning is essential (Principle 2).

Returning valid and relevant results

In general, results that are returned to research participants should be validated, clinically relevant, and provide some degree of personal utility. Analytical validity indicates that the research finding accurately and reliably identifies a particular characteristic that can be attributed with a high degree of confidence to the individual and be independently confirmed (Knoppers et al., 2013; Viberg et al., 2014). Clinical relevance involves an “actionability” threshold, beyond which the intervention has the potential to influence treatment or patient management.

Furthermore, actionability may change over time: results that are not currently actionable may become actionable as technology, science, and understanding advances. For example, genetic variants and other biomarkers of unknown significance may become, in time, interpretable and/or associated with clinically meaningful endpoints. However, the threshold of actionability is often contextual and subjective, and the criteria for actionability may be viewed differently by participant and researcher.

Personal utility indicates that the result can “reasonably be used for decisions, actions or self-understanding which are personal in nature.” (Bunnik et al., 2012) In addition, the information must be meaningful and be capable of being put to use in some reasonable way (Bunnik et al., 2012). Reproductive utility includes the determination that an individual is (or is not) a carrier of a rare pathogenic genetic variant that may not have immediate impact for the individual in terms of his or her own health, but could have utility for family planning. If a genetic variant is correlated with or predictive of future serious illness, there may be personal utility for that individual (e.g., life decisions) even when clinical intervention is not possible. Different cultures and populations might view their health information differently; researchers should explore what individuals consider useful research data. Clinical, reproductive and personal utility of a result should be considered.

While scientific knowledge advances over time, clinical investigators do not have an ongoing responsibility to seek out participants after the trial is over to inform them of results that subsequently become significant. Instead, the investigator’s responsibility ends with the study. The informed consent document should explain the termination of responsibility at the end of study and any other conditions or limitations. Additionally, re-examining test results for new pieces of information is not required. For example, conducting genome sequencing to study certain variants (e.g. those known or suspected to contribute to variability in responses

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to a drug) does not impose the obligation to look specifically for other variants contained in
the sequence that may confer clinically meaningful information. Burdening clinical
investigators with an obligation to search proactively for actionable results that are beyond
the study aims either during the study or after it has completed, or to return results which
become significant after the research study has finished, would significantly divert resources
from the research goals (Presidential Commission for the Study of Bioethical Issues, 2013).

The limits of results derived from research procedures should also be explicit. Not all research
procedures are equivalent to their clinical comparators, and these limitations should be
explained during the informed consent process and in the informed consent document. For
instance, a novel radiographic technique measuring air exchange will not necessarily discern
the same findings as a clinical chest X-ray; this should be stated explicitly. Participants may
not appreciate the technical differences of these procedures, and therefore they deserve a
clear explanation in advance of consenting to participate.

Some experts have recommended that plans be made for appropriate referral for clinical
follow-up prior to the participant being offered the result (Jarvik et al., 2014). In particular,
ambiguity may exist in the interpretation of results (e.g., some genetic results) and specialists
(e.g., genetic counselors) may be necessary to help evaluate risks and benefits of a particular
course of action. In general, counseling should be a key consideration whenever a pathogenic
or likely pathogenic genetic variant is returned; local considerations related to the availability
of qualified specialists, ethical norms, and clinical practice must be taken into account. Of
course, such referral, and the expense thereof, may not be possible or practical, even if
recommended. But it is important to recognize that the responsibilities of the researcher
may, for certain result types, extend beyond simply returning individual results with
appropriate context and may also require that a plan is in place for appropriate confirmatory
diagnostic testing and/or counseling.

There is a risk of overburdening research participants with large amounts of data, with or
without interpretation, and a risk that the data, despite interpretation, may be
misinterpreted. There is also the possibility that the data are, in some cases, wrong. This risk
is greater for results generated in an exploratory environment and for those that do not meet
the standard for analytical validity because of the laboratory testing methodology, limitations
in the current biomedical knowledge base, or other reasons. Nevertheless, if consistent with
the informed consent form, the participant retains the right to request their data, valid or not,
actionable or not, interpreted or not. Sponsors and investigators should address the legal
liability of such return and of a decision not to return. Although informed consent forms
cannot “release” investigators or sponsors from liability, the informed consent form and
process can establish appropriate expectations in regard to return of results.

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36 Many studies are not performed comparably to the clinical setting or subject to a clinical
interpretation.
5.7 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.

The plan for returning research results should safeguard the integrity of the study and the ability to attain the study’s research aims, insofar as the safety and welfare of research participants are not compromised. Timely return of results will help to ensure that any direct or indirect benefits of the results to the participants will be realized. Study design, the specific type of data and the medical importance of the finding may influence the timing of return.

**Timing of results delivery**

Setting realistic expectations for clinical trial participants includes both conveying which results may be returned to the individual (Principles 3 and 7) and helping the participant understand the impact of the timing of the communication.37

Timing of the return of individual research results must be concordant with the research participant’s health, safety and wellbeing. Urgent results should be returned without delay, and the potential need to do this should be appropriately anticipated (Principle 2). If the result is not thought to impact the participant’s immediate health, then the return of results must be balanced with the participant’s desire to know and the scientific integrity of the study that is paramount.

The purpose of research is to create generalizable knowledge dependent on scientific and data integrity. Delivering individual results in “real time” (during the trial) may, for example, result in unintentional unblinding of clinical trial intervention groups or biasing of subsequent data collected. The integrity of the trial may be jeopardized, similar to the effect of insufficient masking during the trial (Schulz et al., 1995).

While delay of communication of results may be necessary for study integrity, the delay may also render the result less impactful or relevant (Presidential Commission for the Study of Bioethical Issues, 2013). In light of these competing factors, it is important for researchers to seek input from ethics committees that have an understanding of the aims and integrity of the research, the needs of the study participants, and the ethics of clinical research. The Presidential Commission for the Study of Bioethical Issues in Recommendations 11-13 has emphasized this interaction and exchange and the need for IRB involvement in the development a realistic data return plan.

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37 In that, often, there will be a long delay before results will be returned.
5.8 Principle 8: The purpose of research is not clinical care, and return of individual research results cannot substitute for appropriate clinical care and advice.

*The purpose of research is to produce generalizable knowledge for the benefit of society. This differs from medical care that is intended to benefit individual patients. Therefore, it is important to define in the informed consent form the limits of the clinical trial and the role and mission of the researchers in that trial.*

**Ethical framework pertaining to research-care distinction**

Principle 6 describes the obligation to return results responsibly while accounting for clinical utility, while Principle 8 focuses on delineating the difference between research and clinical care. These principles may at first appear to conflict. The resolution rests on an appropriate understanding of the purpose of research, the accompanying respect owed to participants for their contributions, and the differentiation between research and clinical care.

The perspectives on the research-clinical care distinction can be viewed along a continuum. At one end of the spectrum:  
*Research and health care are entirely different spheres of activity that do not intersect.*

Research is explicitly aimed at obtaining data at the population rather than the individual level. Participants should be informed not to expect that results discovered in the research context will be shared, nor should the researcher assume an obligation to act on any such result. Participants should be discouraged from viewing research as a surrogate opportunity for healthcare and/or screening; they should be reminded that they always have the opportunity to seek care in the healthcare system and even if the research protocol is offered as a part in or as a component of their healthcare setting, they have the right to decline participation without consequence.

And at the other end of the spectrum:  
*Clinical researchers are generally physicians and carry the normative duties of that profession into their research work.*

Clinical research often utilizes clinically relevant tests that are appropriate to the disease or condition of the population under study. Research participants are partners in the research enterprise, and if practically feasible, have a right to data obtained during research that may be relevant to their own health status and personal decision-making. Research often takes place in the clinical setting and “researchers” are often clinician-investigators, many of whom are caring for their own patients within the clinical research context. Thus, research and care are two aspects of the same enterprise and share a common obligation to the patient-participant.
Treating physician as investigator

In consideration of return of research results, maintaining a distinction – albeit inexact – between clinical care and research is important to avoid the therapeutic misconception. In some cases, however, physicians serve not only as an investigator on a clinical trial but also as the participant’s primary health care provider or specialist; consequently, understanding and appreciating the distinction can be complicated for the participant. The informed consent process should reinforce the understanding of this concept.

This distinction is also challenging for the physician-investigator. It is helpful to draw theoretical boundaries to help “health care professionals to overcome the potentially conflicting demands and duties associated with their different roles” (Hallowell et al., 2009). The physician-investigator should return research results based on the data type (see Figure 1), in a context that reiterates the purpose of research and the potential clinical utility for the participant. Importantly, the physician-investigator must ensure that the return of individual results reflects the participant’s interests and autonomous choice in having access to the data. In complex situations, it may be helpful for the treating physician/investigator to seek input from an IRB or a peer.

What if the investigator is not a physician?

If the clinical investigator is not licensed to practice medicine, a medically responsible individual (usually a physician) must be assigned to the trial. The process of interpreting research results must involve a clinician who is capable of (and credentialed for) interpreting the result, making a determination about the urgency of the clinical findings, and recommending the necessary plans for follow-up. In general, while some interpretation may be provided when individual research results are shared, researchers should not frame results in the context of medical advice; rather, investigators should recommend that the participant consult his/her physician or an appropriate specialist. Encouraging the research participant to involve their medical team will allow results to be considered in the appropriate medical context.

If the investigator is a licensed physician but is not an expert in the therapeutic area pertaining to the result or an incidental finding, a preliminary expert review, if possible, is recommended. This will ensure that the result is assigned the correct urgency prior to notifying the participant and/or the participant’s medical care team.

What if the participant lacks a primary care provider or access to health care?

Some participants in clinical trials are enrolled without an assigned primary care provider or access to health care resources. Returning results and involving a medical care team is particularly challenging in these scenarios, especially when the participant is a healthy volunteer with no other contact or affiliation with the health care system. Alternatively, some participants may identify a primary care provider who cannot be found or who denies knowledge of the participant at the time that results are returned.

These recommendations do not suggest that clinical investigators are required to interpret all results pertaining to all trial participants personally. Rather, there should be a process in place...
to identify and flag results that are out of range, and those should be reviewed and referred appropriately. As part of this process, there is a responsibility, especially with complex results such as genomic results, for the clinical investigator to be provided with enough context that they are able to understand the potential impact a result can have to the health and medical management of the research participant.

5.9 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.

Any plans for return of individual research results should comply with institutional policies of the sponsor and investigator and the sovereign laws and regulations of the jurisdiction in which the participant resides and in which the sponsor, investigator and/or institution operates.

While there is general agreement that the discovery of findings may warrant return of individual results to participants who choose to receive them, there remains a lack of guidance, policy or international alignment on such return. Clinical investigators and researchers need to be aware of differences in national and local legislation, regulation, guidance and institutional policy.

Internationally, each country may have unique considerations that relate to national regulations, clinical guidance and ethical practice. In some jurisdictions, the provision of research-grade test results may not be aligned with law or local clinical practice while, in others, participants may have a legal right to access their individual research results.

For example, in the United States, the Health Insurance Portability and Accountability Act (HIPAA) “Privacy Rule” provides research participants with rights to access their research data held in designated records irrespective of the environment in which they were generated, whereas the Center for Medicare and Medicaid Services (CMS) currently interprets the Clinical Laboratory Improvement Amendments (CLIA) regulations to prohibit the return of non-accredited results for treatment or health assessment purposes (Barnes et al., 2015).  

Norway’s Health Research Act 2008-06-20 no. 44 includes provisions establishing the right of research participants to access all personal health data generated as part of a research study.

38 The HHS Secretary’s Advisory Committee on Human Research Protections (SACHRP) has highlighted the need for clarification of HIPAA and CLIA regulations; while inconsistency remains, researchers in the US should seek appropriate guidance from legal counsel during study planning.  

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Furthermore, many countries have data privacy laws which allow the subject to access all personal data collected or generated about them (Argentina Personal Data Protection Act No. 25326, 2000). In France, a subject has the right to receive a copy of their personal data upon request (Article 39, Loi Informatique Et Libertes Act N°78-17 Of 6 January 1978, 1978).

The EU General Data Protection Regulations (GDPR), \(^{39}\) will become effective on May 25, 2018 in all EU Member States, repealing the EU Data Protection Directive 95/46 EC. It introduces many new privacy, data processing, and consent related rights that will require close consideration and potential operational changes at various levels by the global research community.

The GDPR expands the data subject’s right to access, review and rectify his or her personal data and challenge automated decisions about themselves. Personal data includes genetic data that relates to the inherited or acquired characteristics of the individual which give unique information about the health of that individual. Personal information must be provided within one month of receipt of the request; this period may be extended by two more months where necessary. Where feasible, there should be a means for requests to be made electronically, and for the data to be returned in a commonly used electronic format.

The GDPR places specific requirements around what constitutes a valid consent. It requires a statement or clear affirmative action of the individual, e.g. pre-ticked boxes and implied consent will not be sufficient. A request for consent must be in an intelligible and accessible form in clear and plain language and in accordance with the Directive on unfair terms in consumer contracts. Where the request for consent is part of a written form, it must be clearly distinguishable from other matters. However, consent through a course of conduct remains valid. If the relevant processing has multiple purposes, consent must be given for all of them. Consent will only be valid if the individual has genuine free choice and there are no untoward consequences if they refuse or withdraw consent.

Health and genetic data are considered to be "Special Categories" of personal data, having enhanced control requirements requiring specific consent. Consent must be specific to each data processing procedure, be "explicit and unambiguous" and must be freely given. The use of genetic material, biometric data, and data revealing racial or ethnic origin of trial participants constitutes the processing of sensitive personal data and requires specific consent.

The GDPR also gives people the “right to be forgotten” and, in certain circumstances, the right to data portability, e.g. to obtain their information electronically. Article 17 of the GDPR states that a trial participant can “at any time” request that their data be removed “without

undue delay”. This would require the identification and deletion of any data, whether stored by the sponsor, Contract Research Organization (CRO), hospital or any other third party. The right to be “forgotten” cannot be waived in the consent form. However, Article 89 of the GDPR allows the EU or Member States to limit certain individual rights, when necessary, to enable scientific research.

It is important to consider that the right to withdraw data -- and the consequent data destruction-- may introduce bias into the research and the data set. People who request “to be forgotten” may differ in important respects and in a non-random distribution from those who do not. For instance, trial participants who experience adverse effects or lack of efficacy may disproportionately request data destruction, and the resulting missing data may prevent identification of a subgroup that does not respond well to a therapy. In addition, in the highly regulated environment of a clinical trial, GxP ("good practice") requirements may expressly prohibit data destruction. Thus, the “right to be forgotten” may not apply uniformly to research data that are already created, limiting the extent and timing of data destruction.

In addition to the EU GDPR, some countries have laws specifically addressing return of genomic results (see section 7.7.3). However, some countries and research institutes may lack policy and/or guidance on the return of clinical trial research findings altogether. Thus, in the conduct of international MRCTs, there is the very real possibility that participants may differ in their rights to access their individual research results: while some may be given access to certain data elements, others in different jurisdictions may not—even though the results were analyzed in the same laboratory using the same analytical methods.

A further consideration for clinical trial researchers is what to do if the research participant is deceased, particularly for certain types of research data (e.g., genomic results) that may be of potential benefit to the research participant’s living relatives. When policy exists, there are clear differences among countries (Branum & Wolf, 2015). Clinical investigators understand the requirements in the countries in which they are operating.

Taken together, it is clear that clinical trial researchers are faced with a complex and ever evolving set of requirements that must be navigated and understood when planning the communication of individual research findings to participant. While some information can be found on government websites (U.S. Department of Health Human Services, 2015); National Statement on Ethical Conduct in Human Research (2007); R.D. 14, 2007), interpretation will be necessary. Numerous peer-reviewed publications can help researchers interpret information but it is important to recognize that litigation, guidance and policy are rapidly evolving and that published information may not be up to date. Thus, during study planning, clinical study sponsors should investigate the legal, ethical and clinical frameworks in each jurisdiction where they intend to enroll participants... Clinical trial sponsors and researchers should consider consulting attorneys with experience in each jurisdiction, or global organizations such as Consortium of IRBs (CIRB) to provide advice and referrals as necessary.
6. Considerations for returning individual results

This section presents an overview of considerations for returning individual results identified by the MRCT Center Return of Individual Results Working Group. While the above Principles apply to all categories of clinical trial data, differences in the particular considerations for each scenario lead to variation in their application.

Each individual chooses to participate in a clinical trial for a variety of reasons, and returning individual results to them when feasible and appropriate honors their participation.

In a complex topic such as returning individual study results, the plan for return of individual results may vary from one trial to the next. However, the four underlying questions for creating an appropriate plan are consistent:

**What?** – Which results should be returned? What is typically returned as a component of the trial? Are there national or international regulations or clinical guidelines that should be considered?

**Who?** – Who will communicate which results and to whom? Who will follow-up with the participant? What are the responsibilities of the various stakeholders during the process (sponsor, investigator, health care provider, and participant)?

**How?** – Is the patient provided with a choice as to whether to receive results? What delivery and communication mechanism will be used to provide results based on the patient population? What role should technology play? How should incidental findings be handled? Who bears the responsibility for associated costs of any confirmatory or additional testing? How has the process of return of results been communicated in the informed consent form?

**When?** – When are the results available? Are they available at screening, during the study, or only after the end of the trial? When can these results be provided to research participants without jeopardizing the scientific aims of the study while ensuring the health of the participant is prioritized? Are exploratory post-trial results, generated potentially years after the close of the clinical trial, to be considered differently? How long does an obligation to return results persist?

The Workgroup’s Recommendations are based on the considerations outlined in the following sections. Figure 1 provides an overview of the different types of data and when they are generated during a trial. For data types A-E, researchers should consider during the planning stage of each trial if and how the individual results will be returned (and if results are returned, which data types). This decision should be guided by the eight principles described in Section 5. We have separated these decisions into distinct questions of Who, What, How and When for simplicity; however, the issues are inextricably intermingled and should not be considered in isolation.
6.1. **What** should be returned?

In determining what data to return, the study team should evaluate the entire spectrum of data types generated during the clinical study (see Figure 1). For each of the different data types, a different approach to returning results may be considered. Data types and approaches are described here.

### 6.1.2 Data Types and Recommended Approaches

The Presidential Commission Report on Secondary and Incidental Findings relies upon “anticipatable” and “un-anticipatable” findings, as well as “actionable” and “not actionable” findings. There appear, however, to be gaps in this formulation in regard to research versus clinical care. Given the flow of information among study coordinators, physicians, and principal investigators during a clinical trial, one should distinguish between findings that have immediate and/or urgent implications for clinical care from those that are of a routine nature or of unknown significance. As a result, the following definitions were constructed to guide these recommendations, as illustrated in Figure 1.

Figure 1 gives an overview of the different types of data and when they are generated during a trial. For each of the data types A-E, researchers should consider during the development stage of the trial if and how the individual results will be returned. This decision should be guided by the nine principles described above in Section 5. Notably, the protocol and informed consent document should anticipate these eventualities wherein they may occur.

**Data Type A: Urgent Results & Incidental Findings** are results that require urgent clinical follow-up identified during research procedures undertaken for the medical condition under study (urgent results) or discovered unintentionally related to a previously undiagnosed medical condition (urgent incidental findings) (Presidential Commission for Study of Bioethical Issues, 2011; Presidential Commission for the Study of Bioethical Issues, 2013). Examples include high calcium levels, liver function test results or a mass on an MRI that may indicate a tumor, and a diagnostic discrepancy.

**Data Type A results should always be returned to the medical caregiver or the participant as soon as they are interpreted and confirmed to be valid and both outside of normal ranges and associated with an urgent need to return as a consequence of potential diagnosis, treatment, or care of the individual.** There is no justifiable reason to withhold these results, as the safety of the participant is paramount, even if the return of these results may have negative implications with respect to the scientific integrity of the study. The tension between

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40 Further, we address *when* results are known later in this document.

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scientific integrity and the ethical principle of beneficence is described in detail in Principle 7. Some incidental findings are neither routine nor urgent, and do not necessitate immediate action or intervention (e.g., a mildly elevated cholesterol level or liver function test, a systolic blood pressure that is the upper limit of normal). These types of incidental findings may not require immediate action but do require prompt follow-up. It is not the intent here to determine where that line for urgent / non-urgent should be drawn for each result. Rather, the licensed professional involved in the situation should use best judgment based on the facts at the time. When uncertainty exists, every clinical trial should have assigned a medically responsible person to the trial (usually in addition to the investigator even if the investigator is a licensed professional) who should be consulted.

Data Type B: Routine Results & Non-Urgent Incidental Findings include routine laboratory, imaging and other medically relevant results collected for research purposes that do not require immediate follow-up. For example, results collected at baseline and at regular study visits that do not require immediate action, e.g., weight, blood pressure, heart rate, blood results, and radiographic images. These results may or may not include data unique to the study, regardless of whether similar results could be or could have been collected in normal medical practice.

Data Type B results contain a combination of two discrete data types: routine results and non-urgent incidental findings. While these findings can be categorized differently according to whether they are anticipated, participants may benefit from receiving these results periodically during the study, as opposed to waiting until the study is complete. Information that could be less valuable to the clinical research might be of value to the participant or their healthcare provider who has an overall understanding of the participant’s other health goals. A recent change in weight, a slow but steady increase in blood chemistry values, or trends that are observed over a period of time, could be informative and beneficial and therefore may be appropriate to provide to the participant closer to the real-time collection of data if feasible. Our recommendation is that the balance of potential benefits to the individual participant should be weighed against resource requirements and feasibility of implementing return of routine results.

Data Type C: End of Study Individual Results are research results (other than data type A or B) recorded within a clinical trial dataset and associated with individual participants. These results may be in the form of data collected about an individual participant’s clinical outcome during the trial (e.g. primary and potentially other endpoints). They can also include details of randomization and treatment received. These results could also include data unique to the study that are not collected during normal medical practice.

41 Adapted from Smith et al. (2015).
Data Type C results include results that are generated during the trial and results that cannot be determined until the trial has concluded. After the trial has concluded, it would be desirable to help participants understand how their individual results can be interpreted in light of the aggregate findings. As discussed in Principle 6, it is especially important to communicate results to participants in a format that will facilitate interpretation by their healthcare provider.

While there is a diversity of opinions about the ethical obligation to return an individual’s findings, the recommendation here is that, at a minimum and if feasible, research participants should be offered information regarding the study arm assignment in which they participated after the study concludes. In addition, communication of primary endpoints should be offered at the end of the study, unless returning these data would compromise the integrity of the study or ongoing studies. Safety data that supports understanding of primary endpoints should also be offered. Secondary endpoints should be handled consistently with European (HRA/EU) recommendations (for aggregate results) and need to be considered on a case-by-case basis. Context and justification need to be provided for those results that will be returned (European Commission, 2017; Health Research Authority, 2017). Offering to return these essential clinical trial results to participants honors the contributions that they made to the scientific process and respects their interest in ensuring that the knowledge gained from their involvement will benefit others with similar diagnoses in the future. Even if results do not have clinical decision-making utility, the process of receiving and discussing the results aligns with the ethical principles of beneficence and reciprocity. Returning individual results on adverse events also needs to be considered, if adverse events are not already communicated via other venues, self-reported by the participant or otherwise known by the participant. Communication of these adverse events to individual participants should be placed in context and that return of these types of results does not imply causality explained.

**Data Type D: Exploratory Results** are data generated from exploratory analyses, rather than confirmatory analyses, which may lead to further research questions for future research.\(^{42, 43}\) These data include exploratory endpoints, for example, biomarker analyses of various mutations or gene expression, and often have unclear clinical significance. Exploratory results may be generated during the study, or years after the end of the study.

Data Type D results are exploratory by definition, meaning that their meaning and significance at the time of collection and potentially at the time of analysis were unclear. Returning Type D results should be handled on a case-by-case basis. Options include: (1) clarification in the informed consent form that there are no plans to return exploratory results; (2) prior to return of Type D data, re-consent due to the complexity and timing of information, particularly in the area of genetics; or (3) provide an option for sharing exploratory findings in the initial

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\(^{42}\) Adapted from International Conference on Harmonization (1998).

\(^{43}\) Adapted from International Conference on Harmonization (1998).
informed consent form and if the participant expressed interest in receiving results, then provide those results. However, it is important to communicate the quality and validity of any exploratory data returned, and document that communication. Returning exploratory results encourages continuing engagement in research as well as responsible stewardship of personal and family health.

**Data Type E: Aggregate Results** are the summary of results from a clinical trial. **We recommend returning to participants a summary of primary endpoints and safety data important to the overall results of the trial**, in accordance with EU Guidelines (European Commission, 2017; Health Research Authority, 2017). A separate MRCT Center workgroup has addressed the return of aggregate results in separate documents:

- **MRCT Return of Results Guidance Document, Version 3.0**

- **MRCT Return of Results Toolkit Version 3.0**

6.2. **When should results be returned?**

In deciding when to return individual results, the Principles discussed in Section 4 should be applied; e.g.,

- 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)

In addition, one has to consider:

- The participant’s health, understanding, and well-being
- What data elements become available at which time during the clinical trial

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44 See Toolkit Tool 2.
• 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 close to real-time would be beneficial for the participant over providing data after the trial has ended (which may have more limited usefulness for the participant).

Thus, sponsors and investigators need to plan at the beginning of the trial and carefully think through many scenarios. In this setting, the advice and counsel of patient advocates may be helpful. Case Studies in the Companion Document, Return of Individual Results to Participants Toolkit, illustrate several scenarios for timing of returning data - urgent incidental findings, results shared during the trial, and results communicated after the trial.

6.3. **Who should receive results?** Who returns results?

Four potential avenues exist for **Who** returns results (see Figure 2):

• Communication from Sponsor to Principal Investigator (PI) and PI returns results to participant
• Communication from Sponsor to PI, PI returns results to Primary Care Physician (PCP) and PCP return results to participant
• Communication from Sponsor to PCP and PCP returns results to participant
• Communication from Sponsor via direct website portal (note: (1) may be linked with electronic health records (EHR) and (2) participant identity may nevertheless remain anonymous to Sponsor) and participant may share with PI or PCP
The participant should be the ultimate recipient of the results; however, the following factors would determine who would receive the results from the sponsor first: data type, presence of a primary care physician, modality of return (electronic, paper, etc.) and the patient population. For instance, if the Data Type is B – routine, non-urgent results in an adult population – there may be no need for a physician to be the party who returns the results to the participant. In that case, for example, the participant could access the data directly from a secure website and share it with their physician. On the other hand, if the result was an elevated lab value or an urgent incidental finding (e.g. elevated potassium on chemistries or unanticipated opacification on radiograph), and thus a result that would require interpretation, the PI might involve the participant’s primary care physician or other specialists in the subsequent care and follow-up. In this case, optimally a medical professional should be the initial recipient of the information who would then follow-up promptly with the participant. Special cases involving participants who have died, require a designee, are lost to follow-up, withdraw or involve genetic results should be carefully considered.

Key areas of consideration include:

- Who communicates results to whom (when and how)?
- How to manage the return of (certain) results when the participant lacks a primary care provider?
- Who has the responsibility to follow up on incidental findings, to diagnose and to treat the patient and how is the transfer of responsibility documented?
• Whether and which findings (data types) must be delivered to a physician and how that potential necessity is communicated to the participant?
• Which findings can be handed off to the participants themselves to communicate to their primary physician?
• How to handle findings that are highly technical, particularly as context is paramount in these cases)? Whether and when is it acceptable to entrust these to a participant to hand-off or transition to another provider (consider complexity of results such as genetic data, urgency)?

There are complexities in terms of who is best positioned to deliver information to research participants. These complexities need to be planned for as a data return strategy is developed to ensure information is communicated and presented in a way that allows for informed clinical decision-making.

6.4. **How to return results to participants?**

6.4.1 Considerations
There are many considerations for how to return individual results, after the decisions of “what” when and who to return have been made. For each type of data to be returned, consider:

• Pros and cons of the different modalities of return (see Section 6.4.2).
• Privacy of the participant when reaching out to family or designees, and whether the informed consent was explicit in how the results would be returned and permission to contact has been given.
• Types of data (high/low risk) considered.
• Access of participants to a health care professional to receive both anticipated and unanticipated results.
• Need for interpretation: Some data require more intense interaction with the medical community for their interpretation. In some instances, confirmatory or follow-up testing and counseling may extend beyond the responsibilities of the trial. The study team should prepare and consider these implications. In certain circumstances, specific eligibility criteria may be necessary to ensure that these are in place for patient well-being (e.g., for certain trials, the necessity of the patient having a designated primary care provider or access to genetic counseling may be considered as possible inclusion criteria).

If institutional policies pertaining to returning individual results and incidental/unexpected findings are unclear, outdated, or non-existent, then these issues ought to be addressed prior to launching a clinical trial to ensure clear expectations and mutual cooperation. Further resources for IRBs/RECs and study teams may be found in the companion *Return of Individual Results to Participants Toolkit* (Section 2: Tool 3 Informed Consent Language for Return of
6.4.2 Modalities for returning individual results

Modalities for how results will be returned should be addressed during the study design process, documented in a Data return plan by the team, and reviewed by the IRB/REC. The specific modality chosen should be directly related to the data type (see Figure 1) to be returned. There are many options for returning results and the choice of method will depend, at least in part, on the specific situation. Four (4) common communication methods will be discussed below. All of them require time and resources that necessitate planning from the beginning of the trial and time and resource availability may impact how (and what) is returned. For each modality, it is important to consider how documentation of the exchange of information will be executed. It may also be preferable to employ more than one modality, depending on the circumstances listed above.

1. In-person meeting with clinical research physician, staff member or specialist

This communication method is most often selected for findings that are returned to participants or their designees during an ongoing clinical trial, when study site resources are still available and contact information is up-to-date.

An advantage of an in-person meeting is that it provides an opportunity to ensure that the findings are presented in the proper context and explained, the participant can ask questions and the participant is provided with appropriate referrals for follow up (e.g. genetic counselor) so that they can receive medical advice and clinical care. A disadvantage is the time and resource commitment, and the potential challenge to reach individual study participants and schedule them to meet with a clinical research physician, staff member or specialist.

2. Telephone/video-conference consultation with physician, clinical research staff member or specialist

A telephone consultation may be selected in cases in which a participant is not able to travel to the study site or to a nearby healthcare facility to receive information in person, or in cases when the study has closed and study site resources are no longer available. In this case, the investigator, or clinical research study staff may still be able to make a telephone call. The content of the conversation and the recommended steps for follow-up will differ depending upon the local regulations and the health care infrastructure that is available to the participant.

Advantages of this method are that it does provide an opportunity to ensure that the findings are explained (even if not in person) in the proper context; the participant can ask questions; and the participant is provided with appropriate referrals for follow up to receive medical advice and clinical care. A disadvantage to this method is the time and resource commitment and the potential challenge to reach individual study participants by phone call.

3. Online patient communities or portal
In cases where participants have an interest in taking more ownership of their healthcare and results and have access to the Internet, a secure website may be utilized for return of results. Security and identity management provisions must be considered.

Advantages of this approach include: it allows data to be downloaded or transferred between researchers and participants at any time, during and after the trial, without scheduling a specific appointment; data can be shared as they become available; and participant contact information is not needed once the participants have received the portal URL and established their log-on credentials. This type of modality is enhanced with tools such as video, which can deliver a consistent and thorough message of the general result and available on demand. Interactive questions that can customize the individual information once the context and general data is given. Once established, online access is time and resource efficient. It could also be considered as a supplement to other communication methods utilized throughout the trial. Disadvantages include: the investment needed to design, maintain and secure the Internet portal. Participants, sponsors, and investigators may be concerned about breaches of privacy. Online access to information does not address the participant’s need to ask questions and have results explained.

Notably, if any participant does not have Internet access, is illiterate, or uncomfortable with this approach, alternative modalities of communication should be considered.

4. Confidential Letter

A letter provides a confidential way of sharing results with participants who choose to receive results without requiring a time commitment to attend an in-person meeting.

An advantage of using a letter to communicate individual results is that the participant can refer to this written information at any time and is able to share his/her results accurately with others involved in their health care. Disadvantages include the time and resources for the site to prepare and mail the letters. Additionally, participants may wish to maintain the privacy of their participation in the trial and appropriate safeguards should be taken (e.g. no identifying return address on the outside envelope).

6.4.3 Health Literacy

Many research findings require highly technical understanding of the scientific basis of the research, an understanding of which will not be equally distributed across study participants. Results ought to be returned responsibly, with an adequate degree of explanation and written in such a way that a person without scientific training can understand the essence of what is being communicated. Supplemental information should also be available in writing so that participants can discuss the results with their physician, healthcare provider, or specialist if they require further clarification or clinical guidance in the future as it relates to their individual experience during the clinical trial.
Therefore, communication of results to study participants should follow health literacy principles. Health literacy refers to individuals having the capacity to obtain, process and understand basic health information (U.S. Department of Health and Human Services (HHS), 2010) and to use this capacity to make sound health decisions in the context of everyday life (Kickbusch et al., 2005). Returning research results in a comprehensible and educational manner should actually improve health literacy.

Health literacy principles advocate for writing that uses plain language, makes key messages clear, avoids complex sentences, uses active voice, is appropriately tested for readability, chooses numbers and visuals carefully, and gives numbers meaning and context. For more information on Health Literacy Principles and Numeracy, see Appendices 3 and 4 in the MRCT Return of Results Guidance Document.

7. Special Considerations: Returning Genomic Results

The development of this Recommendations Document for Returning Individual Results illuminated certain conditions that demanded special consideration. Specifically, the complexity of – and the dynamic and growing understanding of – genetic (the study of specific genes) and genomic (the study of an organism's entire genetic makeup) information requires further discussion.

Genetic results may have implications for family and related individuals, a consideration that does not apply generally to other types of results that may be returned, and that have been considered above. We hold to the idea that the overall principles and considerations for returning individual results to clinical trial participants (Sections 5 and 6) can and will apply to genetic and genomic results. The complexity, novelty, national and state/local regulations of clinical laboratories, and evolving nature of the genetic information, however, will require decisions to be made on a case-by-case basis. This chapter is a conceptual discussion rather than a set of additional principles.

Genetic information produced in a clinical trial context is often generated as a result of exploratory research, meaning that a direct association between the genomic variation(s) identified and clinical response is still being hypothesized, tested and validated. It follows that these exploratory results can be generated during the study, years after the end of the study or, in some cases, both. Therefore, it is necessary to discuss the responsibility of the trial sponsors investigators, research institutions and trial investigators to return exploratory data and the timeframe during which they may be provided.

In this section, we begin by discussing, briefly, the nature and significance of genetic information, provide an overview of genomics techniques, discuss why the return of genetic information requires special consideration, and offer specific informed consent content and questions. We then describe what and how results should be returned, as well as some
recommendations about who should return genetic results. Finally, we consider national laws and regulations that apply specifically to this evolving area of research.

7.1 Complexity of Genetic Information

DNA provides information for the growth, development, and biochemistry of humans and all other living organisms. Human genetic mutation is an essentially random process of change in DNA sequence that occurs during the replication of DNA within cells. Such mutation can occur in the germline (the source of DNA for all other cells in the body, originating from the egg and sperm cells that join to form an embryo), in which case it is expected to be found in all nucleated cells of the offspring that inherits it. Germline mutations may occur de novo, in the process of egg or sperm cell formation, or they may be inherited and can result in, or predispose to, various genetic syndromes or diseases.

DNA mutation could also be somatic, meaning that it occurs after conception and therefore cannot be passed on to children. Somatic mutations can happen during normal cell division or as a result of environmental insult (e.g., UV-radiation, carcinogen exposure). While the cellular DNA-repair machinery generally repairs somatic mutations, when this repair does not occur as it should, the end result can be as significant as the development of cancer in one or more areas of the body. However, most genetic variation does not lead to disease and is largely insignificant in the life of the individual.

Genetic information has been characterized in the scientific literature, the popular press, and popular ethical discourse as fundamentally different from other kinds of biological data. The decoding of the human genome resulted in rapid advances in science and medicine and has propelled insights into human disease and variation in drug response. There is already evidence in dozens of drug labels of the contributions genomic research can make to drug development, efficacy, metabolism, and delivery (Food and Drug Administration, 2017). This research is making a contribution to a personalized approach to the practice of medicine.

Compared to other medical information generated during a clinical trial, however, genetic information has broader implications than standard medical test results. A blood test or x-ray provides static knowledge at the point of time it is collected. To understand changes in health, subsequent blood tests and imaging would need to be done. Inherited or germline genetic information, however, is stable: it is our understanding of the significance of genetic variants, association to disease, and risk that is constantly being refined. Similarly, understanding somatic mutations in the context of disease (e.g., cancer) is also critically important—and also an evolving science. It is therefore important to weigh the present, and potential future, utility of genetic data along with the uncertainty of their current interpretation when determining a patient’s current and future health risks. Genetic information may also have implications for immediate family members and a patient’s future reproductive decisions, and these added complexities must be considered.
The debate continues as to whether these considerations are sufficient reason to grant special status to genetic information, a position often referred to as “genetic exceptionalism.” Special laws and policies have already been established to require specific consent for genetic testing and for the disclosure of genetic information, and to disallow the use of genetic information to refuse employment and/or other social benefits. The United States Congress passed the Genetic Information Non-Discrimination Act of 2008 (GINA) to prohibit the use of genetic information in health insurance and employment decisions, and many other countries have similar regulations.

While, in theory, it would seem straightforward to provide individual genetic results upon request, it is a much harder task in practice. Individual genetic results that are both reliable and significant to an individual’s health should, in general, be returned to individuals consistent with their wishes, according to the principles explored in Section 5, assuming that doing so is consistent with applicable law.

In some cases, however, we must also respect a patient’s right to refuse such results, even if highly relevant. Those who refuse will cite many of the same reasons as people who wish to receive these results, such as the aforementioned implications for family members, the lack of clarity around medical implications, and in some instances, the lack of medical actionability. This difference of opinion amongst trial participants should remind the research team that their own personal values should not be assumed to be the same as the personal values of the trial participant and that genetic information should, or should not, be returned based on the participant’s values and express wishes.

The comprehensive content, potential predictive power for future disease phenotypes, and familial nature of the human genome are important points to consider in decisions about the return of research results. However, as stated under Principle 6, clinical investigators do not have an ongoing responsibility to seek out participants after the trial is over to inform them of secondary findings or results that subsequently become known to be significant. The complex relationship between the sponsor, investigator, research participant and primary care provider make delivery of genetic research results particularly difficult especially since these results are often generated years after a clinical trial has been completed, participants may be difficult to contact, and access to genetic counseling and other services has a limited global reach.

7.2 Influence of technologies on genetic information

7.2.1 Genotyping technologies are numerous and diverse.
Understanding available genetic technologies, the breadth of data that they generate, the bioinformatics and computational tools used to interrogate and analyze this data to answer research questions provides further appreciation for why returning genetic data is complex.
1. **Sanger sequencing** was the first widely used form of DNA sequencing, is a valuable research tool due to its accuracy, and due to high cost and low throughput, is used primarily for the interrogation of smaller DNA fragments.

2. **Microarray technology** allows simultaneous genotyping of many thousands of single nucleotide polymorphisms (SNPs). In addition, the application of statistical imputation techniques predict the presence of millions of variants not directly genotyped, thus providing a discovery tool to understand the relationship between genetic variation, disease, and drug response.

3. Microarray technology has allowed **genome-wide association studies (GWAS)** to successfully identify thousands of common genetic risk factors for hundreds of different diseases (http://www.ebi.ac.uk/gwas/). Common variants can describe one’s relative risk of developing conditions such as type 2 diabetes, Crohn’s disease, macular degeneration, and Alzheimer disease. However, genetic risk factors tend to be numerous and of weak or modest penetrance; thus, they rarely have a clear or compelling clinical utility for individual patients at this time.

4. **Next Generation sequencing** (NGS) technology has enabled scalable, simultaneous DNA sequencing reactions in parallel (Mardis, 2017), and is revolutionizing our understanding of the human genome. NGS enables sequencing of whole genomes or exomes and is currently the diagnostic method of choice when many genes or entire genomes must be interrogated for disease-causing mutations (Katsanis & Katsanis, 2013). NGS enables researchers to study common and rare genetic variation. However, buried within the large breadth of genomic data generated by NGS may lie predictors or determinants of a wide array of genetic conditions that can present throughout the lifespan. Thus, the increasingly routine approach of NGS in research, where the analysis aims to identify variants associated with a particular disease or drug response, heightens the probability of “incidental findings” related to undiagnosed, prodromal, or future disease, and the discovery of variants of unknown significance.

Due to the type of genetic information generated from some of these technologies, there is the possibility of encountering genetic mutations that are unrelated to the primary research question but are associated with a known inherited genetic condition. The term “incidental findings” is used to describe findings that are not being sought as a goal of research, but are discovered in the course of genetic data analysis; “secondary findings” are sought specifically in addition to the primary reason for genotyping (e.g., clinical diagnosis, exploratory research, etc.) (Anastasova et al., 2013). Whether a researcher is ethically obligated to interrogate a list of known genomic mutations that are associated with risks for developing serious and treatable genetic conditions is debated. If as part of a primary or secondary objective, the decision is made to perform an analysis for known genetic mutations, the list should be
defined in advance of the research, if possible, and detailed in the consent form. The participant should consent to the analysis and agree, or not, to learn of findings that are of interest to them. Similarly, if researchers do not intend to perform a search for known genetic mutations that are medically actionable, the consent form and process should clearly explain the limited study to which the participant consents.

Whether or not (and how best) to report incidental or secondary findings has been a topic of recent intense debate and discussion, particularly in the American College of Medical Genetics (ACMG), revolving around five main considerations: (1) analytical validity (Rehm et al., 2013); (2) clinical validity (Richards et al., 2015); (3) medical actionability (Kalia et al., 2017); (4) patient and physician preferences (Brothers et al., 2017); and (5) practical considerations including communication of information, health policy implications, and implementation in various settings (e.g., clinical care vs. various research contexts). Of these, the first three considerations are primarily “technical” in nature and are covered below, being functions of diagnostic technology, data analytics, and the clinical genotype-phenotype evidence base, noting that our understanding of the significance of secondary (and incidental) genetic findings is constantly evolving. Regarding the patient and physician preferences, the ACMG has revised its earlier position of mandatory analysis and return of results, in favor of offering to patients an opt-out of the analysis and return of incidental findings. There has been further discussion of the implementation of return of results in research settings. Notably, members of the Clinical Sequencing Exploratory Research (CSER) Consortium and eMERGE (Electronic Medical Records and Genomics) committees discussed and identified areas of consensus regarding the return of results to research participants. They have written that research investigators should return results and incidental findings that are discovered in the course of their research, that are actionable (see section 7.2.4 below) and for which participants have consented to receipt, with referral for appropriate clinical follow up. Researchers have no obligation to search actively for results and research participants have the option to decline receipt of genomic results, even when doing so might threaten their health. Remaining major area of controversy are the return of pathogenic variants for adult-onset conditions to children, the role of CLIA compliance (see section 7.7.1) and the optimal methods of return (Jarvik et al., 2014).

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45 There are times, of course, when creating a list in advance of the research will not be possible. For example, having performed next generation genome sequencing, emerging science may prompt, or a regulatory agency may request, the research to return to the data to test retrospectively for the presence or absence of a mutation.

46 eMERGE (Electronic Medical Records and Genomics) is a US National Human Genome Research Institute (NHGRI)-organized network that couples DNA biorepositories with electronic medical record (EMR) systems for large scale, high-throughput genetic research in support of implementing genomic medicine (https://emerge.mc.vanderbilt.edu). See also (Jarvik et al., 2014) for additional considerations.

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Version 1.1 October 20, 2017
7.2.2. Analytical validity

**Do genotyping results effectively detect the presence or absence of genetic mutation?**

The term “analytical validity” in genetics refers to the degree to which a laboratory assay accurately determines a genotype of interest. The performance of genotyping assays is assessed in terms of analytical sensitivity and analytical specificity. The analytical sensitivity is the “proportion of biological samples that have a positive test result or known mutation and that are correctly classified as positive” (Rehm et al., 2013). The analytical specificity is the “proportion of biological samples that have a negative test result or no identified mutation (being tested for) and that are correctly classified as negative” (Rehm et al., 2013).

If performed according to benchmark quality standards (Rehm et al., 2013), genotyping assays can be of sufficient analytical validity to support high-confidence molecular diagnosis for nearly all disorders caused by single nucleotide mutations throughout most of the human genome. Importantly, procedures should be in place to ensure that the analyzed sample is actually from the person it is believed to be from (Viberg et al., 2014) and the results should be independently confirmed for accuracy (Nuffield Council on Bioethics, 2003). Quality metrics should also be reported in language understandable to the recipient of genetic data. For certain regions of the genome (e.g., within highly repetitive DNA sequence), and for certain types of mutations (e.g., trinucleotide repeats, copy number alteration, insertions-deletions, or somatic mosaic mutations present in only a small percentage of DNA molecules in a sample), the sensitivity of genotyping assays such as NGS and microarray may be reduced compared to methods specifically designed to test the variant in question. Specificity can likewise be suboptimal even for a single nucleotide variant call, for example when there exists another gene with high sequence similarity that creates ambiguity about the true location of the mutation.

7.2.3 Clinical validity

**Is a given mutation pathogenic in a particular patient, and if so, what is the probability that it explains an existing disease phenotype or will increase risk of disease in the future?**

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47 Variant calling is the process of assigning specific genotypes at each analyzed nucleotide. For example, in NGS, a key parameter for maximization of sensitivity and specificity is “depth of coverage,” meaning the number of times that a given nucleotide is included when the innumerable “short reads” are matched up to the human genome reference sequence. The more times a mutation is observed, the more likely it is to be a true mutation rather than an error. A mean read depth of 30X for whole genomes or about 100X for exome analysis generally produces a “quality threshold” > 95% of nucleotides being re-sequenced at least 10X. The greater read depth for exomes is to compensate for uneven capture and enrichment of different sections of the exome, and a small percentage of the exome is not captured at all by exome sequencing. Thus, a subset of patients with genetic disorders may potentially have an exonic mutation detected by whole genome sequencing if prior exome sequencing failed to detect a pathological mutation to explain the patient’s phenotype.
When DNA sequencing is applied for the diagnosis of rare diseases, molecular geneticists, genetic counselors, clinical geneticists, bio-informaticians, and physicians with sub-specialty expertise generally work together as a clinical interpretation team. Incidental and secondary genetic findings in clinical research are equally likely to require a multi-disciplinary team approach to determine relevance to individual research subjects. The key categories into which pathogenicity criteria fit are complex. Although bioinformatics tools can automate certain standardized functions designed to characterize and annotate the likely effects of mutations, a holistic human judgment considering the totality of evidence for and against pathogenicity of particular mutations remains the gold standard in support of medical decision-making.

Critically, experts often disagree about the classification of mutations. In a recent study involving nine molecular diagnostic laboratories in the Clinical Sequencing Exploratory Research (CSER) consortium (Amendola et al., 2016), labs were challenged with 99 selected mutations spanning all clinical significance categories (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign). Discordant categorization of mutations persisted even after extensive discussion for 29 (29%) of the 99 variants assessed in the CSER study, and 5 of the 29 involved a difference substantial enough to affect medical management. At some point in the future, a critical mass of empirical genotype-phenotype correlation data will permit precise probabilistic disease risk estimation. Without such real-world quantitative data, however, legitimate differences of opinion among experts will persist. As we have stated in Principle 6, there is no ongoing responsibility to re-interpret genetic or genomic analyses performed for research. That said, scientific understanding is advancing, and while the appreciation of clinical significance may change over time, the limitations of the research must be communicated effectively to participants and their primary physicians.

7.2.4 Medical actionability

*Can a genetic diagnosis potentially alter clinical management of the patient and lead directly to improved medical outcomes?*

Even in the clinical genetic setting, there is no professional consensus on how secondary findings should be handled, although the American College of Medical Genetics and Genomics

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48 Pathogenicity criteria include data on the relative frequencies of a particular mutation in diseased versus non-disease populations, functional impact of the mutation in relation to known disease mechanisms, co-segregation of mutation with disease in families, appearance as a de novo mutation in an affected child but neither parent, and finally, the details of the specific allele (i.e., transmission in “trans” from each parent on separate chromosomes rather than in “cis” from a single parent in the case of a recessive allele, and also a search for other mutations in cis that would mitigate or eliminate pathogenicity).

49 Examples of bioinformatics tools included InterVar (Li & Wang, 2017); ClinGen Pathogenicity Calculator (Patel et al., 2017); Genetic Variant Interpretation Tool (Kleinberger et al., 2016)

50 Even in the context of Mendelian disease diagnosis, re-interpretation led to new or additional diagnostic findings in 10% (4 of 40) of cases after a 1-3 year interval, according to a recent report (Wenger et al., 2017).
and others have made important preliminary contributions to the ongoing debate. Pathologically mutated genes are considered “medically actionable” if important diagnostic, prognostic, or therapeutic decisions pivot on the genetic finding (Kalia et al., 2017). In many cases, a presumed deleterious mutation may be the only known sign that the patient has the condition in question, and timely implementation of available therapy may improve patient outcomes. Whether researchers who analyze genes considered medically actionable should have the same obligation to return results as their clinical counterparts is a matter of debate, given that classifying individual mutations as pathogenic is often challenging. A mutation may be novel, may have been observed in only a small number of patients or families, or may be predicted—but never previously observed—on the basis of a computer algorithm. The penetrance (i.e., conditional probability of disease, given mutation) and expressivity (i.e., range of pathological and/or benign phenotypes associated with a given mutation) are rarely fully known.

Further, the research context itself adds further complexity. For example, whole genome sequencing (WGS) technology may be selected for hypothesis generation purposes since it enables the full genome to be interrogated for any possible correlation with disease or drug response. While all genes would be included in WGS, any given gene may not be singled out if it is not the object of the research; it would not be identified as a correlative “hit.” Additional screening for mutations that may cause pathogenic disease would add cost and time, and would be of uncertain utility in many cases. These considerations should be addressed in advance of the clinical research, explained in the protocol, reviewed by the IRB/REC, and described in the informed consent document and process.

7.3 Considerations in returning genomic results

Genetic data, collected during clinical studies, may be applied to and correlated with disease heterogeneity and drug response. While the incorporation of genetic data in clinical studies may be exploratory in nature (e.g., see Figure 1, Data Type D)—and therefore not always appropriate for returning individual results—there are special considerations that deserve exploration and for which planning should occur.

The ethical foundations and operational principles that we discussed in Sections 4-6 apply in the return of genetic information, and here we describe an abbreviated list of the key points to consider when applying these principles in the context of genetic results along with a brief description of each.

7.3.1 Balancing autonomy with other values

Respect for persons and participant autonomy are critically important in the context of clinical studies. There are times when respect for persons is in tension with other ethical principles.

51 Of course, correlation or association does not imply that one is a risk factor nor causative of the other.
This seems to be particularly acute in the context of returning genomic information where we may see individuals’ autonomy interests in conflict with duties of non-maleficence and beneficence. For example, since genomic research conducted as part of a clinical trial is often hypothesis-generating and exploratory in nature, results are often poorly understood by researchers and clinicians alike. In these cases, providing data back to research participants could be more harmful than helpful. However, such judgments must be made with caution and should avoid undue paternalism.

7.3.2 The complexity of genetic information
Some monogenic diseases are easier to describe and contextualize for research participants since their inheritance pattern and disease course are well understood. However, genetic disease is often quite complex. Scientists are still trying to understand why certain conditions manifest very differently in different families and in different members of a given family. Dissecting the roles that our environment, compounding genetic factors, epigenetic differences, and other factors may play in explaining this variability is both difficult scientifically and challenging to explain to patients. Further, our understanding of multifactorial genetic diseases, including the nature of disease, and the roles of inherited and acquired mutations, are constantly evolving.

7.3.3 Ambiguity in interpretation of results
Interpretation of genetic information varies. Results generated in an exploratory environment might not meet the standard for analytical validity because of the laboratory testing methodology, quality assurance standards, or informatics tools. Further, our understanding of the significance of genetic data—and its association with disease—is dynamic; current interpretation is subject to refinement or reversal over time, in response to new data. It is important to recognize the potential for misinterpretation of genetic information or differences across labs in interpretation, even when the information is generated in an accredited clinical laboratory environment such as a CLIA-certified lab.

7.3.4 Medical actionability and responsibility changes over time
Medical actionability is contextual and subjective. It is important to situate genetic data around the participant and the current state of knowledge. This will include a detailed conversation between the patient and the treating physician, and a determination of whether updated interpretation of the genetic data generated in a research setting will be communicated in the future, who is responsible for follow-up, and how long this obligation extends.

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52 As genetic technologies improve and associated costs decrease, interpretation of the genetic information will become the primary rate limiting step to empowering people with their genetic data. Each person’s unique genome, history and family history requires careful interpretation. As scientific technologies and the application of big data methodologies advance, artificial intelligence is likely to take a prominent role in the interpretation.
7.3.5 Laboratory testing and consent conditions in which return of results are merited
One subset of results that seems intuitive to return are those that represent a significant health risk to the research participant where not informing them could cause an increased risk of injury. While this type of result is not unique to genetics (e.g., incidental findings on x-ray), the definition of “risk”—and therefore the threshold for return—is difficult in genetic data, as our knowledge base is changing and there are laboratory differences in interpretation. Expert consultation is therefore advisable, and addressing who will advise, and the role of the IRB/REC in the decision, while planning the research is an important preparatory step. When testing is research-grade rather than clinical-grade (e.g., conducted to CLIA-approved standards in the U.S.), it may be illegal to return the finding. In such cases, other mechanisms than return of the specific genetic result might be adopted instead so that the participants and their physicians can seek clinically appropriate testing through licensed laboratories.

7.3.6 To whom one can release genetic information
In many cases, it is unclear whether genetic information should be released directly to clinical trial participants or instead to the treating physician. Benefits, drawbacks, and feasibility of returning genetic information to the patient or the health care provider need to be considered. Questions also arise about ethical obligations to communicate relevant genetic information to members of the trial participant’s family, who themselves may have personal reasons to want this information, but whose access to this information may be limited due to family relationships, potential legal barriers, or regulatory constraints that exist on the return of genetic information.

7.3.7 International regulations and policies regarding return of genetic information
There is a lack of international alignment with respect to guidance or policy on the return of genetic information. Clinical investigators and researchers need to be aware of variation in national and local legislation, regulation, guidance and institutional policy. This includes the requirement, in the U.S., that laboratories be licensed and certified in order for test results to be returned to participants/patients for treatment purposes and the conflict between this policy and certain provisions of the Health Insurance Portability and Accountability Act (HIPAA) (see below, Section 7.7.1).

7.4 Points to consider for genetic/genomic research informed consent
Informed consent for genetic/genomic research is driven by Good Clinical Practices (GCP) consent regulations, and country, state or local requirements, as well as by the research study protocol. If genetic or genomic research is the primary objective of the research study, the entire informed consent form (ICF) is dedicated to describing the applicable regulatory and ethical requirements (e.g., ICH, CFR [FDA, HHS/Common Rule], CIOMS, EU GDPR) for informed consent. However, if the genetic/genomic research is one component of the overall clinical study, the genetic or genomic consent is often included in a separate section of the ICF, in an addendum, or in a separate stand-alone form (Note: some countries require a separate ICF for
genetic/genomic consent). When the genetic/genomic research is an optional component of a clinical study, it is recommended that a separate signature be obtained to document consent.

The following considerations for genetic/genomic research informed consent were adapted from "Issues to be Addressed in Obtaining Informed Consent Involving DNA Banking and Genetic Research" (Selwitz, 2014).

Note that there may be overlap/repetition with components of the main ICF in the considerations listed below that can be omitted if appropriate.

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 de-identified 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

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)
- 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 participants 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

Inform participants of country-specific genetic discrimination law. The U.S. Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans and most employers to discriminate against participants based on their genetic information. The Canadian Genetic Non-Discrimination Act (GNDA) provides similar protections. If genetic testing is anticipated and the data is to be submitted to the National Institutes of Health (NIH) database of Genotypes and Phenotypes (dbGaP) Genome-Wide Association Studies (GWAS) database or other open or controlled-access health research databases (e.g., European Genome Archive) for broad sharing with other researchers, inform participants that de-identified genotype or phenotype data will be submitted to such a database.

7.5 How to return?

When returning genetic research results, it is important to put results in context for research participants. In most cases, the influence of genomics (including genetics, epigenetics, proteomics, transcriptomics and other evolving “-omic” paradigms) on disease is **probabilistic rather than deterministic**. Genomics is often one of several factors -- including but not limited to family history and environmental exposures -- that have an impact on the development, onset, progression, and outcome of human disease. In addition, our knowledge base is rapidly expanding and being refined, such that variants of unknown significance today may become known pathogenic variants tomorrow. It is important to convey that test results may be incorrect (false negatives or false positives), and therefore appropriate measures (e.g., re-testing) should be considered before taking action.

During the consent process, and at the point of return, it is important to convey that the absence of a finding does not necessarily mean there is no disease risk (nor, often, does the
presence of a gene predict disease with certainty). There may be other genomic factors (e.g., variants within the same gene, variants within different genes, epigenetic changes, etc.) that, independent of or together with environmental and lifestyle factors, contribute to whether the participant will develop a disease. In the absence of a particular genetic variant linked to disease, healthy lifestyle recommendations and regular clinical care, including monitoring and screening for conditions that are represented in the participant’s family history, should be advised. In addition, it is important to emphasize that knowledge and understanding of genetic risk, and linkage to disease, are constantly evolving.

If research results are given to a study participant, a result indicating that an individual possesses a genetic variant should be presented in such a way as to communicate both what is known about the variant and the uncertainties involved. In some cases, particularly for research assays or laboratory developed tests involving variants that are not well characterized, a research finding may not be analytically validated. In other instances, confirmation of a finding will be necessary in order to provide the result to the participant. If the original test was not conducted in an accredited laboratory (see Legal Regulations and Policies section), however, confirmatory testing may not be paid for by the participant’s insurance provider, government insurance program, or trial sponsor, meaning that the individual research participant would need to pay out-of-pocket for this testing. For this reason, the benefit and limits of confirmatory testing should be explained alongside the risk associated with out-of-pocket costs, so that participants can make informed choices about whether to receive research findings that have not been validated. As mentioned, the plan for return of genetic research results and the risks and benefits of return should be detailed for the research participant during the informed consent process.

While many individuals may handle the return of genetic test results well and adapt even to serious results, other individuals may experience anxiety, feelings of helplessness, or fear, any of which could lead an individual to take subsequently regrettable actions. All individuals should be provided with information about additional support that may be available (e.g., names of counselors, support groups). Additional research will help us optimize strategies for informing prospective research participants about the potential return of genetic research results, so that they can make informed decisions about whether and when to receive such information.

7.6 Who will return?

While the return of some genetic test results can be simple and straightforward, results with more complex and serious health implications may require a team approach to ensure that results are communicated in a meaningful and relevant manner to a study participant. A major challenge in some settings will be the lack of resources or expertise necessary to enable this
collaborative approach. Of note, additional resources are often needed to return genomic results to minors and their parents or to adults who lack capacity and their caregivers.

At a minimum, it is clear that someone with genetic expertise is needed to interpret complex genomic findings in light of the current understanding of their significance and future health relevance. In some settings, this could be a medical geneticist or a genetic counselor. The treating physician or nurse often lacks the genetic expertise needed to place the result in an appropriate context to enable recommendations regarding the proper prevention, modification or treatment of disease. At sites without a genetics professional, another member of the team might be designated and trained for this role through targeted continuing education materials. Genetic expertise might also be centralized for the study and be made available via phone or videoconference. Educational materials developed for physicians could be helpful in managing the patient, especially in cases where a genetics expert is not available. High quality written materials designed for the participant could also facilitate communication about the meaning and importance of the genomic findings; however, it is important for this to be contextualized in light of the patients’ full medical and family history.

In addition to genetic and medical expertise, the return of some complex, serious results may require psychological and social support. Psychological support may be provided by a psychiatrist, psychologist, social worker, or a support group, and may help the participant or family to receive and contextualize serious or uncertain results in a way that enables them to avoid undue fear and anxiety.

It is important to consider the educational and socio-economic constraints in which genomic results may be returned. In some settings, study team members and participants may not understand the nature of genomic testing, and education must begin from a very basic level. Because follow up or confirmatory testing may be constrained by resources or health insurance coverage, the team may also include a medical insurance advisor who could investigate coverage for confirmatory testing or other follow up interventions.

Finally, some communities and cultures may not endorse individual, autonomous decision-making and, instead, may involve family members, community leaders or elders in important decisions. Professionals who can appreciate local constraints, different levels of understanding of genomic data, and cultural differences are needed to facilitate the design of appropriate frameworks for decision-making and communication of results in a manner that is sensitive to needs of the participant.

7.7 National Laws, Regulations, and Ethics Guidance

Laws, regulations, and guidance (including Ethics Committee and regulatory guidance or position papers) vary considerably across countries on the issue of return of individual research results to study participants. The complexities and challenges faced due to a lack of
agreement in international regulations and guidance are amplified in the context of the evolving landscape of genetic research.

In particular, two types of regulations need to be considered: (1) regulations for the return of genetic results by researchers, and (2) rules governing the individual’s right of access to personal information. Countries may have special regulations for genetic data and results; for example, regarding under what conditions certain tests such as WGS or NGS may be performed, handling genetic results from deceased research participants, and communication of genetic results to family members. In some countries, laws grant study participants broad access to their individual research results upon request; in other countries, laws may place restrictions on access, where exploratory genetic research results may not meet the quality standards for use in clinical decision making. It follows that these laws can conflict; for example, certain regulations may require researchers to return genetic results, while other regulations may require researchers not to return results from non-approved laboratories.

Below are examples illustrating the complexity and variability of the global environment and return of individual genetic research results. This is not intended to be a comprehensive analysis of relevant law or guidance, but rather offers a broad overview of the intricacies for consideration of return of individual genetic research results. Further resources for global regulations can be found in the Toolkit (Tool 3).

7.7.1 United States – CLIA and HIPAA Regulatory Issues Regarding Return of Test Results; FDA Regulatory Considerations

In the United States, the Clinical Laboratory Improvement Amendments of 1988 (CLIA) do not allow the return of results for the prevention, diagnosis or treatment of any disease or the assessment of health of individual patients, unless the test is analytically validated and generated in a CLIA certified laboratory (Laboratory Requirements, 42 C.F.R. § 493). This requirement is intended to help ensure that results used for clinical decision making are valid, reliable and accurate. Genomic research analysis in clinical trials using methodologies, such as WGS, is often performed in non-CLIA research labs, or in a CLIA-certified lab but under research use standards, and may not consist of validated assays.

The CLIA regulations contain an exception to the CLIA certification requirement for research laboratories that do not report individual results for the diagnosis, prevention or treatment of any disease or the assessment of health of individual patients (Laboratory Requirements, 42 C.F.R. § 493.3(b)(2)). The Centers for Medicare and Medicaid Services (CMS), the office within HHS that oversees CLIA, has taken the position that this provision also prohibits a research lab from returning results to study participants, even if accompanied by a disclaimer that these results are not for treatment purposes and a recommendation that the participants consider pursuing additional confirmatory testing (through their treating physician) at a CLIA-certified lab (Meyers, 2015).

In 2014, CMS and the HHS Office for Civil Rights (OCR), which administers the HIPAA Privacy Rule, jointly published a final rule, amending the HIPAA Privacy Rule to provide individuals the right to access test reports directly in their “designated record set” (DRS) from HIPAA covered
entity laboratories, including those test results performed in a non-CLIA-certified research laboratory (CLIA Program and HIPAA Privacy Rule; Patients' Access to Test Reports, 2014, 79 F.R. § 7289). The DRS includes medical and billing records, as well as any other records that may be used in whole or in part to make a decision about an individual (Security and Privacy, 45 C.F.R. § 164.501). The DRS would therefore include research test results if these results are available for the covered entity to make decisions about individuals. For this reason, it is important that all covered entities with research laboratories review how they have defined their DRS in order to understand a patient’s right of access to research records. HIPAA covered entities that conduct research testing should also consider referencing the application of the DRS to research testing in their Notice of Privacy Practices so that patients are aware of the extent of their ability to access research test results. Notably, HHS has broadly interpreted the DRS to include the laboratory test report and all underlying data generated as part of the test.

For example, a clinical laboratory that is a HIPAA covered entity and that conducts next generation sequencing (NGS) of DNA on an individual must provide the individual, upon the individual’s request for PHI [Protected Health Information] concerning the NGS [next generation sequencing], with a copy of the completed test report, the full gene variant information generated by the test, as well as any other information in the designated record set concerning the test. (U.S. Department of Health & Human Services)

This poses an apparent conflict between the CLIA regulations and the HIPAA Privacy Rule with respect to patient right-of-access when the genomic testing is performed in a non-CLIA-certified lab that is part of a HIPAA covered entity.

However, there is no requirement that a HIPAA covered laboratory interpret lab results for an individual.

There is no requirement in the HIPAA Privacy Rule that clinical laboratories interpret test results to patients . . . . Laboratories may continue to refer patients with questions about test results back to their ordering or treating providers. However, while not required, a laboratory providing a test report to an individual . . . may also provide education or explanatory materials regarding the test results to individuals if it chooses to do so. Similarly, a laboratory that wishes to include a disclaimer, caveat, or other statement explaining the limitations of the laboratory data for diagnosis or treatment or other purposes may do so. (Barnes et al., 2015)

At the time of the issuance of this document, this discord between the CLIA and HIPAA regulations regarding return of results to study participants has not been resolved. Resolution of this conflict would greatly aid researchers in understanding requirements for returning genomic test results in the US. In June 2017, the National Academies of Sciences, Engineering, and Medicine announced the launch of a Consensus Study, supported by NIH, FDA, and CMS, to review and evaluate issues regarding the return of individual research results from research laboratories to individuals. One of the aims is to review the regulatory
environment for conducting tests and returning individual research results and regulatory considerations. The consensus study may lead to possible professional standards and regulatory reform in this area, in order to reconcile these apparent contradictions in U.S. regulatory regimes. (http://nationalacademies.org/hmd/Activities/Research/ResearchResultsGeneratedinResearchLaboratories/)

7.7.2 FDA Regulatory Considerations

The Food and Drug Administration (FDA) regulates the use of diagnostic tests in clinical research under the Federal Food, Drug, and Cosmetic Act (FDCA) and its implementing regulations. FDA requires that clinical research involving diagnostic tests from which results are intended to be submitted to FDA to support a research or marketing application comply with regulations on investigational device exemptions (IDE) (21 C.F.R. Part 812), informed consent (21 C.F.R. Part 50), and institutional review board oversight (21 C.F.R. Part 56).

Study protocols may include non-exploratory genetic testing on biospecimens using investigational assays not clinically validated. Lab tests that are classified as in vitro diagnostic (IVD)53 devices are generally subject to FDA regulations on medical devices (in addition to the CLIA regulations) unless the lab test is considered a “laboratory developed test” (LDT). LDTs are designed, manufactured and used within a single laboratory,54 and FDA has historically not enforced applicable regulations except under certain conditions. If the LDT is not clinically validated and is the object of the clinical investigation, FDA likely would apply its clinical research regulations to the conduct of that study.

In general, an IVD may be intended for research use only (RUO) or investigational use only (IUO).55 An IVD intended for RUO is in the laboratory phase of development and should not be used for diagnostic purposes. IVDs labeled RUO are generally exempt from FDA’s clinical research regulations (see 21 C.F.R. § 809.10(c)(2)(i)). In contrast, an IVD intended for IUO is not yet validated for commercial marketing in that its performance characteristics have not

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53 IVD products are those reagents, instruments and systems intended for use in diagnosis of disease or other conditions including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae through the collection, preparation and examination of specimens taken from the human body (21 C.F.R. § 809.3(a)).


been established but it can be used in the research context for diagnostic purposes (see 21 C.F.R. § 809.10(c)(2)(i)).

If a clinical investigation involving an IVD is subject to FDA’s IDE regulations, the return of results to subjects for diagnosis, treatment or prevention of human disease could cause the study to become subject to heightened regulatory requirements. FDA’s IDE regulations apply to clinical investigations involving one or more subjects to determine the safety or effectiveness of a device (see 21 C.F.R. § 812.3(h)). A clinical study of an investigational device may be exempt from IDE requirements if certain criteria are met, one of which is that the investigational IVD will not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure, e.g., an FDA-cleared or approved IVD or culture (21 C.F.R. § 812.2(c)(3)). Requirements for a non-exempt IDE vary depending on whether the IVD presents a significant risk or non-significant risk to subjects (see 21 C.F.R. § 812.2(b)). A significant risk study of an IVD is one in which misdiagnosis and/or error in treatment caused by inaccurate test results could lead to life-threatening harm or permanent injury to the participant.

When a research study involves an IVD, the first step should be to determine whether FDA regulations apply. If so, the IVD study could meet all of the criteria for an IDE exemption if, among other things, any results disseminated to the subject or subject’s physician for diagnostic purposes will first be confirmed by a medically established procedure. Notably, established diagnostic products or procedures may not exist for tests that use new technologies or represent a significant technological advance. If the results will not be confirmed before return, the study will not be IDE-exempt, and a determination must be made by the sponsor, and confirmed by the cognizant IRB, as to whether the IVD is a significant risk or a non-significant risk (see 21 C.F.R. § 812.66). Importantly, however, FDA’s requirements for informed consent and IRB review and approval continue to apply even if the study is IDE exempt (see 21 C.F.R. §§ 50.1 and 56.101).

7.7.3 Outside the United States: Variations in legal treatment of genetic/genomic results

Several countries outside of the United States have laws and/or regulations that explicitly address an individual’s right to access results of genetic testing. Many of these laws and/or regulations also include the requirement to provide access to genetic counseling when applicable. For example, in Brazil, a study participant has the right to access his/her genetic data and may choose whether or not he or she wants to be informed of genetic research results and to receive guidance on their implications, including genetic counseling when applicable (Brazil Ministry of Health CNS Resolution 340/2004, 2004). Similarly, Spain’s Biomedical Research Law 14/2007 establishes the right of a participant to be informed of genetic data in accordance with the terms of the consent to testing that he/she provided (Spanish Parliament Law 14/2007 of 3 July on Biomedical Research, 2007). Italy’s General Authorisation No. 8/2014, issued by the Data Protection Authority, establishes requirements for the processing of genetic data (Italian Data Protection Authority, 2014). This includes the
ability of an individual to be informed of genetic findings if he/she chooses, including unexpected findings that may be helpful to the treatment or prevention of illness or may contribute to the awareness of reproductive choices. In Germany, the Genetic Diagnostic Act of 2010 requires that research participants must be re-tested at an approved genetic laboratory if they wish to receive their individual result (Soini, 2012)

In countries such as Norway, Argentina and France with data privacy laws allowing subjects to access their data (see section 5.9), the definition of personal data may include DNA. Thus, researchers may find themselves legally required to provide access to genetic results in certain countries but with little guidance on exactly how or what is expected to be returned in those jurisdictions. The EU GDPR, which will become effective on May 25, 2018 in EU member states, considers genetic data, along with health data, to be "Special Categories" of personal data, as discussed in section 5.9.

In other jurisdictions, there are laws/regulations that are somewhat contradictory and provide vague guidance on the return of genetic information and on the return of research information. For example, in Taiwan, the Human Biobank Management Act explicitly prohibits participants from accessing information concerning biological specimens and prohibits use of specimens for anything other than biomedical research (Taiwan Human Biobank Management Act, 2010). The restriction on access rights does not apply to personal information that can identify the participant. The same law also establishes that a participant must be informed of “any possible impacts of the genetic information derived from the biological specimens on the participant, and his/her relatives or an ethnic group.” Thus, similar to the CLIA-HIPAA conflict in the US, the contradiction in regulation makes it difficult for the researcher to navigate requirements.

7.7.4 Research Ethics Committee requirements and positions

In addition to complexity created by laws and regulations, research ethics committees also differ in their interpretation of local requirements, resulting in variability in conditions imposed on a single research study within the same country (Warner et al., 2011). Furthermore, certain research ethics committees may issue guidance documents or position statements on genetic testing that impact return of results in their jurisdiction. In Denmark, for example, the National Committee on Health Research Ethics (DNVK) has issued a guideline on research projects involving “comprehensive mapping of personal genomes” which are defined as research studies utilizing next generation sequencing technologies (DNVK Guideline on Mapping of Personal Genomes, 2013). Such research projects must allow for the return of information regarding serious genetic diseases under certain conditions unless the participant explicitly indicates he/she does not wish to receive this information. These conditions include if there is a reasonable degree of likelihood that the genetic predisposition is present, there is a proven link between genetic predisposition and disease progression, and the disease can be substantially prevented or treated. Similarly, the Marsilius College at the University of Heidelberg in Germany has issued a position paper on ethical and legal aspects of WGS (Project EURAT – Marsilius College at the University of Heidelberg, 2013). This paper suggests that critical individual results that indicate risk of additional harm or increased suffering must be returned.
In Australia, the National Health and Medical Research Council (NHMRC) issued a *Statement on Ethical Conduct in Human Research (2007) (updated May 2015)* (“National Statement”), which includes a chapter on human genetics. Citing the National Statement, Human Research Ethics Committees in Australia require that, for research that may discover or generate information of potential importance to the future health of participants, or their blood relatives, that researchers prepare and follow an ethically defensible plan to disclose or withhold that information. The elements of an “ethically defensible plan” is outlined in Chapter 3.5 that can be accessed at [https://www.nhmrc.gov.au/book/chapter-3-5-human-genetics](https://www.nhmrc.gov.au/book/chapter-3-5-human-genetics).

As noted, many laws concerning the return of individual genetic results are broadly and vaguely written with no supporting guidance, leaving them open to varying interpretations. It is also important to recognize the distinction between binding laws and regulations, and position papers and guidance issued by research ethics committees or non-regulatory authorities. To complicate matters further, there may be regional differences in interpretive guidance within the same country, as well as an evolving regulatory landscape. As such, it is incumbent upon the researcher to be aware of all legal requirements as well as ethical positions pertaining to the return of genetic research results in the jurisdictions in which the study is being conducted. Ideally, harmonized guidance within and across jurisdictions will be developed.

### 7.8 Additional Information

This chapter was finalized in late 2017. Technologies, the state of knowledge, laws and regulations will change over time and most current information needs to be sought for interpretation of genetic data.

One of the currently-developed projects for returning genomic information is Geisinger’s MyCode ([https://www.geisinger.edu/research/departments-and-centers/genomic-medicine-institute/mycode-health-initiative](https://www.geisinger.edu/research/departments-and-centers/genomic-medicine-institute/mycode-health-initiative)), which began returning results in 2015, and includes a web-based portal (GenomeConnect) that enables participants to connect with other individuals in the project. Another tool is My46, an interactive web-based information management system developed by University of Washington researchers as part of a project funded by NIH National Human Genome Research Institute. The tool is designed to return genetic test results and educate patients about genetic traits, and includes in-line access to a genetics counselor. Holly K. Tabor et al, *My46: a Web-based tool for self-guided management of genomic test results in research and clinical settings*, *Genetics in Medicine* (Sept. 2016). This is an area that is actively evolving.

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8. Conclusions

Ethical values (Section 4) and Return of Individual Results Principles (Section 5) should be carefully weighed on a case-by-case basis when considering the responsibility to return individual research results. Additional considerations apply to the return of genetic and genomic results (Section 7). The obligation to return results is mitigated by a variety of factors including lack of feasibility, insufficient validity, and the absence of clinical utility.

We encourage sponsors and stakeholders in the clinical trial enterprise to voluntarily promote, adopt and implement the principles that have been developed by the MRCT Center Multi-Stakeholder Workgroup for the purpose of sharing individual research results with study participants. We appreciate any feedback.
Appendix 1: Return of Individual Results Workgroup members

Members of the Return of Individual Results MRCT Center workgroup contributed to providing concepts and content for this document, and participated in review of sections of this document.

Co-chairs had additional responsibilities in conceptualizing the approach and the document and in writing selected sections. Those in bold were part of the core writing group for this document.

Disclaimer: This document represents a consensus viewpoint, and does not necessarily represent the point of view of any individual member organisation. Further, the individuals served in their individual capacity not as a representative of the affiliated organization or entity.

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Appendix 2: Genetic and Genomic Research Data Types and Results

There is a distinction between research “data” and research “results” in the context of genomic sequencing. For example, research using whole genome sequencing methodology generates raw or uninterpreted data. There are no research “results” until the data is analyzed through a research query.

**Methods and Technology.** Genomic data and research results may be generated using various methodologies, such as:

- Whole genome sequencing (WGS)
- Next generation sequencing (NGS), including DNA sequencing and RNA sequencing
- Whole exome sequencing (WES)

**Analysis.** Genetic/genomic and protein information identified by a method performed on DNA/RNA extracted from a biosample (e.g., tumor tissue, blood)

- Analysis of somatic mutation(s) (may be pre-specified)
- Analysis of germ-line mutation(s) (may be pre-specified)
- Comprehensive targeted NGS genomic panels (e.g., FoundationOne®)
- Biomarker expression (e.g., PD-L1, HER2)
- Circulating tumor DNA (ctDNA)
- Identification of germline versus somatic mutations involving collection of tissue and blood samples to allow for comparison of DNA from tissue samples with DNA from blood samples
- Future exploratory research on biorepository biosamples

**Timeline.** Analyses may occur along a timeline of the clinical study

- Pre-screening or screening assessment to determine eligibility
- Pre-treatment assessments for patient stratification (may be blinded study)
- During the ongoing study
- At the end of the study
- Months or years after of the close of the study

**Classification.** In vitro diagnostic (IVD) assay used may be (1) investigational (including lab developed tests (LDTs)); (2) research use only; or (3) approved/cleared by regulatory authority (e.g., FDA)

- Assay may have been performed in either an accredited (e.g., CLIA) lab or in a research lab
**Biosamples.** Collection of biosample(s) may be required under the main protocol ("mandatory"), or optional under an additional signed consent.

- May be single-coded or double-coded
References


In Vitro Diagnostic Products for Human Use, 21 C.F.R. § 809.3 C.F.R.


Investigational Device Exemptions, 21 C.F.R. § 812.2(c)(3) C.F.R.


Laboratory Requirements, 42 C.F.R. § 493 C.F.R.
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