



Human Research Protection Program (HRPP)

Standard Operating Procedures

-February 2022-

NOTE:

- Reference to 'Pre-2018 Rule' refers to research initially approved before January 21, 2019.
- Reference to '2018 Rule' refers to research initially approved on or after January 21, 2019
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1. Human Research Protection Program

National Jewish Health (NJH) fosters a research environment that promotes respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of the Organization. In support of this, NJH has established a Human Research Protection Program (HRPP). The NJH HRPP, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under NJH's auspices.

1.1 Mission

The mission of the HRPP is to:

- Safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety and well-being are protected;
- Provide guidance and support to the research community in the conduct of research with human subjects;
- Assist the research community in ensuring compliance with relevant regulations;
- To provide timely and high-quality education, review, and oversight of human research projects; and
- To facilitate excellence in the conduct of human subjects research

The HRPP includes mechanisms to:

- Monitor, evaluate and continually improve the protection of human research participants
- Exercise responsible oversight of human subjects research
- Educate investigators, and staff about their ethical responsibility to protect research participants
- When appropriate, intervene in research and respond directly to concerns of research participants.

1.2 Organizational Authority

NJH Human Research Protection Program operates under the authority of these standard operating procedures (SOPs). These SOPs are made available to all NJH investigators and research staff and are posted on the HRPP website (www.nationaljewish.org/research-science/support/compliance/irb).

1.3 Definitions

Clinical Trial. Per the Common Rule and NIH Policy, clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or

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behavioral health-related outcomes. FDA regulations refer to “clinical investigations” (see definition of “research” below).

Common Rule. The Common Rule refers to the [“Federal Policy for the Protection of Human Subjects”](#) adopted by a number of federal agencies. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in 45 CFR 46 Subpart A. For the purposes of this document, references to the Common Rule will cite the DHHS regulations.

Human Subject Research. Human Subject Research means any activity that meets the definition of “research” and involves “human subjects” as defined by either the Common Rule or FDA regulations.

Note: The terms “subject” and “participant” are used interchangeably in this document and have the same definition.

Research. The Common Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge. Activities which meet this definition constitute research whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this part [the Common Rule], the following activities are deemed not to be research: (1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected. (2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters). (3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes. (4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions. [45 CFR 46.102(l)]

For the purposes of these Standard Operating Procedures (SOP)s, a **“systematic investigation”** is an activity that involves a prospective study plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a study question. Investigations designed to develop or contribute to **generalizable knowledge** are those designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

The **FDA** has defined “research” as being synonymous with the term “clinical investigation.” A **clinical investigation**, as defined by FDA regulations, means any experiment that involves a test

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article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [[21 CFR 50.3\(c\)](#), [21 CFR 56.102\(c\)](#)]

Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act means any use of a drug other than the use of an approved drug in the course of medical practice. [[21 CFR 312.3\(b\)](#)]

Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act means any activity that evaluates the safety or effectiveness of a device. [[21 CFR 812.2\(a\)](#)]

Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [[21 CFR 50.3\(c\)](#), [21 CFR 56.102\(c\)](#)]

Human Subject. A human subject as defined by the Common Rule is a living individual about whom an investigator conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

- **Intervention** means both physical procedures by which information or biospecimens are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
- **Interaction** means communication or interpersonal contact between investigator and subject.
- **Private information** means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).
- **Identifiable private information** means private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information. [Note: This definition is within the Common Rule. For a discussion of identifiability under HIPAA, please see Section 25].
- **Identifiable biospecimen** means a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

For research covered by **FDA** regulations, **human subject** means an individual who is or becomes a participant in a clinical investigation, either as a recipient of the test article or as a control. A subject

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may be in normal health or may have a medical condition or disease. In the case of a medical device, a human subject also includes any individual on whose specimen an investigational device is used or tested or used as a control. [[21 CFR 50.3\(g\)](#), [21 CFR 312.3\(b\)](#), [21 CFR 812.3\(p\)](#)]

Test Article. The FDA defines “*Test article*” as meaning any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act [42 U.S.C. 262 and 263b-263n]. [[21 CFR 50.3\(j\)](#)]

Test articles covered under the FDA regulations include, but are not limited to:

1. **[Human drugs](#)** – A drug is defined as a substance recognized by an official pharmacopoeia or formulary; a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance (other than food) intended to affect the structure or any function of the body; a substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process). The primary intended use of a drug product is achieved through chemical action or by being metabolized by the body.
2. **[Medical Devices](#)** - A device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

The 21st Century Cures Act amended the FD&C Act to specifically exclude certain software functions from the definition of medical device. Summarized, these include exclusions for software functions intended for administrative support of a health care facility; for maintaining or encouraging a healthy lifestyle; to serve as electronic patient records; for transferring, storing, converting formats, or displaying clinical laboratory tests or other device data and results and related information; and for displaying, analyzing, or printing medical information, for supporting or providing recommendations to a health care professional, and enabling the health care professional to independently review the basis for such recommendations.

Additional information regarding the application of these exclusions is available on FDA’s “[Guidances with Digital Health Content](#)” website.

3. **[Biological Products](#)** - include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic

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proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.

4. **Dietary Supplements** – A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains one or more "dietary ingredients." The "dietary ingredients" in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and other substances found in the human diet, such as enzymes. When a dietary supplement meets the definition of [drug](#), it is regulated as such.
5. **Medical Foods** – A medical food, as defined in section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee(b) (3)), is a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.
6. **Mobile Medical Apps** - Mobile apps are software programs that run on smartphones and other mobile communication devices. They can also be accessories that attach to a smartphone or other mobile communication devices, or a combination of accessories and software. Mobile medical apps are medical devices that are mobile apps, meet the definition of a [medical device](#) and are an accessory to a regulated medical device or transform a mobile platform into a regulated medical device.
7. **Radioactive Drugs** – The term radioactive drug means any substance defined as a [drug](#) which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term "radioactive drug" includes "radioactive biological product".
8. **Radiation-Emitting Electronic Products** - a radiation-emitting electronic product as any electrically- powered product that can emit any form of radiation on the electromagnetic spectrum. These include a variety of medical and non-medical products such as mammography devices, magnetic resonance imaging (MRI) devices, laser toys, laser pointers, liquid crystal displays (LCDs), and light emitting diodes (LEDs).
9. **Digital Health** -certain medical and decision support software have been excluded from the definition of medical device under the 21st Century Cures Act and thus are not subject to FDA’s regulations. These include exclusions for software functions:
 - Intended for administrative support of a health care facility, including the processing and

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maintenance of financial records, claims or billing information, appointment schedules, business analytics, information about patient populations, admissions, practice and inventory management, analysis of historical claims data to predict future utilization or cost-effectiveness, determination of health benefit eligibility, population health management, and laboratory workflow;

- Intended for maintaining or encouraging a healthy lifestyle and unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition;
- Intended to serve as electronic patient records, including patient-provided information, to the extent that such records are intended to transfer, store, convert formats, or display the equivalent of a paper medical chart, so long as—
 - such records were created, stored, transferred, or reviewed by health care professionals, or by individuals working under supervision of such professionals;
 - such records are part of health information technology that is certified under section 300jj– 11(c)(5) of title 42; and
 - such function is not intended to interpret or analyze patient records, including medical image data, for the purpose of the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition
- Intended for transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results, findings by a health care professional with respect to such data and results, general information about such findings, and general background information about such laboratory test or other device, unless such function is intended to interpret or analyze clinical laboratory test or other device data, results, and findings; and
- Not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system; and
 - Is intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines);
 - Is intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition; and
 - Is intended for the purpose of enabling such health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient.

Research involving software excluded from the definition of medical device will be evaluated by the BRANY IRB in accordance with any other applicable regulations (e.g., the Common Rule, HIPAA) and the criteria outlined in this SOP. Other digital health products may be subject to FDA

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regulations and will be evaluated accordingly. FDA has provided a website listing of Guidances with Digital Health Content to help the regulated community understand FDA's interpretation and application of the regulations and to describe when FDA will practice enforcement discretion in regards to certain requirements such as those for pre-market review and for device reports. Investigators are encouraged to consult these guidances in advance of their submission to the BRANY IRB and to consult directly with the FDA as needed.

1.4 Ethical Principles

NJH is committed to conducting research with the highest regard for the welfare of human subjects. With the exception of transnational research, where consideration of alternative ethical principles may apply (see Section 26.8), NJH upholds and adheres to the principles of [The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research](#) by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. These principles are:

1. **Respect for Persons**, which involves the acknowledgment and support of autonomy, and protection of those with diminished autonomy
2. **Beneficence**, which involves ensuring that possible benefits of research are maximized and possible harms are minimized
3. **Justice**, which involves the fair distribution of the benefits and burdens of research through the equitable selection of subjects

NJH HRPP, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under its auspices.

1.5 Regulatory Compliance

The HRPP facilitates compliance with federal regulations, state and local law and organizational policies (including tribal laws passed by the official governing body of an American Indian or Alaska Native tribe). Human subjects research at NJH is conducted in accordance with applicable regulations and requirements including, but not limited to, the following:

Research conducted, supported, or otherwise subject to regulation by any federal department or agency which adopts the [Common Rule](#) is reviewed and conducted in accordance with the Common Rule. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in [45 CFR 46 Subpart A](#). For the purposes of this document, references to the Common Rule will cite the DHHS regulations.

Research subject to FDA regulations is reviewed and conducted in accordance with applicable regulations including, but not limited to, [21 CFR 50](#), [21 CFR 56](#), [21 CFR 312](#) and [21 CFR 812](#).

Research involving the use of Protected Health Information is reviewed and conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA), [45 CFR Part 160](#), [162](#), and [164](#).

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Research supported by the Department of Defense (DoD) is reviewed and conducted in compliance with [32 CFR 219](#), [10 USC 980](#), applicable parts of title [21 CFR](#) (50, 56, 312, 600, 812), [DoD Instruction 3216.02](#), [DoD Directive 3210.07](#), and applicable additional requirements from respective DoD component(s).

1.5.1 Management of studies approved, waived under .101(i), or determined exempt before January 21, 2019

The revised Common Rule ('2018 Rule') establishes that all studies approved, waived under .101(i), or determined exempt before January 21, 2019 will be subject to the Pre-2018 Rule through the close of study. All protocols approved or determined exempt on or after January 21, 2019 will be subject to the 2018 Rule. NJH does not have plans at this time to transition individual studies from the Pre-2018 to the 2018 Rule on or after that date, but may consider it on a case-by-case basis.

1.6 International Conference on Harmonization-Good Clinical Practice (ICH-GCP)

NJH applies the International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines (sometimes referred to as ICH-GCP or E6) to clinical trials when required by a sponsor or funding agency. NJH applies the ICH-GCP guidelines only to the extent that they are compatible with FDA, DHHS, and other applicable regulations.

1.7 Federalwide Assurance (FWA)

The federal regulations require that federally-funded human subject research only be conducted at facilities covered by a Federalwide Assurance (FWA) approved by the DHHS Office for Human Research Protections (OHRP). An FWA is an organization's assurance to the federal government that human subject research conducted at that site complies with federal regulations pertaining to the protection of human subjects.

When human subjects research is not subject to the Common Rule or FDA regulations, National Jewish Health ensures that human research subjects benefit from equivalent protections by applying the Common Rule standards, with purposeful deviations that do not meaningfully diminish protections as noted within this manual.

The [HHS registration system database](#) can be used to verify the status of NJH's FWA and IORG.

National Jewish Health's Federal Registration Numbers	
FWA	FWA00000778
IORG	IORG0000018

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1.8 Research Under the Auspices of National Jewish Health

Research under the auspices of NJH includes research conducted at or using any property or facility of NJH, conducted by or under the direction of any employee or agent of NJH (including students) in connection with his or her NJH position or responsibilities, or involving the use of NJH's non-public information (e.g., medical records) to identify, contact, or study human subjects. The research may be externally funded, funded from internal sources, or conducted without direct funding.

All human subjects research under the auspices of NJH is under the jurisdiction of the NJH HRPP. Human subjects research that NJH is engaged in (per OHRP or FDA guidelines) is under the jurisdiction of the BRANY IRB, unless NJH chooses to rely upon another IRB for review and ongoing IRB oversight of the research (the IRB of record for the research).

Employee or Agent. For the purposes of this document, *employees or agents* refers to individuals who: (1) act on behalf of the organization; (2) exercise organizational authority or responsibility; or (3) perform organizationally designated activities. "Employees and agents" can include staff, affiliates, students, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.

Engagement. The Department of Health and Human Services (DHHS) regulations [[45 CFR 46.103\[a\]](#)] require that an institution "engaged" in human subject research conducted or supported by a Federal Department or Agency provide the Office for Human Research Protection (OHRP) with a satisfactory assurance of compliance with the DHHS regulations, unless the research is exempt under 45 CFR 46.104. *"In general, an institution is considered engaged in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research."* Institutions that receive an award through a grant, contract, or cooperative agreement directly from DHHS for the non-exempt human subjects research (i.e. awardee institutions), are also considered engaged in research even where all activities involving human subjects are carried out by employees or agents of another institution.

FDA regulations are oriented to the responsibilities of IRBs, investigators, and sponsors as opposed to institutions. In general, FDA-regulated research conducted in NJH facilities or by NJH Principal or Sub- Investigators (as defined on the FDA 1572 or equivalent, or the delegation of responsibilities log) requires review by BRANY IRB, or other IRB of Record approved through NJH HRPP. Exceptions to this requirement may be granted on a case-by-case basis (e.g., when NJH's involvement in the research is limited to the provision of a common diagnostic procedure and associated reading or analysis).

When external organizations and researchers wish to conduct research that is under the auspices of NJH, the external organization or researchers must consult with the NJH HRPP or HRPP Administrator prior to initiating any research activities at or involving NJH.

The HRPP Administrator, with the assistance of the Compliance and Regulatory Affairs Office as needed, is authorized to determine whether NJH is engaged in a particular research study.

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Investigators and other institutions may not independently determine whether NJH is engaged in a particular research study.

When NJH is engaged in research, the Institutional Official may choose to enter into an agreement to cede review to an external IRB.

For additional information on engagement please refer to OHRP's [Guidance on Engagement on Institutions in Human Subjects Research](#).

1.9 Written Procedures and the Electronic Management System

These SOPs for Human Research Protections detail the procedures, standards, and requirements for research with human subjects under the auspices of NJH. This is not a static document. The SOPs are reviewed at a minimum of annually and revised by the HRPP Administrator with the assistance of others as needed. The Institutional Official (IO) approves all revisions of the SOPs.

The NJH HRPP will keep the research community apprised of new information that may affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues on its website, through email, and other forums. These SOPs will be available on the NJH HRPP website. Changes to the SOPs are communicated to investigators and research staff, HRPP Administrator, and BRANY IRB (when applicable) by way of emails, and other forums, as appropriate.

IRBManager is the product selected to be used for the registration, and post-approval submissions and monitoring, of active protocols conducted under the auspices of NJH. For the purposes of this document, when referencing the electronic management system, this is referring to IRBManager.

1.10 National Jewish Health HRPP Structure

The HRPP consists of individuals, departments, and committees with responsibilities for human research protections such as Institutional Official, BRANY IRB, Research Administration, legal counsel, the Institutional Biosafety Committee (IBC), Research Radiation Safety Committee (RSC), Corporate Compliance Officer (for individual and Institutional COI), HRPP Administrator, investigators, research staff, and others. The objective of this system is to assist the organization in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

The following officials, administrative units and individuals have primary responsibilities for human subject protections:

1.10.1 Institutional Official

The ultimate responsibility of the HRPP resides with the **Institutional Official (IO)** of the program. The IO is legally authorized to represent NJH. The IO is the signatory of the FWA and assumes the obligations of the FWA. At NJH, the Vice President of Legal and Regulatory Affairs is the Institutional Official. The IO is responsible for ensuring that the NJH HRPP has the resources and

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support necessary to fulfill their responsibilities and to comply with the regulations and requirements that govern human subject research. Such resources include, but are not limited to:

- Staffing commensurate with the size and complexity of the research program;
- Appropriate office space, investigator and study team meeting space, equipment, materials, and technology;
- Resources for the production, maintenance, and secure storage of HRPP and internal and external IRB records;
- Resources for auditing and other compliance activities and investigation of noncompliance;
- Access to legal counsel; and
- Ensuring that investigators, and staff receive training related to human research protections.

At least annually, the IO reviews the HRPP SOPs, requirements, and resources and makes adjustments as needed.

The IO is also responsible for:

- Fostering, supporting and maintaining a culture that supports the ethical conduct of research involving human subjects and compliance with applicable regulatory and other requirements;
- Oversight of the relationship between the NJH HRPP and BRANY IRB;
- Oversight over the conduct of human subjects research under the auspices of National Jewish Health;
- Providing training and educational opportunities for NJH HRPP staff to support their ability to handle the administration of NJH research in accordance with ethical standards and applicable regulations;
- Providing training and educational opportunities for investigators and research staff to support their ability to conduct research in accordance with ethical standards and applicable regulations; and
- Taking action as necessary to ensure the protection of human subjects and compliance with regulatory and other requirements.

The IO has the authority to suspend, terminate, or disapprove research or take other actions, such as sanctions or restrictions of research privileges or uses of research data, as necessary, to ensure the proper conduct of research, the protection of human subjects, the autonomy and authority of the BRANY IRB, compliance with regulatory and other requirements, or to protect the interests of National Jewish Health. However, the IO may not approve research that has been disapproved (or not yet approved) by the internal or external IRB.

The IO must complete the OHRP Human Subject Assurance Training. The HRPP Administrator will support the continuing education of the IO by providing information and updates on topics

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related to human research protections.

The IO is made known to employees of the organization and is accessible by phone, email, in person or other methods of communication. The HRPP Administrator and BRANY Administration have access to the IO for any concerns or issues related to the NJH HRPP.

In the performance of these duties, the IO has the authority to delegate such activities as may be necessary in order to effectively administer the program. However, the IO is ultimately responsible and is expected to be knowledgeable about human subject protections and research at the organization.

1.10.2 HRPP Administrator

The HRPP Administrator is selected by, and reports to, the Institutional Official (IO). The HRPP Administrator's job performance is evaluated by the IO on an annual basis. This individual is responsible for:

- Developing, managing and evaluating policies and procedures that ensure compliance with state, and federal regulations and NJH policies. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing the administration of NJH research;
- Advising the IO on key matters regarding human subjects research;
- Implementing the organization's HRPP SOPs;
- Overseeing the administration of the HRPP;
- Overseeing the administration of NJH IRB Reliance Agreements and Independent Investigator Agreements;
- Submitting, implementing and maintaining an approved FWA through the IO and the Department of Health and Human Services Office of Human Research Protection (OHRP);
- Assisting the Director of Academic Affairs with the management of the finances of the HRPP;
- Assisting the BRANY IRB in its efforts to review research and ensure the protection of human subjects;
- Assisting investigators in their efforts to carry out the organization's research mission;
- Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program;
- Developing training requirements as required and as appropriate for NJH investigators, and staff, and ensuring that training is completed on a timely basis;
- Serving as the primary contact at NJH for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services, the Food & Drug Administration (FDA), and other regulatory agencies on matters of human research protections; and

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- Serving as an internal expert resource for questions and other matters regarding the protection of human subjects including but not limited to Conflicts of Interest.

1.10.3 Institutional Review Board (BRANY IRB)

NJH designates the Institutional Review Board of the Biomedical Research Alliance of New York (BRANY) as its IRB, through an agreement executed between the two entities. The BRANY IRB prospectively reviews and makes decisions concerning all non-exempt human subjects research under the auspices of NJH unless it has been determined that NJH is not engaged in the research or NJH has entered into agreement with an external IRB to serve as the IRB of record. BRANY IRB may also review studies qualifying for exemption on a case by case basis (e.g., if an exempt study requires limited IRB review). The IRB is responsible for the protection of the rights and welfare of human research subjects, through review and oversight of safe and ethical research. It discharges this duty by complying with the requirements of federal, state and DoD regulations, the FWA, and organizational policies.

The BRANY IRB works with the NJH HRPP to ensure that their regulatory review of human subjects research does not commence until NJH HRPP's responsibilities are met concerning investigator resources, required trainings, financial disclosures, and other institutional endorsements and approvals. The BRANY IRB, however, makes independent determinations whether to approve, require modification in, or disapprove research based upon whether human subjects are adequately protected.

As part of its review, BRANY IRB addresses a study's scientific validity by addressing (in the reviewer checklists) whether or not:

- the research uses procedures consistent with sound research design and
- the research design is sound enough to reasonably expect the research to yield the expected knowledge.

Research that has been reviewed and approved by the BRANY IRB may be subject to review and disapproval by officials of NJH. However, those officials may not approve human research that has not been approved or has been disapproved by the IRB (internally or externally).

NJH may also use the services of external IRBs pending execution of appropriate reliance agreements.

1.10.4 Legal & Regulatory Affairs

The NJH HRPP relies on the Legal and Regulatory Affairs Department and engages outside counsel for the interpretation of state law and the laws of other jurisdictions where research is conducted as they apply to human subjects research. Counsel is available to provide guidance on other relevant topics as needed.

This department also confirms that the contract and the consent documents are consistent

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in terms of costs to subjects and who pays in case of injury.

1.10.5 Chief Compliance Officer (CCO):

Appointed by the NJH CEO, the CCO oversees and manages all issues of individual or corporate compliance, including COIs. The CCO also serves as NJH's VP of Legal and Regulatory Affairs. The process outlined in the NJH Conflict of Interest and Commitment Policy is followed. Section 23 of these SOPs addresses the COI process as it relates to the protection of human research participants at NJH, including the role of the IRB in either affirming or requiring changes to strengthen any management plan proposed.

1.10.6 Department Chairs and/or Organizational Leaders

Department Chairs and organizational leaders are responsible for ensuring that investigators are credentialed appropriately for their institutional responsibilities. The Department Chairs sign an Internal Research Review (IRR) form to signal institutional approval of research that is proposed for funding by an external agency.

1.10.7 Principal Investigators

The Principal Investigator (PI) is ultimately responsible for the protection of the human subjects participating in research they conduct or oversee. The PI is expected to abide by the highest ethical standards when developing a research plan and to incorporate the principles of the [Belmont Report](#). The PI is expected to conduct research in accordance with the IRB approved research plan and to personally conduct or oversee all aspects of the research. In addition to complying with all applicable regulatory policies and standards, PIs must comply with organizational and administrative requirements for conducting research. The PI is responsible for ensuring that all investigators and research staff complete all organization required trainings as well as training for their specific responsibilities in any given research study. When investigational drugs or devices are used, the PI is responsible for ensuring an appropriate plan for their storage, security, dispensing, accounting, and disposal.

The BRANY IRB reviews investigator qualifications when reviewing research and may determine that an investigator may not serve as PI or may require the addition of other investigators to supplement the expertise available on the research team or to conduct or oversee certain aspects of the research.

The Principal Investigator for research under National Jewish Health's jurisdiction generally must be employed by or have privileges at a National Jewish Health entity. Students and fellows must work under the mentorship of appropriate National Jewish Health personnel and may not serve as PI but may serve as a sub-investigator. Fellows, because they are more advanced in training, may serve as PI but mentorship by an appropriate leader is encouraged.

In limited situations, the IO may conduct a special review and allow someone to serve as PI who is not employed by National Jewish Health and who does not have privileges at a

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National Jewish Health entity. The IO will take the following into consideration:

- The basis for the request
- The credentials of the proposed PI
- The expertise and experience of the proposed PI
- The ability of the proposed PI to fulfill the responsibility to personally conduct or supervise the research and other PI responsibilities
- Pertinent compliance information including the results of any prior audits or inspections

Investigators approved to serve as PI under a special review may be asked to sign an Investigator Agreement or Assurance. IO will work with COO to determine any other agreement necessary.

Persons who are debarred, disqualified, or otherwise restricted from participation in research or as a recipient of grant funds for research by a federal, state, or other agency **may not** serve as PI.

Persons with a history of compliance issues related to the conduct of research (e.g., recipients of a FDA Warning Letter; investigators whose research approval has been suspended or terminated by an IRB for serious or continuing noncompliance) will be considered on a case-by-case basis. Factors to consider include whether corrective actions have been accepted as adequate, whether information from an audit or quality review indicate that the issues have been resolved, and similar considerations.

1.10.8 Other Related Units

1.10.8.1 Grants and Contracts Office

Grants and contracts staff review all research agreements with grantors and sponsors including federal, foundation, industry, and non-profit. This review ensures that all terms of the award (grant or contract) are in compliance with organizational policies. Only designated senior individuals within Grants and Contracts have the authority to approve funding proposals and to execute research agreements on behalf of the organization.

When the grant or contract agreement includes human research activities that will be conducted by investigators who are not employees or agents of National Jewish Health, a subcontract is executed between National Jewish Health and the collaborating institution. The subcontract includes the requirement for the collaborating institution to assure compliance with federal regulations for the protection of human subjects in research and to provide documentation of current and ongoing IRB approval. The collaborating institution must also ensure that key personnel involved in human subject research are in compliance with the NIH policy on education in the protection of human research subjects and provide documentation of education of key personnel to National Jewish Health.

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1.10.8.2 National Jewish Health Pharmacy

NJH Pharmacy is delegated responsibility by the Principal Investigator for storage, accounting for, dispensing, and compounding of investigational drugs and biologics used in research. This delegation is accomplished by having investigators submit a “Drugs or Biologics Service Request Form” to the NJH Pharmacy.

Investigators requesting an exception from this requirement must submit an “NJH Pharmacy Exception Request Form” to the NJH Pharmacy. Exceptions will be considered on a case by case basis by the Pharmacy director or designee, with review of required information from the PI regarding storage, accounting, dispensing etc. The NJH Pharmacy-approved Exception Request Form must be included in the initial study registration submission in NJH IRB Manager.

NJH Pharmacy dispenses investigational product only in accordance with the current protocol approved by the IRB of record. Investigational product will not be dispensed by the NJH Pharmacy without prior proof of the applicable study’s IRB approval.

1.10.9 Relationship Among Components

The HRPP Office provides a centralized process through which requests to conduct human subjects research by all NJH investigators undergo review to ensure appropriateness of chosen IRB, confirmation of compliance with training and financial disclosure requirements, and approval or endorsement from other impacted HRPP components (e.g., Biobank) or regulatory committees (e.g., IBC). The HRPP Administrator signs the IRR form once documentation of approval by the IRB of record is received. This endorsement signifies the ability of the researcher to commence with the research pending satisfaction of outstanding ancillary reviews.

1.10.10 Study-Specific Coordination

The following components are involved in the review (and approval, as applicable) of research that impact their areas, including, but not limited to:

- Privacy Officer
- Information Security
- Health Information Management Office
- Research Informatics Services
- Biobank
- Pharmacy
- Radiology
- Facilities where research activities will occur

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- Institutional Biosafety Committee
- Corporate Compliance Office (for COI)

Documentation of permission or approval may be required as a component of the IRB (BRANY or external) application. The HRPP Administrator may request review or consultation with any of the above or other organizational committees or components even when such review or consultation is not technically required by policy.

If the research sites, or research personnel, are also under the jurisdiction of an external IRB, documentation of the external IRB's approval or agreement to cede or waive review is required.

Other committees and officials may not approve research involving human subjects to commence that has not been approved or has been disapproved by the IRB (BRANY or external).

2. Quality Assurance

The HRPP Administrator performs Quality Assurance and Improvement activities for the purposes of monitoring the safety of ongoing studies and measuring and improving human research protection effectiveness, quality, and compliance with organizational policies and procedures and applicable federal, state, and local laws.

2.1 Audit and Inspection Reports

The HRPP Office should be notified in advance, whenever possible, of upcoming audits or inspections of research whether the study is reviewed by the BRANY IRB or an external IRB on NJH's behalf. The HRPP Administrator may participate in entrance and exit interviews and otherwise observe or support the audit or inspection. Likewise, NJH representatives may assist in the development of any responses to audits or inspections.

All reports from auditors or inspectors must be submitted to the HRPP Office for review via IRBManager. The HRPP Administrator will forward reports with findings to the IO, who will review such reports to monitor for issues that could impact the rights or welfare of human subjects and for issues indicative of possible serious or continuing noncompliance. If such issues are identified, the report will be forwarded to the IRB of Record to determine what additional actions, if any, are necessary.

When NJH is engaged in research reviewed by an external IRB, all reports from audits or inspections must be submitted for review to the HRPP Office via IRBManager. Corrective and preventative actions (CAPA), a follow up review, or other actions as needed may be required to ensure the protection of human subjects and to support compliance.

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2.2 Investigator Compliance Reviews

The HRPP Administrator and others, as required, conduct post-approval directed (for cause) and routine (not for cause) compliance reviews of human subjects research conducted under the auspices of NJH.

Compliance reviews are conducted to assess investigator compliance with federal, state, and local laws; NJH policies; to identify areas for improvement; and to provide recommendations based on existing policies, procedures, and SOPs. The results of compliance reviews will be reported to the HRPP Administrator, the IO, the investigator, the IRB of Record, and other NJH leadership, as appropriate. Any IRB (BRANY or external) reporting an evaluation of noncompliance will be handled according to the procedures of the IRB of record.

If it is identified during the course of a review that subjects in a research project may have been exposed to unexpected serious harm or risk of harm, the reviewer will promptly report such findings to the HRPP Administrator, who will immediately consult with the IO.

If issues are identified that indicate possible misconduct in research, the NJH procedures for investigating research misconduct will be initiated.

Compliance reviews may include:

- Requesting progress reports from investigators
- Examining investigator-held research records and records held by pharmacy or other ancillary services
- Reviewing source documentation
- Reviewing the recruitment process and materials
- Reviewing consent materials and the documentation of consent
- Observing the consent process and other research activities
- Verifying HIPAA authorization
- Interviewing investigators and research staff
- Interviewing research subjects
- Reviewing projects to verify from sources other than the investigator that no unapproved changes have occurred since previous review
- Conducting other monitoring or auditing activities as deemed appropriate by the HRPP or IRB.

Additionally, the BRANY IRB has a Quality Assurance division that may also conduct for-cause or not for-cause compliance review of NJH studies under its jurisdiction. Details of this program are available in BRANY IRB SOPs, section II.9.

2.3 IRB Compliance Reviews

The HRPP Administrator, or, on occasion, others, may review the activities of the BRANY IRB or other

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IRBs of record to ensure compliance with regulatory and NJH local context requirements. Identified issues will be handled in accordance with the relevant reliance agreement (master or otherwise).

3. Education & Training

3.1 Training / Ongoing Education of Investigators and Research Team

As stated previously, a vital component of a comprehensive human research protection program is an education program for all individuals with human subject responsibilities. NJH is committed to providing training and on-going education for investigators and research staff members on human subject protections and other relevant topics.

3.1.1 Initial Education

Investigators and research staff who interact or intervene with subjects, or who use subject's identifiable information or biological specimens for the purposes of research, must affiliate with NJH on the CITI site and take the following courses:

- Biomedical Research **OR** Social/Behavioral Research (as applicable)
- Health Information Privacy and Security (HIPS) Course - Information for Investigators
- Conflicts of Interest (COI)
- Good Clinical Practice, US FDA Focus (if conducting a federally-funded clinical trial, or are otherwise required to do so by an industry sponsor, or a condition of a grant or contract)

Current training for each member of the research team is confirmed by the HRPP Administrator with every new and continuing study application, as well as requests to add personnel. Ability to submit to an IRB will be withheld until all research team members are current in training.

3.1.1.1 Waiver of Initial Education

If individuals can provide documentation verifying that they have successfully completed human subject research training equivalent to that required by NJH, they may request a waiver of NJH's specific training requirements. The HRPP Administrator will review the documentation and determine if it satisfies organizational standards. Any individual issued a waiver must certify in writing that s/he has reviewed NJH's specific standard operating procedures.

3.1.2 Continuing Education

Initial training is considered current for three years at which time investigators and research staff must complete applicable refresher CITI training or provide evidence of equivalent training as described above. There is no exception to this requirement.

Training will be verified at the time of continuing review for those studies requiring such

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review, or at the time of annual progress report for those studies not subject to the continuing review requirement. Training will also be verified at time of applications to add study personnel. If training has not been completed or has lapsed and is not completed in a timely manner, the investigator or staff member may be removed from the study or otherwise restricted from participating in the research.

In addition to the basic requirements described above, NJH will periodically provide training on topics relevant to human subject protections, regulations, policies and standards, and IRB (BRANY and external) submission processes and requirements. Training may be provided via in-service, workshops, webinars, e-Learning, or through the distribution of articles, presentations, and other materials. Investigators and staff may request training or offer training suggestions by contacting the HRPP Office.

4. “Human Subjects” and “Research” Determinations

The responsibility for initial determination whether an activity constitutes “research” rests with the NJH HRPP. The NJH HRPP Administrator will make this determination based on the definitions of “research” and “clinical investigation” as provided by the Common Rule and FDA regulations, respectively.

Similarly, the responsibility for the initial determination of whether research involves “human subjects” rests with the NJH HRPP. Under the Common Rule, information is considered identifiable, and thus involving human subjects, when the identity of the subject is or may readily be ascertained by the investigator or associated with the information. Note that this differs from what is considered identifiable according to HIPAA standards, where the presence of certain identifiers determine whether or not the health data are identifiable. Further, FDA regulations do not incorporate the concept of “identifiability” at all in the evaluation of whether an activity is a clinical investigation (or research) subject to FDA regulations.

Investigators may not make their own determination as to whether an activity constitutes human subject research. Any proposed activity involving data and/or specimens from humans, either via direct interaction or via record access, must be submitted for an official human subjects research determination. Such requests should be made via the “Human Subjects Determination” xForm in NJH IRB Manager.

A case report or case series of three or fewer patients is not considered human subjects research and does not need to be submitted for an official determination (See Section 26.3 for additional requirements).

Human Subjects Research Determination requests must be submitted and determined prospectively (i.e., before the proposed activity or research begins). Conducting an activity that constitutes human subjects research without HRPP approval or exemption is noncompliance and will be managed as described in Section 17.

Determinations regarding whether an activity constitutes human subject research will be made by the HRPP Administrator or designee, with input from others as deemed necessary, in accordance

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with the definitions in Section 1.3, applicable federal regulations, and federal guidance. A determination letter will be issued by HRPP Administrator and sent via IRBManager to document the determination. Investigators conducting research under the auspices of NJH may not rely upon determinations made by other organizations or through the use of electronic (or other) determination tools.

Note: With the implementation of the 2018 Rule, the requirement of the Newborn Screening Saves Lives Reauthorization Act of 2014 that federally-funded "research on newborn dried blood spots shall be considered research carried out on human subjects" is eliminated. Whether such research approved under the 2018 Rule involves human subjects shall now be considered using the same standards as are used for other research involving human biospecimens (e.g., whether the identity of subjects may be readily ascertained, whether the specimens are coded and who has access to the key, whether the research involves the evaluation of the safety or effectiveness of an FDA-regulated device, etc.).

5. Exempt Determinations

All research using human subjects must be prospectively granted either exemption by NJH HRPP (or BRANY IRB, on a case by case basis), or approval from BRANY IRB (or external IRB of record). Although certain categories of human subject research are exempt from IRB oversight, at NJH the determination of exempt status must be made by the HRPP Administrator, or designee.

Individuals involved in making the determination of an exempt status of a proposed research project cannot be involved in the proposed research. Reviewers must not have any apparent conflict of interest.

Unless otherwise required by law or by Federal department or agency heads, exempt studies are excused from the requirements of the [Common Rule](#) (i.e., IRB approval and full research consent are not required) other than as specified within the regulations (e.g., the conditions that permit exemption, and when limited IRB review is required). Exempt research is not exempt from ethical considerations, such as honoring the principles described in the [Belmont Report](#). The individual/s making the determination of exemption will determine whether to require additional protections for subjects in keeping with ethical principles (e.g., requiring disclosure/consent, etc.).

Finally, it is important to note that for Exemptions 2(iii) and 3(i)(C) below, limited IRB review is required for privacy and confidentiality protection under 45 CFR 46.111(a)(7). Limited IRBs review will be conducted by BRANY IRB.

5.1 Limitations on Exemptions

The following limitations on exemptions apply to all research regardless of funding:

Children: Exemption #2(i) and (ii) for research involving survey or interview procedures or observations of public behavior does NOT apply to research in children, except for research involving observations of public behavior when the investigator does not participate in the activities being

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observed. Exemption #2(iii), where identifiable information is obtained and BRANY IRB conducts a limited IRB review, is NOT applicable to research in children. Exemption #3 does NOT apply to research involving children. [45 CFR 46.104(b)(3)]

Prisoners: Exemptions do not apply except for research aimed at involving a broader subject population that only incidentally includes prisoners. [45 CFR 46.104(b)(2)]

5.2 Categories of Exempt Research

With the above-referenced limitations and any other limitations or restrictions due to applicable law, regulation, or agency policy, research activities not regulated by the FDA (see Section 5.3 for FDA Exemptions) in which the only involvement of human subjects are determined to be in one or more of the following categories may be determined exempt:

1. Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact fellows' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:
 - i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
 - ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
 - iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by .111(a)(7): *When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.*
3. Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and

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information collection and at least one of the following criteria is met:

- i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
- ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
- iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by .111(a)(7): *When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.*

For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

4. Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
 - i. The identifiable private information or identifiable biospecimens are publicly available;
 - ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
 - iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for

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- “public health activities and purposes” as described under 45 CFR 164.512(b); or
- iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.
5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.
- i. Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal website or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.
6. Taste and food quality evaluation and consumer acceptance studies:
- i. If wholesome foods without additives are consumed, or
 - ii. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Note: Exemption categories #7 and #8, involving broad consent, has not been adopted by this institution at

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this time. For more information on categories # 7 and #8 please refer to Refer to 45 CFR 46.104(d)(7), 46.111(a)(8), and 46.116(d) of the [revised Common Rule](#).

5.3 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements for prior IRB of record review and approval:

1. Emergency use of a test article, provided that such emergency use is reported to the BRANY IRB within 5 working days. Any subsequent use of the test article is subject to IRB review. [[21 CFR 56.104\(c\)](#)]. See Section 15.5 for detailed discussion of this exemption.
2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [[21 CFR 56.104\(d\)](#)]

5.4 Procedures for Exemption Determination

To request an exempt determination, investigators must submit the following materials in the NJH IRBManager:

1. The study protocol
2. Principal Investigator and Co-Investigator CVs
3. NJH COI Disclosure Forms for all study personnel;
4. Any study materials/tools such as recruitment materials, information sheets, consents, scripts, and questionnaires, diaries, surveys, or data collection sheets;
5. Letter(s) of permission from any non-NJH sites; or, when applicable, documentation of IRB approval or exemption from the external site;
6. The grant application (if the project is federally-funded)
7. Internal Research Review (IRR) form

The HRPP Administrator or designee reviews all requests for exemptions and determines whether the request meets the criteria for exempt research. The reviewer's determination is documented within NJH IRBManager, and the determination is sent to the PI within the system. If the request does not appear to meet the definition of human subject research, the human research determination form may need to be completed by the PI, and the reviewer evaluates the re-submitted proposal as described in Section 4.

When the research requires limited IRB review or a HIPAA determination (i.e., waivers or alterations of the requirement for HIPAA authorization), the review may be conducted using expedited review procedures by the BRANY IRB (Chair or an experienced Chair-designated member of the IRB). As with

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all other research subject to IRB review requirements, when conducting limited IRB review the IRB has the authority to approve, require modifications in (to secure approval), or disapprove all research activities; and to suspend or terminate IRB approval. Actions of disapproval may only be made by the convened IRB. [45 CFR 46.109(a), 45 CFR 46.110]

Proposed modifications to the aspects of research subject to limited IRB review must be submitted to and approved by BRANY IRB prior to implementation, except when necessary to eliminate apparent immediate hazards to the subject(s), in which case the change must be promptly reported (but no later than 5 days after the Investigator's first knowledge) to the BRANY IRB. [45 CFR 46.108(a)(3)(iii)]

The individual making the determination of exemption will determine whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report. The exempt application, review documentation, and determination letter are maintained within NJH IRBManager (or BRANY IRBManager, as applicable).

Continuing review is generally not required for research determined to be exempt, even when that research is subject to limited IRB review. However, the BRANY IRB may determine that continuing review is required for a particular study subject to limited IRB review, in which case it shall document the reasons for its determination in the IRB record and communicate the requirement to the investigator in the IRB determination letter. [45 CFR 46.109(f)(ii), 45 CFR 46.115(a)(3)]

Exempt determinations do not have an expiration date. However, Investigators must submit a closure in NJH IRBManager when an exempt research project is complete so that the organization can maintain an accurate database of research activities. Until a closure form has been processed by the IRB, study teams will receive annual check-in notifications requesting a brief summary of the study's progress. If a study team does not respond to this notice within 30 days, the NJH HRPP will administratively close the study.

In addition, Investigators must report any proposed modification to the research to the HRPP office via NJH IRBManager for a determination of whether the research still qualifies for exemption. They must also report any PI changes or personnel additions, so that training and COI issues can be assessed.

6. Multi-site and Collaborative Research

When engaged in multi-site research, research involving external collaborators, or research that is otherwise under the jurisdiction of more than one IRB, NJH acknowledges that each organization is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. NJH may choose to review the research in its entirety, only those components of the research NJH is engaged in, rely on the review of another qualified IRB, or make other arrangements for avoiding duplication of effort. When NJH is the prime awardee on an HHS grant, it will ensure that at least one IRB reviews the research in its entirety (see Section 9 regarding the single IRB requirement for multicenter grants awarded from NIH, where all sites are conducting all research procedures).

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When relying upon an external IRB or when serving as the reviewing IRB for an outside organization or external investigator, a formal relationship must be established between NJH and the outside organization or investigator through an IRB Authorization Agreement, Investigator Agreement, a Memorandum of Understanding, or other such written agreement. The written agreement must be executed before NJH will accept any human research proposals from the outside organization or investigator or rely on the review of an external IRB.

IRB reliance agreements establish the authorities, roles, and responsibilities of the reviewing IRB and the relying organization. The procedures for reliance, including for communication, information-sharing, and reports, may be outlined in the reliance agreement or in companion SOPs or other materials. The HRPP Administrator utilizes a checklist to ensure that reliance agreements and any accompanying materials address all requirements and are consistent with NJH's standards. To support compliance, NJH will make every effort to ensure as much consistency as possible across reliance agreements.

NJH has signed the SMART IRB joinder agreement. When the organizations participating in the research are signatories to the joinder agreement, IRB reliance may be requested and documented utilizing the [SMART IRB](#) online reliance platform. NJH will determine on a study-by-study basis whether the SMART IRB SOPs or alternative procedures will be utilized to implement the reliance via a reliance arrangement agreed upon between the relying and reviewing sites.

Requests for NJH to either rely upon an external IRB or to have BRANY IRB serve as the IRB of record for an external organization or investigator should be submitted as early as possible in the grant/contract process by submitting a reliance request following the instructions in Section 8 of these SOPs.

7. Research Previously Approved by An External IRB

When an investigator transfers research to NJH that was previously approved by another IRB, the investigator must either submit a reliance request for NJH to rely upon the current IRB of record, or submit the research for de novo review under NJH procedures covered by these SOPs. No research activity may take place under NJH auspices without the appropriate reliance, or IRB review and approval.

For research transfers where stopping research interventions or procedures might harm subjects, the investigator can request permission from the IRB to continue research interventions under the oversight of the prior organization's IRB until final NJH IRB approval is obtained.

8. IRB Reliance Arrangements in Multi-Site Research

NJH investigators involved in multi-site, investigator-initiated research are encouraged to discuss with collaborators the possibility of shared IRB review; i.e., having one IRB review on behalf of all sites.

If the research is part of a multicenter grant awarded from NIH, single IRB (sIRB) review is required

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under most circumstances (<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html>). Refer to Section 9 for details specific to compliance with the NIH sIRB policy.

Investigators should contact the HRPP Office early in the multi-site grant/contract process to discuss possible sIRB options as discussed in Sections 8.2 (BRANY IRB, on behalf of NJH, serving as the Reviewing IRB) and 8.3 (NJH Ceding Review to an External IRB) below.

8.1 Reliance Agreements

Reliance agreements must be in place for all ceded IRB review arrangements. The HRPP Office ensures that these agreements are negotiated to reflect study-specific, respective responsibilities of the reviewing IRB and the relying Institutions. The Reliance Agreement:

- Documents the respective authorities, roles, responsibilities, and communication between an organization providing the ethical review and a participating organization relying on a reviewing IRB.
- Describes the responsibilities of all parties and how communication between parties will occur, for example, notifications of the outcome of regulatory review and management of federally-mandated reports such as reports of unanticipated problems, serious or continuing noncompliance, and suspensions or terminations of IRB approval.
- When IRB certification requirements apply (e.g., for NIH Genomic Data Sharing etc.), the agreement or written procedures will indicate who is responsible for meeting the certification requirements.
- Specifies contact information and personnel for both the sIRB and relying institution(s).
- Address whether the relying organization applies its FWA to some or all research, and ensure that the IRB review is consistent with requirements in the relying organization's FWA.
- Address which organization is responsible for obtaining any additional approvals from DHHS when the research involves Subpart B, C, or D determinations, or any applicable federal agency or department (e.g., DOD, etc.).

The institution that is awarded the funding for the research is responsible for maintaining all agreements and for ensuring that adequate and appropriate communication channels between the sIRB and participating sites are in place. Participating sites are responsible for maintaining copies of the site agreement in accordance with the terms of their FWA.

8.2 BRANY IRB (on behalf of NJH) Serving as the Reviewing IRB

8.2.1 Responsibilities of the BRANY IRB

Policies and procedures in the conduct of review for all sites (NJH and external) will mirror those outlined throughout these SOPs. Possible exceptions are noted in 8.4 below. Additionally, the following BRANY IRB responsibilities are to be applicable for all sites:

- Have the final authority to decide whether NJH or external researcher or research staffs'

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COI and its management, if any, allows the research to be approved

- Have the authority to request or conduct an audit of research being reviewed.
- Make relevant IRB policies readily available to relying external sites, including their HRPP Administrator, researchers, and research staff, and ensure that changes to those policies are communicated as well.
- Ensure that an NJH HRPP and BRANY IRB contact person along with contact information is specified for researchers and research staff to obtain answers to questions, express concerns, and convey suggestions regarding the BRANY IRB.

The process for adding sites to an already approved IRB study is detailed in BRANY IRB SOPs (Section III.1.d.4).

8.2.2 Responsibilities of the NJH Principal Investigator

- Submission of a plan for review to the IRB to ensure that the PIs at collaborating sites have access to current information regarding study status and current protocols, consent documents, etc. regarding the study. (Alternatively, the IRB can review the plan provided by the NJH PI to ensure open communication with the collaborating site(s)).
- Coordinate with BRANY IRB to ensure submission to the IRB information pertaining to the particular characteristics of each site's local research context to be considered either (a) through knowledge of its local research context by the IRB, (b) through consultants, or (c) through review by appropriate designated institutional officials at external site(s). Additionally, the submission will also include details for the IRB's evaluation regarding the management plan for information that is relevant to the protection of participants (e.g., unanticipated problems involving risks to participants or others, Interim results, protocol modifications). When the NJH researcher is the lead researcher of a multi-site study, this information will also be made known to the IRB of record (e.g., Independent IRB, IRB, etc).

8.3 NJH Ceding IRB Review to an External IRB

8.3.1 Standing Reliance Agreements

NJH has standing agreements in place to engage the services of external IRBs for the review of specific categories of research including:

- BRANY (as above)
- WIRB-when WIRB is the Central IRB of Record
- Advarra-when Advarra is the Central IRB of Record
- National Cancer Institute's CIRBs via SWOG

Requests for use of any other sIRB will be assessed on a case-by-case basis based on factors outlined in Section 8.3.2.

NJH is a participating institution in the SMART IRB initiative as well, having signed an overarching

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agreement indicating willingness to cede to other institutions' IRBs, pending satisfactory evaluation of factors identified below.

8.3.2 Factors Considered by the HRPP Office in the decision to allow NJH to Cede to an External IRB

NJH may choose to enter into an agreement to rely upon other external IRBs, most commonly when required as a condition of a grant or contract. The HRPP Administrator evaluates the following factors, and others as appropriate, when considering a request to rely upon an external IRB:

1. The accreditation status of the proposed IRB;
2. The compliance history of the IRB (e.g., outcomes of prior audits or inspections, corrective actions);
3. Prior experience with the IRB;
4. The federal IRB registration and organizational FWA, as applicable;
5. The expertise and experience of the proposed IRB (e.g., with reviewing the type of research, research procedures, and subject population(s));
6. The research activities to be conducted at NJH
7. The risks and complexities of the proposed research;
8. The proposed reliance terms and procedures, including acceptance of NJH local context issues, as well as the procedures for collaborative management of matters such as conflicts of interest processes, investigator training, noncompliance, unanticipated problems, and federal reports;
9. The plan for review and allowance of the incorporation of site-specific consent language; and
10. The plan for incorporation of other relevant local requirements or context information in the review process.

The HRPP Administrator will present relevant factors for consideration by the IO, who will make the final decision regarding whether or not to cede to the requested External IRB. The PI will be notified of the decision.

8.3.3 External IRB, NJH, and NJH Investigator Responsibilities When NJH Cedes Review

8.3.3.1 Responsibilities of the External IRB

The External IRB has the same authority as the BRANY IRB and all determinations and requirements of the external IRBs are equally binding. See Section 8.4 for possible exceptions to external IRB vs. NJH responsibilities.

8.3.3.2 Responsibilities of NJH

NJH remains responsible for the conduct of the research in which it engages. Research reviewed by external IRBs remains subject to review, approval, oversight, and monitoring by NJH (in cooperation with the reviewing IRB when appropriate) and must adhere to all applicable policies, procedures, and requirements of NJH HRPP. Officials of NJH may not approve research that is subject to a reliance

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agreement if it has not been approved by the reviewing IRB. See Section 8.4 for possible exceptions to external IRB vs. NJH responsibilities. HRPP Administrator is responsible for notifying the reviewing IRB when NJH policies that may impact IRB review are updated.

8.3.3.3 Responsibilities of the NJH Investigator When Using an External IRB

1. General Compliance Requirement:

- The NJH Investigator must be familiar with, and comply with, the external IRB’s policies and procedures for initial and continuing review, record keeping, prompt reporting, and any additional requirements or procedures outlined in the IRB reliance agreement or companion materials (e.g., reliance SOPs). All information requested by the reviewing IRB must be provided in a timely manner. NJH will support investigator compliance with the terms of reliance agreements by reminding them to become familiar with the requirements of the IRB of record.
- Expectations of PI compliance, as detailed in these SOPs, remain in place regardless of the reviewing IRB.
- Even though the External IRB may be reviewing the study, it must not commence at NJH until all training, COI disclosures, local consent review, and other required ancillary reviews and certifications have been satisfied.
- **National Cancer Institute (NCI) Strictly Limits Local Modifications to Consent Forms-** NCI recently informed participating institutions and investigators that local modifications to research consent forms (so-called "local boilerplate language") will be restricted under updated NCI CIRB guidelines. Under the guidelines the only permitted deletion of language will be deletions of reproductive language by faith-based institutions.
 - **Only three types of additions will be allowed:** Local contact information; State and local laws pertaining to informed consent; and Institutional policy related to research only as specified in the CIRB Quick guide.

2. Institutional Registration Requirement:

- All non-exempt human research studies that will be reviewed by any external IRB must first be registered in NJH IRB Manager using the “Study Registration xForm” along with required documents detailed in the form. Registration must be done prior to submission to the reviewing IRB.
- Expanded Access and Humanitarian Use Device (HUD) protocols must also be registered in NJH IRB Manager when relying on an external IRB other than BRANY IRB.
- Exempt research requiring limited IRB review is exempt from this registration requirement and may be submitted directly to BRANY IRB for the determination.

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- The HRPP Administrator will review the information and verify that CITI training, COI review, any other applicable institutional approvals and requirements have been completed. The HRPP Administrator will also determine the need for relaying local context information to the external IRB in accordance with the reliance agreement. Where waivers or alterations of HIPAA authorization are requested, BRANY IRB is authorized to review on behalf of NJH; NJH does not permit other external IRBs to render decisions involving HIPAA compliance.
- The HRPP Office will notify the investigators via NJH IRB Manager once the proposed research has been cleared for submission to the external IRB. This notification will specify documents that must be submitted in IRB Manager upon approval from the external IRB. Once these documents have been submitted, investigators will receive a final notification listing any outstanding ancillary reviews and instruction on post-approval requirements.

3. Post-IRB Approval Requirements:

1. Research reviewed by BRANY IRB

The following must be reported in NJH IRB Manager concurrent with submission to BRANY IRB:

1. Local unanticipated problems, complaints, and any serious and continuing noncompliance.
2. Notices about, and reports from, DSMB's, external monitors, auditors, or inspectors.

The following must be reported in NJH IRB Manager promptly:

3. Removal of any study team member responsible for contributing medical or psychological expertise to the conduct of the study.

2. Research reviewed by other external IRBs

The following must be submitted in NJH IRB Manager concurrent with submission to the IRB of record:

1. Local unanticipated problems, complaints, and any serious and continuing noncompliance.
2. Notices about, and reports from, DSMB's, external monitors, auditors, or inspectors.
3. Study closures.

The following must be submitted in NJH IRB Manager for review and approval regardless of requirements by the IRB of Record:

4. Changes in PI and all study team member additions.
5. Removal of any study team member responsible for contributing medical or psychological expertise to the conduct of the study.

The following must be promptly submitted in NJH IRB Manager once documentation of approval from the IRB of Record is received:

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6. Copies of approved continuing review/status report submissions, approved local-site modifications/amendments (including any updated protocols, updated consent forms, etc.), and corresponding IRB approval notification.

8.4 Exceptions to IRB vs. Local Site Responsibilities

Certain areas of responsibility can be handled by either the reviewing IRB or the NJH HRPP, provided they have been agreed to in the reliance agreement or outlined in a companion document. For example, alternative procedures may be used for any of the following:

1. Conducting and documenting scientific review
2. Management and documentation of ancillary reviews and institutional permissions for research;
3. Training requirements and verification of qualifications and credentials for external investigators and staff;
4. For-cause and not-for-cause compliance reviews;
5. Site-specific consent language
6. HIPAA compliance
7. Handling of matters concerning noncompliance, including which institution is responsible for deciding whether each allegation of non-compliance has a basis in fact, whether an incident of noncompliance constitutes serious or continuing noncompliance, and who will handle reporting to federal agencies
8. Handling of unanticipated problems, and responsibility of reporting to federal agencies when required;
9. Review of grant and IRB protocol for congruence.
10. Review of investigator financial disclosures for COI (note: the reviewing IRB must provide final approval of any management plans generated to mitigate investigator FCOI)
11. Managing organizational conflict of interest relating to the research
12. Procedures for submission and review of interim reports and continuing review materials; and/or
13. The communication of IRB determinations and other information to external investigators and organizations.

In the case of the termination of a reliance agreement, identification of the party responsible for continued oversight of active studies until closure or a mutually agreed upon transfer of the study must be specified.

9. NIH Single IRB (sIRB) for Multi-Site Research

The NIH sIRB policy applies to grant applications proposing non-exempt human research which are received for due dates on or after January 25, 2018. For contracts, the policy applies to all solicitations issued on or after January 25, 2018. The policy does not apply to career development, research training, or fellowship awards, nor to sites that are not conducting the same protocol as the other sites (e.g., sites providing statistical support or laboratory analysis only) or to foreign sites.

Exceptions to the policy are automatic when local IRB review is required by federal, tribal, or state law/regulation/policy. Such exceptions and the basis should be cited in the proposed sIRB plan (see

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below) and apply only to the site(s) to which the law/regulation/policy applies. Other exceptions will be considered when there is compelling justification. The site(s) and justification for why the site(s) cannot rely on the single IRB of record should be included in the proposed sIRB plan. NIH will consider the exception request and inform the applicant of the outcome.

9.1 Selection and Designation of a sIRB

NJH investigators submitting applications for NIH-funded multi-site research must describe the sIRB plan in the funding proposal (grant application or contract proposal), and, if applicable, may request direct cost funding to cover additional costs related to the requirements of the NIH policy.

The HRPP Office should be contacted as early in the grant writing process as possible to either confirm with BRANY IRB that they can provide IRB services for the study, or to assist the investigator in making alternative arrangements (e.g., use the IRB at one of the participating sites, SMART IRB, etc.).

9.2 Reliance Agreements for sIRB Studies

A Reliance Agreement (or “Authorization Agreement”) between the sIRB and the participating sites is required.

9.3 sIRB Responsibilities

1. Per the NIH Policy, the sIRB is responsible for conducting the ethical review of NIH-funded multi-site studies for participating sites and for carrying out the regulatory requirements as specified under the HHS regulations at 45 CFR Part 46.
2. The sIRB must have the necessary infrastructure to support the required activities (e.g., administrative or regulatory staff, policies, procedures, workflows and technology).
3. In reviewing multi-site research protocols, the sIRB may serve as a Privacy Board, as applicable, to fulfill the requirements of the HIPAA Privacy Rule for use or disclosure of protected health information for research purposes.
4. The sIRB can delegate to relying institutions the ability to monitor or observe the conduct of the research and/or the consent process.
5. The sIRB must review and approve proposed management plans for investigators determined to have a financial conflict of interest.

9.4 Participating Site Responsibilities

All sites participating in a multi-site study are expected to rely on a sIRB to carry out the functions that are required for institutional compliance with IRB review set forth in the HHS regulations at 45 CFR 46. Participating sites are responsible for meeting other regulatory obligations, such as HIPAA compliance, obtaining informed consent, overseeing the implementation of the approved protocol, and reporting unanticipated problems and study progress to the sIRB. Participating sites must communicate relevant information necessary for the sIRB to consider local context issues and

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state/local regulatory requirements during its deliberations. Participating sites are expected to rely on the sIRB to satisfy the regulatory requirements relevant to the ethical review. Although IRB ethical review at a participating site would be counter to the intent and goal of this policy, the policy does not prohibit any participating site from duplicating the sIRB with an additional local review.

However, if this approach is taken, NIH funds may not be used to pay for the cost of the duplicate review. Additionally, the participating site is responsible for:

1. Reporting incidents of protocol deviations or noncompliance to the sIRB;
2. Monitoring or observing the conduct of the research and/or the consent process, when specified in the Reliance Agreement;
3. Ensuring disclosure and management of conflicts of interest according to the participating sites' policies and procedures and submit for approval to the sIRB management plans related to investigator FCOI's in human subject research;
4. Reporting to the sIRB changes to research implemented to eliminate apparent immediate hazards to participants;
5. Ensuring ancillary reviews by Pharmacy, Radiation Safety, IBC etc. are conducted prior to commencement of the research (or IRB approval of the research, depending on local policy).

When an external IRB serves as the sIRB for a study in which NJH is engaged, investigators must register the study in NJH IRB Manager prior to submission to the external IRB following the procedures outlined in Section 8.3.3.3. Post-approval requirements for investigators are also detailed in this Section. Research reviewed by external IRBs remains subject to review, approval, and oversight by NJH HRPP and must adhere to all applicable policies, procedures, and requirements required for the safe and ethical conduct of the study.

10. BRANY Institutional Review Board

NJH has engaged BRANY IRB to serve as its primary Institutional Review Board (IRB) to ensure the protection of human subjects in research conducted under its auspices.

For full detail concerning the regulatory authority, review procedures, and roles and responsibilities of the BRANY IRB, please refer to their Standard Operating Procedures available within the BRANY IRB Manager electronic system. Additional considerations:

10.1 NJH Investigator Qualifications

BRANY IRB relies upon NJH processes (e.g., credentialing) to satisfy their need to ensure that investigator credentials, curriculum vitae, resumes, or other relevant materials support the requirement that the investigators and members of the team are appropriately qualified to conduct the research.

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10.2 NJH Conflicts of Interest (COI)

NJH registration processes include collection of study team financial disclosures, and coordinates review of any significant financial interests relating to the research. Proposed management plans are sent to BRANY IRB for review and to assess whether the conflict and the management plan, if any, allow the study to be approved. (See Section 23 for a more detailed discussion of COI).

10.3 Advertisements and Recruitment Materials

Prior to submission to the IRB of Record, the HRPP Office reviews all advertising materials to be used for local recruitment. This information must be submitted to the IRB with the initial application, or, if proposed after study approval, as a modification request.

Advertising materials must include the following information:

- A statement that the study is research.
- The purpose of the research.
- Basic eligibility criteria.
- The location where the research will be conducted.
- Study team contact information (e.g., a work phone number, email address, etc.).

Advertising materials should not include the following:

- Claims, either explicitly or implicitly, that the drug, biologic, device or other type of intervention is safe or effective for the purposes under investigation.
- Claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic, device or intervention.
- Terms such as “new treatment,” “new medication,” or “new drug” without explaining that the test article is investigational.
- Specific amount of financial remuneration or overemphasis that remuneration is available

Advertisements must meet [NJH branding requirements](#).

The first contact prospective study subjects should make is with an individual who has a treatment or other clear relationship to the subject unless the patient has given verbal or written permission to be contacted by other NJH research personnel. The individual should follow a script to determine basic eligibility for the specific study. If this script does not mirror the consent, contact the IRB of record to determine their requirement for review (to ensure that the screening procedures adequately protect the rights and welfare of the prospective subjects). Investigators may attempt to contact a potential subject (or a subject lost to follow-up) up to three times.

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10.4 State and Local Laws

BRANY IRB considers and adheres to all applicable state and local laws in the jurisdictions where the research is taking place. The NJH HRPP and BRANY IRB may consult with the Compliance Office for the interpretation and application of Colorado law as required.

11. Suspensions and Terminations

BRANY IRB approval may be suspended or terminated if research is not being conducted in accordance with IRB or regulatory requirements or has been associated with unexpected problems or serious harm to subjects. (See BRANY IRB SOPs for discussions of unanticipated problems and noncompliance.) The IRB's authority to suspend or terminate research applies to all research subject to IRB approval, including exempt research with limited IRB review and research for which continuing review is no longer required.

The NJH Institutional Official (IO) has the authority to suspend or terminate the organization's approval of research. Such actions will be promptly reported to the BRANY IRB so that the IRB can review the circumstances and take any necessary actions relevant to IRB review and oversight.

Full details concerning processes and reporting requirements associated with suspensions and terminations may be found in the BRANY IRB SOPs.

12. Documentation and Records

NJH HRPP and BRANY IRB prepare and maintain adequate documentation of the HRPP and IRB's activities, respectively. All records are accessible for inspection and copying by authorized representatives of the FDA, OHRP, sponsors, and other authorized entities at reasonable times and in a reasonable manner.

12.1 Records

IRB records include, but are not limited to:

1. Written operating procedures; (HRPP, BRANY)
2. IRB membership rosters; (BRANY)
3. IRB member files including documentation of appointments, experience, education/training, and expertise; (BRANY)
4. IRB correspondence including reports to regulatory agencies; (BRANY)
5. IRB Protocol Files; (BRANY)
6. Documentation of exemptions; (HRPP, BRANY-as applicable)
7. Convened IRB meeting minutes; (BRANY)
8. Documentation of review by an external IRB, when appropriate; (HRPP)

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9. Documentation of IRB reliance and cooperative review agreements; (HRPP, BRANY)

For nonexempt research involving human subjects covered by the Common Rule that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, the institution and the organization operating the IRB shall document the institution's reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of this policy (e.g., in a written agreement between the institution and the IRB, by implementation of an institution-wide policy directive providing the allocation of responsibilities between the institution and an IRB that is not affiliated with the institution, or as set forth in a research protocol);

10. Documentation of independent or external investigator agreements, when appropriate; (BRANY)

11. Federal Wide Assurances; (HRPP, BRANY)

12. Federal IRB Registrations; (BRANY) and

13. Documentation of complaints and any related findings and/or resolution. (HRPP, BRANY)

12.2 Documentation of Exemptions

Documentation of verified exemptions consists of the reviewer's citation of a specific exempt category and written concurrence that the activity described in the investigator's request satisfies the conditions of the cited exempt category as detailed in Section 5. When an exemption includes limited IRB review, the documentation will include this fact and BRANY IRB action taken on those aspects of the research subject to limited IRB review, or need for HIPAA waiver requests, in accordance with the procedures described for the review procedures used (see BRANY IRB SOPs).

13. Obtaining Informed Consent from Research Subjects

No investigator conducting research under the auspices of NJH may involve a human being as a subject in research without obtaining the legally effective informed consent of the subject or the subject's legally authorized representative (LAR) unless a waiver of consent has been approved by the IRB of record. Except waived by the IRB in accordance with federal criteria, informed consent must be documented using a written consent form approved by the IRB.

The informed consent process involves three key features: (1) disclosing to the prospective human subject information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the Research.

Informed consent is more than just a signature on a form. It is a process of information exchange to include reading, discussing, receiving answers to any questions, and signing the consent document. The informed consent process is the critical communication link between the prospective human subject and an investigator, beginning with the initial approach by an investigator and continuing through the completion of the research study. Investigators must have received the appropriate

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training and be knowledgeable about the study procedures, potential risks, anticipated benefits, and alternatives in order that they may appropriately describe the research and answer questions. The exchange of information between the investigator and study participant can occur via one or more of the following modes of communication, among others: face to face dialogue, mail, electronic interface, telephone, or fax. However, obtaining informed consent must allow for a dialogue so that the potential subject has the opportunity to ask questions and receive responses. Investigators must obtain consent prior to entering a subject into a study, gathering data about a subject, and/or conducting any procedures required by the research plan, unless consent is waived by the IRB.

If someone other than the investigator conducts the interview and obtains consent, the investigator needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. The person so delegated must be knowledgeable about the research to be conducted and the consenting process, and must have the expertise be able to answer questions about the study including those regarding risks, procedures, and alternatives. The BRANY IRB application solicits information regarding who will obtain consent; proposed changes to the personnel authorized to obtain consent must be submitted to the BRANY IRB for approval.

Sample or draft consent documents may be developed by a sponsor or network. However, the IRB of record is the final authority on the content of the consent documents that are presented to prospective subjects.

The IRB will evaluate both the consent process and the procedures for documenting informed consent to ensure that adequate informed consent is obtained from participants.

The following procedures describe the requirements for obtaining consent from subjects in research conducted under the auspices of NJH. When the BRANY IRB is serving as the IRB of record for external sites or personnel, the below requirements may be adapted as appropriate based upon the local context where the research will occur (e.g., who may serve as a LAR).

13.1 General Requirements

Except as provided elsewhere in these Standard Operating Procedures:

1. Before involving a human subject in research, an investigator shall obtain the legally effective informed consent of the subject or the subject's LAR
2. An investigator shall seek informed consent only under circumstances that provide the prospective subject or the LAR sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence
3. The information that is given to the subject or the LAR shall be in language understandable to the subject or the LAR
4. The prospective subject or the LAR must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information
5. Informed consent must begin with a concise and focused presentation of the key

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information that is most likely to assist a prospective subject or LAR in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension

6. Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or LAR's understanding of the reasons why one might or might not want to participate
7. No informed consent may include any exculpatory language through which the subject or the LAR is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

These informed consent requirements are not intended to preempt any applicable federal, state, or local laws (including tribal laws passed by the official governing body of an American Indian or Alaska Native tribe) that have additional requirements for informed consent to be legally effective.

13.2 Additional Requirements

Informed consent must be obtained under the following circumstances:

1. Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, permission must be obtained from a legal guardian with appropriate authority to make decisions regarding the activities called for in the research or a legally authorized representative (LAR);
2. The informed consent information must be presented in language that is understandable to the subject (or LAR/guardian). To the extent possible, the language should be understandable by a person who is educated to 8th grade level and layman's terms shall be used in the description of the research. The IRB may require or allow different readability standards based upon the characteristics of the target subject population;
3. For subjects with [Limited English Proficiency](#) (LEP), informed consent must be obtained in a language that is understandable to the subject (or LAR/guardian). In accordance with this policy, the NJH HRPP requires that informed consent discussions include a reliable interpreter when the prospective subject does not understand the language of the person who is obtaining consent, and, in most circumstances, that consent materials are translated;
4. The investigator is responsible for ensuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

13.3 Legally Authorized Representative (LAR)

A Legally Authorized Representative (LAR) is defined by [45 CFR 46.102\(c\)](#) and [21 CFR 50.3](#) as "*an individual or judicial or other body authorized under applicable law to consent on behalf of a*

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prospective subject to the subject's participation in the procedure(s) involved in the research.”

Colorado state law does not specifically address informed consent by LARs of incapacitated persons for participation in clinical research. Thus, the applicable guidelines for determining the most appropriate LAR for research are based upon the guidelines that apply in the clinical setting.

NJH legal counsel has determined that, in Colorado, the following persons meet the definition of legally authorized representative and, thus, can give proxy consent:

- A court appointed guardian of the person with medical decision-making authority.
- A health care agent appointed by the person in a Durable Power of Attorney for Health Care (DPAHC) provided that the DPAHC specifies that the individual also has the power to make decisions of entry into research.
- A person appointed by the person in a Designated Beneficiary Agreement that specifies the individual who may make medical decisions and has the power to make decisions of entry into research.
- Pursuant to Colorado Revised Statute (C.R.S.) 15-18.5-103, a proxy decision maker may provide consent under certain conditions as stated in NJH’s research protocols. *Investigators shall consult with the IRB for this category of consent.

NOTE: Investigators shall consult with the IRB when conducting research outside of Colorado to determine what the requirements for a legally authorized representative in the jurisdiction in which the research is taking place.

Proxy consent may be requested and accepted only when the prospective research participant has an impaired decision-making capacity, as determined and documented in the person’s medical record in a signed and dated progress note. The determination must be made in accordance with the following requirements:

- The IRB will require investigators to conduct an assessment for capacity to consent whenever there is a possibility of either impaired mental status or decision-making capacity in prospective subjects.
- If feasible, the investigator must explain the proposed research to the prospective research subject and obtain assent, in addition to the permission of the proxy. Under no circumstances may a subject be forced or coerced to participate in a research study.

When the BRANY IRB serves as the IRB of record for external sites and the use of LARs is proposed, information regarding relevant state law and local policy will be obtained (local context information) and applied.

LARs should be well informed regarding their roles and responsibilities when asked to provide proxy consent. In addition to the consent information, LARs should be informed that their obligation is to try to determine what the potential subject would do if able to provide consent, or if the potential subject's wishes are not known or cannot be determined, what they think is in the person's best interest.

Investigators must describe the intended use of LARs in their submission to the IRB. The IRB

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determines whether the use of LARs is appropriate for a given research study and that there is a potential for therapeutic benefit to the research subject.

Further discussion and procedures for assessment of capacity and inclusion of adults with impaired decision-making capacity in research are described in BRANY IRB SOPs.

13.4 Elements of Informed Consent

The BRANY IRB SOPs identify the federally-required basic and ‘as applicable’ elements of informed consent. These, and NJH-specifically required elements are provided in the NJH-BRANY informed consent form (ICF) template, available on the NJH HRPP website at <https://www.nationaljewish.org/research-science/support/compliance/irb/submissions>.

Note: The ICF template also addresses the following important considerations regarding subject withdrawal or termination from a study:

1. **For FDA-regulated clinical trials:** When a subject withdraws from a study, the data collected on the subject to the point of withdrawal remain part of the study database and may not be removed; or
2. **For research not subject to FDA regulations:** The investigator should inform subjects whether the investigator or study sponsor intends to either: (1) retain and analyze already collected data relating to the subject up to the time of subject withdrawal; or (2) honor a research subject’s request that the investigator or study sponsor will destroy the subject’s data or that the investigator or study sponsor will exclude the subject’s data from any analysis.

When a subject’s withdrawal request is limited to discontinuation of the primary interventional component of a research study, research activities involving other types of participation for which the subject previously gave consent may continue. Investigators should ask a subject who is withdrawing whether the subject wishes to participate in continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and procedures and continued follow-up in person, by phone, or via records review.

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up as described in the previous paragraph, the investigator must obtain the subject’s informed consent for this limited participation in the study (assuming such a situation was not described in the original consent document). IRB approval of consent documents for these purposes would be required.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up, the investigator must not access or gather private information about the subject for purposes related to the study. However, an investigator may review study data related to the subject collected prior to the subject’s withdrawal from the study, and may consult public records, such as those establishing survival status.

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13.5 Documentation of Informed Consent

Informed consent must be documented by the use of a written consent form approved by the IRB, unless waived under federally defined criteria.

1. Informed consent is documented by the use of a written consent form approved by the IRB and signed (including in an electronic format) and dated by the subject or the subject's LAR at the time of consent;
2. For research conducted in accordance with ICH-GCP E6 or in facilities subject to Joint Commission requirements, the name of the person who obtained consent and the date they did so is documented on the written consent form;
3. A written copy of the signed and dated consent form must be given to the person signing the form. The investigator should retain the signed original in the research records. When appropriate, a copy of the consent form is uploaded into the electronic health record;

The consent form may be either of the following:

1. A written consent document that embodies the basic and required additional elements of informed consent. The investigator shall give either the subject or the subject's LAR adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject or the subject's legally authorized representative; **or**
2. A short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's LAR and that the required key information was presented first to the subject, before other information, if any, was provided. When this method is used:
 - a. The oral presentation and the short form written document should be in a language understandable to the subject; and
 - b. There must be a witness to the oral presentation; and
 - c. The IRB must approve a written summary of what is to be said to the subject (the approved full consent document may serve as this summary); and
 - d. The short form document is signed by the subject;
 - e. The witness must sign both the short form and a copy of the summary; and
 - f. The person actually obtaining consent must sign a copy of the summary; and
 - g. A copy of the summary must be given to the subject or representative, in addition to a copy of the short form.

When the short form procedure is used with subjects who do not speak or read English, or have [Limited English Proficiency](#) (LEP), (i) the oral presentation and the short form written document should be in a language understandable to the subject; (ii) the IRB-approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject. When the person obtaining consent is assisted by an

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interpreter, the interpreter may serve as the witness. Finally, FDA guidance states that the summary that was used to consent the subject must be translated and provided to the subject as soon as possible after enrollment.

The IRB must receive all foreign language versions of the short form document as a condition of approval. Expedited review of these versions is acceptable if the protocol/research plan, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB. Alternatively, the IRB can review and approve the content of a template short form (independent of any specific study) and all translations of it; the investigator would then indicate to the IRB the intent to use one such a priori approved short form.

13.6 Special Consent Circumstances

13.6.1 Braille consent

For blind subjects who read Braille, the IRB may approve a consent document prepared in Braille. To ensure that a Braille consent document is accurate, the IRB may require a transcription into print text or review of the document by an IRB member or other person who reads Braille. If possible, the subject will sign the Braille consent; otherwise oral consent will be obtained, witnessed and documented as described under “Oral Consent” (see Section 13.6.2).

13.6.2 Oral Consent

When subjects are unable to read a written consent form (such as blind or illiterate subjects), the BRANY IRB may approve an oral consent process, provided the subject (1) retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained orally and (2) is able to indicate approval or disapproval to study entry.

For research that is no more than minimal risk, documentation of consent may be waived by BRANY IRB according to federal criteria.

For greater than minimal risk research, the consent form must be read to the subjects and the subjects must be given an opportunity to ask questions. An audiotape approved by the IRB may also be used. If capable of doing so, the subject signs, or marks an X to signify consent. If that is not possible, the subject will provide oral consent. The person obtaining consent and a witness will sign the written study consent form with a statement that documents that an oral process was used and that the subject gave oral consent or made their mark. The consent process will also be documented in the subject’s research record. Signed copies of the consent form are given to the subject and, whenever possible, these documents should be provided to the subject on audio or video-tape.

See BRANY IRB SOPs for details concerning procedures to be followed under other special consent circumstances including enrollment of persons with Limited English Proficiency, deaf, and other

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physically challenged subjects.

13.6.3 Electronic and Remote Consent

Consent may be obtained electronically either to supplement or replace paper-based informed consent. The electronic consent form must contain all elements of informed consent required by HHS and/or FDA regulations (45 CFR 46.116 and 21 CFR 50.25).

If the consent process occurs remotely (e.g., via video conference or over the phone), study teams must verify the identity of the individual prior to signing the consent form. If possible, study teams should use video conferencing and ask the potential subject to hold up a valid ID (e.g., driver's license) prior to signing. If video conferencing is not available, or a valid ID is not available or appropriate (e.g., minors under 16 years of age), one of the following identity verification methods should be used:

1. Establish a subject-specific "PIN" that will only be known/available to the potential subject/LAR and study team. Only individuals with the correct PIN should be given access to the consent form. This PIN should be stored in the subject's study record.
2. Establish subject-specific security questions (three or more) agreed upon by both the potential subject/LAR and study team. Only individuals who answer all questions correctly should be given access to the consent form. The questions, and their respective answers, should be stored in the subject's study record.
3. Require the potential subject/LAR to upload a scanned image or photo of a valid ID (e.g., passport, driver's license) with their signed e-Consent. Study teams will need to review the uploaded document to confirm the subject's identity.

Study teams may request alternative methods for identity verification. These requests must be accompanied by a justification for why one of the above methods is not appropriate for the study. The IRB will review these requests on a case-by-case basis.

NJH REDCap may not be used to obtain electronic signatures for FDA-regulated research. FDA regulated research obtaining electronic signatures must use an Electronic Data Capture system that is Part 11 compliant. Study teams should include documentation from the sponsor or system administrator ensuring NJH REDCap may be used to obtain electronic signatures for non-FDA regulated research.

Subjects must be provided with a signed version of the consent form (either hard card copy or electronic depending on the subject's preference). Study activities must not begin until the study team has received an electronically signed consent form and verified identity.

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13.7 Waiver of Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergencies where the requirement to obtain prospective informed consent has been waived by the IRB is covered by [21 CFR 50.24](#) for FDA-regulated research and by the waiver articulated by DHHS at [61 FR 51531-33](#) for research that is not FDA-regulated.

The FDA exception from informed consent requirements for emergency research under FDA regulations permits planned research in an emergency setting when human subjects who are in need of emergency medical intervention cannot provide legally effective informed consent themselves, and there is generally insufficient time and opportunity to locate and obtain consent from their legally authorized representatives (LARs).

The Secretary of Health and Human Services (DHHS) has implemented an Emergency Research Consent Waiver under [45 CFR 46.101\(i\)](#) with most provisions equivalent to those of the FDA. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

See BRANY IRB SOP's for definitions and requirements to be followed for planned emergency research.

13.8 Posting of Clinical Trial Consent Forms

For each clinical trial conducted or supported by a Federal department or agency, one IRB approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms.

If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal Web site (e.g. confidential commercial information), such Federal department or agency may permit or require redactions to the information posted.

The informed consent form must be posted on the Federal Web site after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, or as required by the protocol.

14. Vulnerable Subjects in Research

When participants in research conducted under the auspices of NJH are likely to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these participants. BRANY IRB must ensure that all of the regulatory requirements for the protection of subjects are met and that appropriate additional protections for vulnerable subjects are in place.

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14.1 Definitions Specific to NJH

Children. Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted [[45 CFR 46.402\(a\)](#)].

According to Colorado State Law, minors are persons under the age of eighteen. The general rule is that a person may sign legally-binding agreements and consent for his or her own medical care at the age of eighteen. Therefore, NJH HRPP defines children as persons who are under eighteen years of age. Certain statutes and case law, however, provide minors with "majority" status in some circumstances, giving them the right to consent to their own medical care. Colorado law enumerates certain categories of individuals who, although under the age of 18, have the right to make medical decisions on their own behalf, such as minors who are married, widowed or divorced, minors who are parents, etc. Colorado law also permits minors to seek care for drug addiction, sexually transmitted diseases, emotional disorders, or abortion or mental health treatment without parental permission.

Because Colorado law does not specifically address consent of children with majority status to research, NJH HRPP will review issues of consent related to enrollment of these children in research on a case-by-case basis.

NOTE: For research conducted in jurisdictions other than Colorado, the research must comply with the laws regarding the legal age of consent in the relevant jurisdictions. Legal counsel will be consulted with regard to the laws in other jurisdictions or such "local context" information will be sought through other means (e.g., according to the terms of a reliance agreement).

Guardian. A guardian is an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care [[45 CFR 46.402\(e\)](#)].

In Colorado a "Guardian" of a child means a court-appointed person with the duty and authority to act in the best interests of the minor, subject to residual parental rights and responsibilities, to make important decisions in matters having a permanent effect on the life and development of the minor and to be concerned with his or her general welfare.

NOTE: For research conducted in jurisdictions other than Colorado, the research must comply with the laws regarding guardianship in all relevant jurisdictions. Legal counsel will be consulted with regard to the laws in other jurisdictions or such "local context" information will be sought through other means (e.g., according to the terms of a reliance agreement).

14.2 Involvement of Vulnerable Populations in Research

When an IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process should include one or more individuals who are knowledgeable about or experienced in working with these participants. When the IRB does not have the relevant expertise among its membership, expertise may be sought through the use of consultants.

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45 CFR 46 has additional subparts designed to provide extra protections for certain defined vulnerable populations which also have additional requirements for IRBs.

[Subpart B](#) - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

[Subpart C](#) - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

[Subpart D](#) - Additional Protections for Children Involved as Subjects in Research

DHHS-conducted or supported research that involves any of these populations must comply with the requirements of the relevant subparts. Research regulated by the FDA includes equivalent protections and obligations when research involves children ([Subpart D](#)). Research conducted, supported, or otherwise regulated by other federal agencies may or may not be covered by the subparts.

In its FWA, NJH limits its commitment to apply Subparts B, C, and D to non-exempt human subjects research conducted or supported by DHHS or any other federal agency that requires compliance with the Subpart(s) (B, C, or D) applicable to the research.

14.3 Procedures

BRANY IRB SOPs should be reviewed for submission and review procedures concerning children, pregnant women (and nonviable or questionably viable neonates), prisoners, and adults with diminished capacity.

- For research involving children, BRANY IRB generally requires assent to be documented as follows: For children 6 years and younger, by an affirmative statement documenting such in the subject's research record by the study team member obtaining assent
- For 7-12 year olds, via their signature on an assent form, based on the template provided on NJH HRPP website
- For 13-17 year olds, via their signature on the main (parental) consent form

15. FDA-Regulated Research

FDA regulations apply to research that involves a FDA-regulated *test article* in a *clinical investigation* involving *human subjects* as defined by the FDA regulations. For FDA-regulated research, the IRB must apply the FDA regulations at [21 CFR 50](#) and [21 CFR 56](#). If the research is conducted or supported by a Common Rule agency or department, or if compliance with the Common Rule is required by state law or the terms of an award or contract, then the Common Rule must also be applied.

Clinical investigations of investigational drugs and biological products must be conducted according to FDA's IND regulations, [21 CFR Part 312](#), and other applicable FDA regulations. Evaluations of the safety or effectiveness of a medical device must be conducted according to FDA's IDE regulations, [21](#)

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[CFR Part 812](#), and other applicable FDA regulations.

Procedures describing the review of FDA-regulated research by the BRANY IRB may be found in the BRANY IRB SOPs.

15.1 Additional Definitions

Human Cells, Tissues, or Cellular or Tissue-based Products (HCT/P's) – HCT/P's means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.

The following articles are not considered HCT/P's: vascularized human organs for transplantation; whole blood or blood components or blood derivative products subject to listing under parts 607 and 207, respectively; secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered an HCT/P; minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow); ancillary products used in the manufacture of HCT/P; cells, tissues, and organs derived from animals other than humans; in vitro diagnostic products as defined in 809.3(a); blood vessels recovered with an organ, as defined in 42 CFR 121.2, that are intended for use in organ transplantation and labeled "For use in organ transplantation only."

HCT/P's may be regulated as drugs, devices, and/or biologics when the use does not qualify for an establishment exception or regulation solely under section 361 of the PHS Act and [21 CFR 1271](#).

Generally, research involving HCT/P's regulated as drugs, devices, and/or biologics will require an IND or IDE depending on how the HCT/P is categorized. Because the regulatory and policy framework for HCT/P's is complex, consultation with the FDA prior to submission to the IRB is encouraged to appropriately categorize the HCT/P, understand which regulations and requirements apply, and to obtain an IND or IDE if necessary (or FDA determination that such is not required).

In Vitro Diagnostic Product (IVD). In vitro diagnostic products are those reagents, instruments, and systems intended for use in the 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. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. [[21 CFR 809.3\(a\)](#)]

15.2 FDA Clinical Investigator Responsibilities

The investigator holds additional responsibilities when conducting a clinical investigation subject to FDA regulations. These responsibilities include, but are not limited to, the following:

1. The investigator is responsible for indicating on the IRB application that the proposed research is FDA-regulated and for providing relevant information regarding the test article.

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2. The investigator is responsible for ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs (including biological products) or agreement for clinical investigations of medical devices, the investigational plan and other applicable regulations, and any requirements imposed by the FDA or IRB.
3. The investigator is responsible for personally conducting or supervising the investigation. When study- related tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.
4. The investigator must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., it can refer to an individual's CV on file and/or training conducted by the investigator or sponsor), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.
5. The investigator is responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial. This responsibility includes:
 - a. Informing subjects that the test articles is being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met
 - b. Providing or arranging for reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention
 - c. Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, or when specialized care is needed)
 - d. Adhering to the protocol so that study subjects are not exposed to unreasonable risks
 - e. As appropriate, informing the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed.
6. The investigator is responsible for reading and understanding the information in the investigator brochure or device risk information, including the potential risks and side effects of the drug or device.
7. The investigator is responsible for maintaining adequate and accurate records in accordance with FDA regulations and to making those records available for inspection by the FDA. These records include, but are not limited to: correspondence with other investigators, the IRB, the sponsor, monitors, or the FDA; drug and device accountability records; case histories; consent forms; and documentation that consent was obtained prior to any participation in

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the study. Records must be obtained for a minimum of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such. For clinical investigations of medical devices, required records must be maintained for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.

8. The investigator is responsible for controlling test articles according to FDA regulations and the Controlled Substances Act, if applicable.
9. For research reviewed by the BRANY IRB, the investigator proposing the clinical investigation will be required to provide a plan – to be evaluated by the IRB - that includes storage, security, and dispensing of the test article.
 - a. The investigator must delegate responsibility of investigational drug accountability (including storage, security, dispensing, administration, return, disposition, and records of accountability) to the NJH Pharmacy.
 - b. Requests to delegate this responsibility outside of NJH Pharmacy must be reviewed and approved NJH Pharmacy prior to submission of the study to the HRPP Office.
 - c. Investigational drugs and devices must be labeled in accordance with federal and state standards.
 - d. All devices received for a study must be stored in a locked environment under secure control with limited access. When applicable, proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device, and the disposition of remaining devices at the conclusion of the investigation.
10. The investigator shall furnish all reports required by the sponsor of the research including adverse events, progress reports, safety reports, final reports, and financial disclosure reports.
11. The investigator will permit inspection of research records by the sponsor, sponsor representatives, HRPP and IRB representatives, the FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under regulation, organizational policy, or contractual agreement.

15.3 Dietary Supplements

Research involving dietary supplements may or may not fall under FDA regulations. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, a dietary supplement is not

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considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose). Whether a study falls under FDA oversight is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, FDA research regulations do not apply. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, then FDA regulations do apply. Studies involving the ingestion of dietary supplements that are not subject to FDA oversight are still research, and therefore must be reviewed by the IRB.

Similarly, whether an IND is needed for a study evaluating a dietary supplement is determined by the intent of the study. If the study is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required. Due to a partial stay [80 FR 66907] on FDA's guidance "Investigational New Drug Applications – Determining Whether Human Research Studies Can Be Conducted Without an IND", at this time FDA also does not require an IND for studies intended to evaluate whether a dietary supplement may reduce the risk of a disease or studies intended to support a new or expanded health claim, unless the studies include individuals less than 12 months old, those with altered immune systems, or those with serious or life-threatening medical conditions. All other studies intended to evaluate a dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, require an IND unless FDA grants an exception to the requirement.

As with any research involving a test article, the investigator must supply the IRB with sufficient information to determine that the criteria for approval are satisfied and to determine or verify whether the research requires an IND. Applications should provide detail consistent with that expected on a drug protocol and consistent with the level of risk associated or anticipated with the research. At a minimum, the research plan should provide the following information regarding the supplement: Name, Manufacturer, Formulation, Dosage, Method/Route of Administration, Mechanism of Action, Known Drug Interactions, Risk Profile, IND number (or justification for why an IND is unnecessary), documentation of approval for use in humans, documentation or certification of Quality or Purity. As with drugs and devices there should be an accountability plan for the product describing where the product will be stored and how it will be dispensed, usage tracked, and disposal or return. If the study entails greater than minimal risk, a plan for Data and Safety Monitoring must be included.

15.4 Expanded Access to Investigational Drugs, Biologics, and Devices

Expanded access pathways, also referred to as "compassionate use", are designed to make investigational medical products available as early in the drug and device evaluation process as possible to patients without therapeutic options, because they have exhausted or are not a good candidate for approved therapies and cannot enter a clinical trial. Expanded access refers to the use of investigational or unapproved/uncleared medical products (all referred to as "investigational" throughout this section) outside of a clinical trial, where the primary intent is treatment, rather than research. Because the products have not yet been approved by FDA as safe and effective, it is

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important to remember that the product may not be effective and there may be unexpected serious adverse effects and to take appropriate measures to ensure that this is understood by the patient or their LAR and to monitor for safety.

Charging for expanded access use of investigational products is discussed in Section 15.6.

15.4.1 Expanded Access to Investigational Drugs and Biologics

The FDA's expanded access rule for investigational drugs, including biologics classified as drugs, is intended to improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from the investigational agent. Expanded access is sometimes referred to as compassionate use or treatment use.

For the purposes of expanded access to investigational drugs, *immediately life-threatening disease or condition* means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. *Serious disease or condition* means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. [[21 CFR 312.300\(b\)](#)]

Expanded access may also apply to (1) situations when a drug has been withdrawn for safety reasons, but there exists a patient population for whom the benefits of the withdrawn drug continue to outweigh the risks; (2) use of a similar, but unapproved drug (e.g., foreign-approved drug product) to provide treatment during a drug shortage; (3) use of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS); and (4) use for other reasons. All are referred to as "investigational" for the purposes of these SOPs.

Under the FDA's expanded access rule, access to investigational drugs for treatment purposes is available to:

- Individual patients, including in emergencies [[21 CFR 312.310](#)]
- Intermediate-size patient populations [[21 CFR 312.315](#)]
- Widespread use under a treatment protocol or treatment IND [[21 CFR 312.320](#)]

The following section addresses expanded access for individual patients. Investigators seeking expanded access for intermediate-size populations or widespread use should review the "[Expanded Access Information Sheet](#)" and consult with the HRPP office as needed. Convened IRB review is required for intermediate or widespread expanded access unless the FDA has issued a waiver.

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Physicians seeking access to investigational drugs under expanded access should work closely with the sponsor or manufacturer, the FDA, and the NJH HRPP, to determine the appropriate access mechanism and ensure that proper regulatory procedures are followed. The FDA provides information about the procedures and requirements for expanded access on a [website](#), including a link to FDA's [contact information](#).

15.4.1.1 Expanded Access to Investigational Drugs for Individual Patients

Expanded access to investigational drugs may be sought under an "Access Protocol" or an "Access IND". FDA generally encourages Access Protocols, which are managed and submitted by the sponsor of an existing IND, because it facilitates the review of safety and other information. However, Access INDs for the treatment of individual patients are also available and commonly used when: (1) a sponsor holding an existing IND declines to be the sponsor for the individual patient use (e.g., because they prefer that the physician take on the role of sponsor-investigator); or (2) there is no existing IND.

Sponsor or Manufacturer Approval:

Prior to submitting to the FDA or IRB, physicians seeking expanded access to an investigational drug should contact the sponsor (e.g., for investigational drugs under a commercial IND) or manufacturer (e.g., for approved drugs under a REMS) to: (1) ensure that the investigational drug can be obtained; (2) determine whether the patient may be treated under an existing IND study, sponsor-held Access Protocol, or if the physician should seek an Access IND; and (3) determine if the drug will be provided free or if there will be a charge. A Letter of Authorization (LOA) from the sponsor or manufacturer should be obtained.

FDA Approval:

When a commercial sponsor agrees to provide access under an Access Protocol, the sponsor is responsible for managing and obtaining FDA approval and all other sponsor responsibilities. A licensed physician under whose immediate direction an investigational drug is administered or dispensed for expanded access is considered an "investigator" under FDA regulations and is responsible for all investigator responsibilities under [21 CFR 312](#), to the extent they are applicable to expanded access.

If the sponsor or manufacturer declines treatment of the patient under an existing IND study or Access Protocol but agrees to make the investigational drug available for the patient, physicians may apply to the FDA for an individual patient Access IND using Form FDA 3926, a streamlined IND application specifically designed for such requests. Form FDA 3926, and [related guidance](#), is available on a FDA [website](#). Form FDA 3926 includes a section where an investigator can request approval from the FDA for alternative IRB review procedures; these alternative procedures enable review by the IRB Chair (or a Chair-designated IRB member) in lieu of review by the convened IRB. This alternative review procedure is referred to as a "concurrence review" in FDA guidance; however, the IRB Chair must review the same materials and make the same determinations as the convened board would. IRB Chair review

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can also be used for any post-approval reviews (e.g., unanticipated problems, continuing review, closure, etc.).

When there is an emergency situation and insufficient time to submit a written application to the FDA prior to treatment, a request to FDA for emergency use may be made by telephone (or other rapid means). A written expanded access application must be submitted within 15 days of the FDA's authorization. For more information on emergency use, see Section 15.5.

A physician who obtains an Access IND is considered a "sponsor-investigator" and is responsible for the responsibilities of both sponsors and investigators under [21 CFR 312](#), as applicable, including IND safety reports, annual reports, and maintenance of adequate drug accountability records.

IRB Review:

Unless the conditions that permit an emergency use exemption (see Section 15.5) are satisfied, IRB approval must be obtained prior to initiating treatment with the investigational drug. When the FDA has authorized the use of alternative IRB review procedures (which can be presumed when the request is made on Form FDA 3926 unless the FDA specifically states that the request is denied), the review may be conducted by the IRB Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

Physicians using investigational drugs under compassionate use should develop and submit an appropriate plan and schedule for treating and monitoring the patient, taking into consideration the nature of the drug and the needs of the patient. The plan should include monitoring to detect any possible problems arising from the use of the drug.

To request IRB approval for single patient expanded access, investigators should contact BRANY IRB and submit the following via e-mail:

1. A letter justifying expanded access, e.g., patient clinical history supporting its use, and any additional documentation noted within it;
2. A copy of the LOA from the Commercial Sponsor or Manufacturer or other documentation supporting sponsor/manufacturer approval;
3. A copy of the information submitted to the FDA (and FDA approval, if available);
4. A copy of the Investigator's Brochure or similar documentation that provides information regarding the potential risks and benefits of the investigational drug;
5. A copy of the plan for treating and monitoring the patient; and
6. A copy of the draft informed consent document.

The IRB may review the expanded access application prior to FDA approval being received but cannot finalize approval until documentation of FDA approval is provided. The IRB will provide the investigator with written documentation of its review.

NJH will consider reliance upon an external IRB for expanded access when the IND is held by a

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commercial sponsor and an external IRB has approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the HRPP Office, to discuss IRB reliance for expanded access protocols.

Post-Approval Requirements

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. Additionally, copies of any follow-up submissions to the FDA related to the expanded access use must be submitted to the IRB within 7 business days of the date of submission to the FDA.

15.4.2 Expanded Access to Investigational and Unapproved/Uncleared Medical Devices

As with investigational drugs, unapproved medical devices may normally only be used in humans in an approved clinical trial under the supervision of a participating clinical investigator. However, there are circumstances under which a health care provider may use an unapproved device outside of a clinical study when it is not possible to enroll a patient in a clinical study and the patient is facing life-threatening circumstances or suffering from a serious disease or condition for which no other alternative therapy or diagnostic exists or is a satisfactory option for the patient.

FDA has made the following mechanisms available for these circumstances:

- Emergency Use
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use

Investigators seeking access to investigational or unapproved devices under one of the above provisions should work closely with the sponsor or manufacturer, the FDA, and the NJH HRPP, to ensure that proper regulatory procedures are followed. An “[Expanded Access Information Sheet](#)” also is available.

FDA has made information about expanded access to medical devices available on a [website](#).

15.4.2.1 Compassionate Use of Investigational/Unapproved Medical Devices

The compassionate use provision under expanded access provides a mechanism for accessing investigational devices for an individual patient or small groups of patients when the treating physician believes the device may provide a diagnostic or treatment benefit. Compassionate use can be used for devices being studied in a clinical trial under an IDE for patients who do

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not qualify for inclusion in the trial, and for devices for which an IDE does not exist. The following criteria must be satisfied:

1. The patient has a life-threatening or serious disease or condition; and
2. No generally acceptable alternative treatment for the condition exists.

The medical device company must agree to make the medical device available for the proposed compassionate use. FDA and IRB approval are required before the device may be used under the compassionate use provision.

FDA Approval:

When **there is an IDE** for the device, the IDE sponsor submits an IDE supplement requesting approval for the compassionate use under [21 CFR 812.35\(a\)](#).

When **there is not an IDE** for the device, the physician or manufacturer submits the following information to the FDA:

1. A description of the device (provided by the manufacturer);
2. Authorization from the device manufacturer for the use;
3. A description of the patient's condition and the circumstances necessitating treatment or diagnostics (when seeking small group access, the number of patients to be treated);
4. A discussion of why alternative therapies/diagnostics are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition; and
5. The patient protection measures that will be followed, including:
 - a. A draft of the informed consent document that will be used;
 - b. Clearance from the institution as specified by their policies (see below);
 - c. Concurrence (approval) of the IRB Chair or Chair-designated IRB member (prior to FDA request when possible); and
 - d. An independent assessment from an uninvolved physician.

When IRB Chair approval cannot be obtained in advance of the submission to the FDA, the request should indicate that approval from the IRB Chair will be obtained prior to use of the device. Proof of IRB Chair approval must be submitted with the follow-up report to the FDA after the patient is treated (or the diagnostic is used).

When the compassionate use is conducted under an IDE, a licensed provider who receives an investigational device is an "investigator" under FDA regulations and is responsible and accountable for all applicable investigator responsibilities under [21 CFR 812](#) (IDE regulations), [21 CFR 50](#) (Informed Consent), and [21 CFR 56](#) (IRB).

When the provider obtains an IDE for compassionate use, the provider is considered a

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“sponsor-investigator” and is responsible for the responsibilities of both sponsors and investigators under [21 CFR 812](#), as applicable, including medical device reports and progress reports .

IRB Review:

Unless the conditions that permit an emergency use exemption are satisfied (see Section 15.5), IRB approval must be obtained prior to initiating treatment with the investigational device. When the request is for single-patient compassionate use, the review may be conducted by the IRB Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

Physicians using medical devices under compassionate use should develop and submit an appropriate plan and schedule for treating and monitoring the patient, taking into consideration the nature of the device and the needs of the patient. The plan should include monitoring to detect any possible problems arising from the use of the device.

To request IRB approval for compassionate use, investigators should contact BRANY IRB and submit the following via email:

1. A letter justifying expanded access, e.g., patient clinical history supporting its use, and any additional documentation noted within it;
2. A copy of the information submitted to the FDA (and FDA approval, if available);
3. A copy of the device brochure, Instructions for Use, or other similar documentation that provides information regarding the potential risks and benefits of the device;
4. A copy of the plan for treating and monitoring the patient; and
5. A copy of the draft informed consent document.

The IRB may review the expanded access application prior to FDA approval being received but may condition approval upon receipt of FDA approval. The IRB will provide the investigator with written documentation of its review.

NJH will consider reliance upon an external IRB for Compassionate Use protocols on a case-by-case basis when the IDE is held by a commercial sponsor and an external IRB has already approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the HRPP office, to discuss IRB reliance for Compassionate Use protocols.

Post-Approval Requirements

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), reporting of

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unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. Additionally, a follow-up report to the FDA is required following a compassionate use by whomever submitted the original request to the FDA. The report should include summary information regarding patient outcome and any problems that occurred as a result of the device. A copy of the follow-up report to the FDA and any other post-approval submissions or reports to the FDA must be submitted to the IRB within 7 business days of the date of submission to the FDA.

15.4.2.2 Treatment Use of Investigational/Unapproved Medical Devices

During the course of a clinical trial under an IDE, if the data suggest that the device under study is effective, the trial may be expanded to include additional patients with life-threatening or serious diseases under the Treatment Use provision for expanded access. "Treatment Use" also applies to the use of a device for diagnostic purposes under these same conditions. [[21 CFR 812.36](#)]

The following criteria must be satisfied for Treatment Use to apply:

1. The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
2. There is no comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population;
3. The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or all clinical trials have been completed; and
4. The sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence.

The IDE sponsor is responsible for applying for a Treatment Use IDE.

A licensed provider who receives an investigational device for treatment use under a Treatment Use IDE is an "investigator" under FDA regulations and is responsible and accountable for all applicable investigator responsibilities under [21 CFR 812](#) (IDE regulations), [21 CFR 50](#) (Informed Consent), and [21 CFR 56](#) (IRB).

IRB Review:

IRB approval is required before the investigational device/diagnostic is used.

NJH will consider reliance upon an external IRB for Treatment Use IDE protocols on a case-by-case basis when an external IRB has already approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the HRPP office, to discuss IRB reliance for Treatment Use IDEs.

Post-Approval Requirements

Investigators are responsible for complying with any sponsor or FDA reporting requirements.

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The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), for reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. Additionally, the semi-annual (applicable until the marketing application is filed) or annual (applicable after the marketing application is filed) progress report from the sponsor must be submitted to the IRB within 7 business days of receipt.

15.5 Emergency Uses

15.5.1 Emergency Use of Investigational Drugs

FDA regulations permit the use of an investigational drug without IRB approval when an appropriately trained and licensed health care provider determines that IRB approval for the use of the drug cannot be obtained in time to prevent serious harm or death to a patient. The provider is expected to assess the potential for benefit from the use of the drug and to have substantial reason to believe that benefits will exist. The criteria and requirements for this Emergency Use Exemption are explained in Section 15.5 below.

Sponsor/Manufacturer and FDA approval must be obtained prior to initiating treatment with the drug.

Providers invoking the emergency use exemption must comply with any applicable FDA follow-up requirements including submission of safety reports, amendments, a summary following completion of treatment, and annual reports.

Note: DHHS regulations do not permit research activities to be started, even in an emergency, without prior IRB approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject under [45 CFR Part 46](#). However, nothing in the DHHS regulations at [45 CFR Part 46](#) is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state or local law.

15.5.1.1 Emergency Use Exemption from Prospective IRB Approval

Under FDA regulations [[21 CFR 56.104\(c\)](#)], FDA exempts the emergency use of an investigational drug (or biologic classified as a drug) from the requirement for prospective IRB approval, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article in the facility requires IRB review. However, FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue. If in the review of the emergency use, it appears likely that the test article may be used again, the IRB may request that a study application is submitted which would cover future uses.

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FDA defines emergency use as the use of a test article in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval [[21 CFR 56.102\(d\)](#)]. If all conditions described in [21 CFR 56.102\(d\)](#) exist, then the emergency exemption from prospective IRB approval found at [21 CFR 56.104\(c\)](#) may be used.

Life-threatening, for the purposes of [21 CFR 56.102\(d\)](#), includes both life-threatening and severely debilitating.

- Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.
- Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Unless the provisions for an emergency exception from the informed consent requirement are satisfied (see Section 15.5), informed consent must be obtained in accordance with [21 CFR 50](#) and documented in writing in accordance with [21 CFR 50.27](#).

BRANY IRB must be notified within **5 working days** after an emergency exemption is used with explanation of patient's clinical condition that supported the use, and justification provided for meeting the criteria for emergency use. Independent physician evaluation and endorsement of the use must be provided. An IRB Chair will review the report to verify that circumstances of the emergency use conformed to FDA regulations. This must not be construed as IRB approval, as an exemption from the requirement for prospective IRB approval has been invoked. When appropriate, in the event a manufacturer requires documentation from the IRB prior to the emergency use, the IRB Chair or designee will review the proposed use, and, if appropriate, provide a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of [21 CFR 56.104\(c\)](#). Reports of emergency uses will be brought to the convened IRB for their information.

Investigators are reminded that they must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved drugs or device.

15.5.2 Emergency Use of Investigational Devices

FDA regulations permit the emergency use of an investigational or unapproved device without prior approval by the FDA or IRB when an appropriately trained and licensed health care provider determines that:

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- The patient has a life-threatening or serious disease or condition that needs immediate treatment;
- No generally acceptable alternative treatment for the condition exists; and
- Because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

FDA expects the provider to make the determination that the above criteria are satisfied, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. Because prior FDA approval is not required, FDA expects providers planning the emergency use of an investigational device to obtain as many of the following as possible:

- An independent assessment from an uninvolved physician;
- Authorization from the device manufacturer;
- Concurrence of the IRB Chair or designee;
- Institutional clearance; and
- Informed consent from the patient or legally authorized representative.

At NJH, providers planning the emergency use of an investigational or unapproved device should contact the HRPP office as early as possible to coordinate Institutional and IRB processes.

Reports of emergency uses should be submitted to BRANY IRB via their Emergency Use Notification Form. Such notifications will be reviewed by the IRB Chair (and, only if deemed warranted, forwarded to the IRB) and acknowledged. The convened IRB will be informed of such activity for informational purposes.

The emergency use must be reported to the FDA by the IDE Sponsor, when one exists, or by the provider if no IDE exists. Information regarding what to include in the report and where to submit it is available on FDA's website. When the provider is responsible for the FDA report, a copy of the report and any related correspondence must be submitted to BRANY IRB.

Providers are reminded that they must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved devices.

15.5.3 Emergency Exception from the Informed Consent Requirement

An exception under FDA regulations at [21 CFR 50.23\(a-c\)](#) permits the emergency use of an investigational drug without informed consent when the investigator and an independent physician who is not otherwise participating in the clinical investigation (the emergency use) certify in writing all four of the following conditions:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article;
2. Informed consent cannot be obtained because of an inability to communicate

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- with, or obtain legally effective consent from, the subject;
3. Time is not sufficient to obtain consent from the subject's LAR; and
 4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the subject.

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent physician determination in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The IRB must be notified within **5 working days** when an emergency consent exception is invoked, with information and justification as detailed above. Independent physician evaluation and endorsement of the use must be provided. An IRB Chair will review the report to verify that circumstances of the emergency exception conformed to FDA regulations.

15.6 Charging Subjects for Investigational Products

FDA regulations do not prohibit charging subjects or their insurers for investigational products so long as those charges comply with specified criteria. FDA approval of such charges does not obviate the investigator's and IRB's responsibility to minimize risks to subjects (Beneficence), to ensure that the risks and burdens associated with research are equitably distributed (Justice), and to ensure that subjects are properly informed and not unduly influenced to accept an otherwise unacceptable risk or cost in order to access a benefit (Respect for Persons).

Any costs to subjects or insurers must be described in the IRB application and informed consent document.

15.6.1 Charging for Investigational Medical Devices and Radiological Health Products

IDE regulations allow sponsors to charge for an investigational device, however, the charge may not exceed the amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device [[21 CFR 812.7\(b\)](#)]. Sponsors must justify the proposed charges for the device in the IDE application, state the amount to be charged, and explain why the charge does not constitute commercialization [[21 CFR 812.20\(b\)\(8\)](#)].

15.6.2 Charging for Investigational Drugs and Biologics

In 2009, FDA updated its rules at 21 CFR 312 regarding charging for Investigational Drugs Under an IDE. These rules:

- Provide general criteria for authorizing charging for an investigational drug [[21 CFR 312.8\(a\)](#)]
- Provide criteria for charging for an investigational drug in a clinical trial [[21 CFR 312.8\(b\)](#)]

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- Set forth criteria for charging for an investigational drug for an expanded access for treatment use [[21 CFR 312.8\(c\)](#)]

Establish criteria for determining what costs can be recovered when charging for an investigational drug [[21 CFR 312.8\(d\)](#)]. Additional information is available in FDA guidance: [Charging for Investigational Drugs Under an IND — Questions and Answers](#).

16. Unanticipated Problems Involving Risks to Subjects or Others

Regulations require an organization to have written procedures for ensuring prompt reporting of “unanticipated problems involving risk to subjects or others” (also referred to as UPs, UAPs, and UPIRTSOs).

This section provides definitions and procedures for the reporting to the NJH HRPP of UPIRTSOs conducted under the auspices of NJH, in addition to any reporting requirements of the IRB of record. NOTE: Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the NJH internal reporting requirements outlined in Section 8.3.3.

In conducting its review of protocol deviations, violations, noncompliance, subject complaints, and other reportable events, the NJH HRPP will also consider whether the event or issue was caused by, contributed to, or otherwise related to an UPIRTSO.

16.1 Definitions

Unanticipated problems involving risks to subjects or others (UPIRTSOs) refer to any incident, experience, outcome, or new information that, in the preliminary opinion of the investigator:

1. Is unexpected; and
2. Is at least possibly related to participation in the research; and
3. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, legal or social harm) than was previously known or recognized

UPIRTSOs can also encompass Unanticipated Adverse Device Effects, as defined below, and information that sponsor are required to report to the FDA in IND Safety Reports under 21 CFR 312.32.

Unexpected. The incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the study-related documents, such as the IRB-approved research protocol/research plan and informed consent documents; and the characteristics of the subject population being studied.

Related. There is a reasonable possibility that the incident, experience, or outcome may have been caused by their participation in the research.

Adverse Event. For the purposes of these policies and procedures, an adverse event (AE) is any

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untoward or unfavorable occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research. For interventional studies, protocols can provide further definition of adverse events. Furthermore, adverse events can be determined at the investigator's discretion. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

Serious Unexpected Suspected Adverse Reaction. For clinical trials subject to FDA's IND regulations, a Serious Unexpected Suspected Adverse Reaction refers to any suspected adverse reaction to study treatment, including active comparators, that is both serious and unexpected. Sponsors are responsible for determining whether an event meets all three components of this definition, and thus must be reported to the FDA in an IND Safety Report.

Unanticipated Adverse Device Effect. An Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subjects [21 CFR 812.3(s)].

16.2 Procedures

16.2.1 Reporting

Adverse events in FDA-regulated clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. Unless specifically required by the IRB of Record for a given protocol, the NJH HRPP does not accept reports of adverse events that are not UPIRTSOs.

Investigators must report the following events or issues to the IRB of record within the timeframe specified in their SOPs. These events or issues must also be submitted to the NJH HRPP concurrent with the report to the IRB of record. The documentation submitted to the IRB is acceptable for submission to NJH HRPP. This information should be submitted in NJH IRB Manager using the "Interim/Event Report" xform. If investigators are uncertain but believe that the event might represent an UPIRTSO, a report should be submitted.

Examples of **UPIRTSOs** include:

1. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome)
2. A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy)

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3. Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). A summary and analyses supporting the determination should accompany the report
4. An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. A discussion of the divergence from the expected specificity or severity should accompany the report
5. A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). A discussion of the divergence from the expected rate should accompany the report
6. AEs involving direct harm to subjects enrolled by the local investigator which in the opinion of the investigator or sponsor, may represent an UPIRTSO
7. IND Safety Reports from sponsors that meet the criteria for reporting to the FDA under 21 CFR 312.32. Such reports must be accompanied by confirmation that the sponsor has submitted the report to the FDA. For more information on IND safety reporting, see FDA's guidance "[Safety Reporting Requirements for INDs and BA/BE Studies](#)";
8. Unanticipated Adverse Device Effects (UADEs);
9. Any other AE or safety finding (e.g. based on animal or epidemiologic data) that indicates subjects or others might be at risk of serious, unanticipated harms that are reasonably related to the research. These would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. An explanation of the conclusion should accompany the report.
10. Reports (including reports from DSMBs/DMCs) that indicate that risks are greater than previously known or that indicate that the research should be modified, suspended, or halted.
11. Sponsor or lead investigator/coordinating center imposed suspension or termination of some or all research activities
12. An unanticipated event related to the research that exposes subjects or others to potential risk but that does not involve direct harm to subjects

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13. A breach of confidentiality or loss of research data (e.g., a laptop or thumb drive is lost or stolen, nonphysical harm)
14. An unanticipated event related to the research that results in actual harm or exposes individuals other than the research subjects (e.g., investigators, research assistants, students, the public, etc.) to potential risk
15. New information that indicates increased risk, new risk(s), or decrease to potential benefit from what was previously understood. Examples include
 - a) An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits may be different than initially presented to the IRB
 - b) A report or publication that indicates the risks, benefits, or merit of the research are different from what was previously understood.

16.2.2 Review Procedures

1. Upon receipt of the information describing the event, the HRPP Administrator will assess if the event constitutes a UPIRTSO, consulting with the IO as necessary. If additional information is required in order to make such an assessment, the HRPP Administrator will contact the investigator for corrections or additional information. If the information provided suggests that subjects may be at risk of harm without immediate intervention, the IO will be notified so that necessary steps can be taken (e.g., suspension of study etc.) to ensure the safety of subjects or investigate the matter.
2. If immediate Institutional action is not required, the HRPP Administrator will await outcome of review by the IRB of record. Discrepancies between NJH and IRB of Record assessment regarding whether or not an event constitutes a UPIRTSO (including any additional actions* required as a result to ensure the protection of human subjects) will be addressed on a case by case basis. Such review may be undertaken by an ad hoc committee comprised of individuals with appropriate expertise.

*Additional actions that may be required by NJH HRPP may include, but are not limited to additional training of investigator and/or study staff; auditing/monitoring of the research; reporting or referral to appropriate parties (e.g., the IO, Corporate Compliance, Privacy Officer etc.); suspension/termination of institutional approval to conduct the study/studies in question at NJH.

3. When the IRB determines that an event is an UPIRTSO, procedures agreed upon in the reliance agreement between NJH and the IRB of Record will be followed for reporting to regulatory agencies, sponsors, and organizational officials in Section 20.

When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions. IND Safety Reports, UADE Reports, and any other reports that have already been reported to the federal oversight agency (e.g.,

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by a Sponsor, Coordinating Center, or sIRB) do not also need to be reported by NJH HRPP.

17. Noncompliance

This section provides definitions and procedures for the reporting to the NJH HRPP of known or suspected noncompliance in research under the auspices of NJH, in addition to any reporting requirements of the IRB of record. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the NJH internal reporting requirements outlined in Section 8.3.3.

In conducting its review of protocol deviations, unanticipated problems, subject complaints, and other reportable events, the NJH HRPP will also consider whether the event or issue was caused by, contributed to, or otherwise related to noncompliance.

17.1 Definitions

Noncompliance is defined as any failure to follow:

- Applicable federal regulations, state or local laws, or institutional policies governing human subject protections, or
- The requirements or determinations of the IRB, including the requirements of the approved investigational plan (i.e., protocol deviations).

Noncompliance can result from performing an act that violates these requirements of failing to act when required. Noncompliance may be minor or sporadic or it may be serious or continuing.

Protocol Deviation is a kind of Noncompliance. Protocol Deviation means any variation from the IRB approved research plan that happens without prior review and approval of the IRB.

Serious Noncompliance is defined as noncompliance that increases risk of harm to subjects; adversely affects the rights, safety, or welfare of subjects; or adversely affects the integrity of the data or the research. Willful violation of policies and/or federal regulations may also constitute serious noncompliance.

Continuing Noncompliance is defined as a pattern of repeated noncompliance that which continues after it has been determined that noncompliance occurred, including inadequate effort to take corrective actions or comply with IRB requirements within a reasonable timeframe.

Allegation of Noncompliance. Allegation of Noncompliance is defined as an unproved assertion of noncompliance.

17.2 Reporting

Investigators and their study staff are required to report instances of possible noncompliance to the NJH HRPP as soon as possible but within the time period required by the IRB of record.

Noncompliance should be submitted in NJH IRB Manager using the "Interim/Event Report" xForm.

The documentation submitted to the IRB is acceptable. Additionally, anyone may report concerns of

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possible noncompliance to the HRPP Administrator verbally, by email, or other means. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and, unless reporting anonymously, cooperating with any subsequent fact-finding in relation to the report.

If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report noncompliance, he or she may contact the HRPP Administrator to discuss the situation informally.

17.3 Review Procedures

1. Upon receipt of the information describing the event, the HRPP Administrator will assess if the event constitutes noncompliance, consulting with the IO as necessary. If additional information is required in order to make such an assessment, the HRPP Administrator will contact the investigator for corrections or additional information. If the information provided suggests that subjects may be at risk of harm without immediate intervention or that research misconduct may have occurred, the IO and/or Research Integrity Officer will be notified so that they can take any necessary steps (e.g., suspension of study etc.) to ensure the safety of subjects or investigate the matter.
2. If immediate Institutional action is not required, the HRPP Administrator will await outcome of review by the IRB of record. Discrepancies between NJH and IRB of Record assessment regarding whether or not an event constitutes noncompliance (and if so, if it is serious and/or continuing compliance), including any additional actions* required as a result to ensure the protection of human subjects, will be addressed on a case by case basis. Such review may be undertaken by an ad hoc committee comprised of individuals with appropriate expertise.

*Additional actions that may be required by NJH HRPP may include, but are not limited to additional training of investigator and/or study staff; auditing/monitoring of the research; reporting or referral to appropriate parties (e.g., the IO, Corporate Compliance, Privacy Officer etc.); suspension/termination of institutional approval to conduct the study/studies in question at NJH.

3. When the IRB determines that an event is serious and/or continuing noncompliance, procedures agreed upon in the reliance agreement between NJH and the IRB of Record will be followed for reporting to regulatory agencies, sponsors, and organizational officials in Section 20.

When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.

18. Complaints

The HRPP Administrator will be responsive and sensitive to the complaints or concerns expressed by

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subjects or others and will respond to all complaints or concerns in a confidential and timely manner. The PI and all other research team members are responsible for the safety and welfare of all subjects enrolled in their studies. When investigators or team members hear complaints or concerns from subjects, he or she will try to resolve them.

Investigators conducting research under the auspices of NJH must report complaints to the HRPP Administrator using the Interim/Event Report Form in NJH's IRBManager, regardless of who serves as the IRB of record. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 8.3. Investigators are encouraged to contact the HRPP Administrator or IO when they are having difficulty resolving a complaint or concern, and whenever circumstances warrant (e.g., immediate attention is needed).

When the HRPP Administrator is the direct recipient of complaints or concerns, they will do the following:

1. Document the complaint or allegation. When appropriate, they may request that the subject submit the complaint in writing.
2. Reassure the subject that the HRPP will take all necessary measures to inquire into the circumstances and to address the issue.
3. Provide written confirmation of receipt of the complaint to the subject, if the subject is willing to provide contact information.
4. Convey the information to the IRB of record in a timely manner.
5. When appropriate, contact the investigator for additional information or to assist with resolution.
6. When appropriate, contact other resources (e.g., Privacy Officer etc.) to assist with information- gathering or resolution.

The HRPP/IRB Staff will maintain written copies of complaints and concerns and will document the investigation and resolution. The complainant will be notified promptly following resolution of the complaint or concern, when appropriate, and if contact information has been provided. If the HRPP Administrator receives a complaint, or identifies information while investigating a complaint, that is indicative of possible misconduct in research, NJH's Research Integrity Officer will be notified immediately.

19. Other Reportable Information

NJH HRPP requires notification (via the Interim/Event Report Form in IRBManager) of other reportable information which includes, but is not limited to, the following:

1. Changes made to the research without prior IRB approval to eliminate apparent immediate hazards to the subject(s)
2. Monitoring, Audit, and inspection reports
3. Data Safety Monitoring reports, including reports from DSMBs, DMCs, and others

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4. Suspensions, or terminations of a study, in part or in full, by an investigator, sponsor, or others
5. Changes that impact the ability of the PI to conduct or supervise the study, temporarily or permanently
6. Changes that impact the qualifications of investigators or research staff members such as actions taken by regulatory authorities, licensing boards, or credentialing committees
7. Any other new information that may impact the rights, welfare, or willingness of subjects to continue in the research.

19.1 Review Procedures

1. Upon receipt of the information describing the event, the HRPP Administrator will assess if the event constitutes a reportable event, consulting with the IO as necessary. If additional information is required in order to make such an assessment, the HRPP Administrator will contact the investigator for corrections or additional information. If the information provided suggests that subjects may be at risk of harm without immediate intervention or that research misconduct may have occurred, the IO and/or Research Integrity Officer will be notified so that they can take any necessary steps (e.g., suspension of study etc.) to ensure the safety of subjects or investigate the matter.
2. If immediate Institutional action is not required, the HRPP Administrator will await outcome of review by the IRB of record. Discrepancies between NJH and IRB of Record assessment regarding whether or not an event constitutes a reportable event, including any additional actions* required as a result to ensure the protection of human subjects, will be addressed on a case by case basis. Such review may be undertaken by an ad hoc committee comprised of individuals with appropriate expertise.

*Additional actions that may be required by NJH HRPP may include, but are not limited to additional training of investigator and/or study staff; auditing/monitoring of the research; reporting or referral to appropriate parties (e.g., the IO, Corporate Compliance, Privacy Officer etc.); suspension/termination of institutional approval to conduct the study/studies in question at NJH.

3. When the IRB determines that an event is a UPIRTSO, or serious and/or continuing noncompliance, procedures agreed upon in the reliance agreement between NJH and the IRB of Record will be followed for reporting to regulatory agencies, sponsors, and organizational officials in Section 20.

When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.

20. Reporting to Federal Agencies, Departments, and Organizational Officials

Federal regulations require prompt reporting to appropriate institutional officials and, as applicable, the federal department or agency (e.g., OHRP, FDA), of:

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1. Any unanticipated problems involving risks to subjects or others;
2. Any serious or continuing noncompliance with the applicable federal regulations or the requirements or determinations of the IRB; and
3. Any suspension or termination of IRB approval. Reporting responsibilities and timelines will be guided by the terms of the agreement between NJH and the IRB of Record. Where NJH is the reporting party, the NJH IO will be the signatory, and the reporting will be made within 30 days of the determination.

When research is under the oversight of an external IRB, the terms of the agreement with that IRB will guide reporting.

21. Investigator Responsibilities

Principal Investigators (PIs) are ultimately responsible for the conduct of research. PIs may delegate tasks to appropriately trained and qualified members of their research team. However, PIs must maintain oversight and retain ultimate responsibility for the proper conduct of the research.

Within the regulations, the term 'investigator' refers to individuals involved in the design, conduct, or reporting of the research. Such involvement could include one or more of the following:

- Designing the research
- Obtaining information about living individuals by intervening or interacting with them for research purposes
- Obtaining identifiable private information about living individuals for research purposes
- Obtaining the voluntary informed consent of individuals to be subjects in research
- Studying, interpreting, or analyzing identifiable private information or data for research purposes.

21.1 Responsibilities

Investigators who conduct research involving human subjects must:

1. Develop and conduct research that is in accordance with the ethical principles in the Belmont Report;
2. Develop a research plan that is scientifically sound and minimizes risk to the subjects;
3. Develop a research plan that ensures the just, fair, and equitable recruitment and selection of subjects;
4. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, include additional safeguards in the study to protect the rights and welfare of these subjects;
5. Ensure that the research plan includes adequate provisions for the monitoring of subjects and data to ensure the safety of subjects;

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6. Ensure that there are adequate provisions to protect the privacy interests of subjects;
7. Ensure that there are adequate provisions to protect the confidentiality of data;
8. Have sufficient resources necessary to protect human subjects, including:
 - a. Access to a population that would allow recruitment of the required number of subjects;
 - b. Sufficient time to conduct and complete the research;
 - c. Adequate numbers of qualified staff;
 - d. Adequate facilities;
 - e. Necessary equipment;
 - f. A plan to ensure proper supervision of the research including a plan for periods of absence or decreased availability; and
 - g. When appropriate, a plan to ensure the availability of medical, psychological, or other services that subjects might require as a result of their participation.
9. Ensure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the laws of Colorado and the policies of NJH;
10. Ensure that all study personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based;
11. Ensure that all persons assisting with the research are adequately trained and informed about the protocol and research implementation plan and their specific duties and functions;
12. Promptly report any changes in, addition to, or departure of investigators or research staff in NJH IRBManager as a modification, so that training and financial disclosure responsibilities can be confirmed. The investigator should contact the IRB of record for their requirements for reporting personnel changes;
13. Protect the rights, safety, and welfare of participants;
14. Ensure that when PHI is used, legally effective HIPAA authorization is obtained for each subject unless a Privacy Board or IRB has approved a waiver of the requirement;
15. Ensure that the language in the consent form is consistent with that in the protocol, any associated grant or contract, and, when applicable, the HIPAA authorization;
16. Obtain and document informed consent and ensure that no human subject is involved in the research prior to obtaining consent or consent/permission from their LAR, unless a waiver of the requirement has been approved by the IRB;
17. Have a procedure to receive questions, complaints, or requests for additional information from subjects and respond appropriately;

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18. Ensure that all information provided to the IRB is accurate and complete so that the IRB may fulfill its responsibilities to review the research and make the required determinations;
19. Ensure that all research involving human subjects receives IRB review and approval in writing or a determination of exemption before the research begins;
20. Ensure that all required reviews and approvals (e.g., privacy, COI disclosures, etc.) are in place before initiating the research;
21. Comply with all IRB decisions, conditions, and requirements;
22. Ensure that studies receive timely continuing IRB review and approval;
23. Report unanticipated problems, deviations, complaints, noncompliance, suspensions, terminations, and any other reportable events to the IRB and the organization, as required by regulations and policy;
24. Notify the IRB if information becomes available that suggests a change to the potential risks, benefits, merit, or feasibility of the research;
25. Obtain IRB review and approval before changes are made to the research unless a change is necessary eliminate apparent immediate hazards to the subject(s);
26. Seek HRPP or IRB assistance when in doubt about whether proposed research requires IRB review;
27. Retain records for the time-period and in the manner described to and approved by the IRB and as required by required by regulations, agreements, and policies;

Additional investigator responsibilities, including specific responsibilities for investigators engaged in FDA- regulated research are described throughout this SOP.

21.2 Record Retention

Investigator research records, including, but not limited to, signed consent forms and HIPAA authorizations, subject records and data, test article records, IRB records (submission materials, IRB determinations and associated documentation, correspondence to and from the IRB, etc.), and sponsor/grant records must be retained in accordance with regulatory, organizational, IRB, sponsor or grantor, and journal or publication standards. Records must be maintained securely with limited access. Disposal of investigator records must be done in such a manner that no identifying information can be linked to research data. When research is sponsored or grant-supported, consult the contract, grant terms, or other relevant agreements prior to destroying or transferring any records. If there are questions or allegations about the validity of the data or the appropriate conduct of the research, all records must be retained until such questions or allegations have been completely resolved.

The following summarizes a few of the more common regulatory requirements:

OHRP – research records must be retained for at least 3 years after the completion of the research

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HIPAA – Research authorizations, or documentation of waivers or alterations of authorization, must be held for a minimum of 6 years after the authorization or waiver/alterations was last obtained or in effect, whichever is later

FDA – Drugs (& biologics classified as drugs) - For a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified

FDA – Devices (& biologics classified as devices) - For a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

21.3 Investigator Concerns

Investigators who have concerns regarding the conduct of research at National Jewish Health, NJH's HRPP, or the external IRBs upon which NJH relies should convey them to the HRPP Administrator, the IO or other responsible parties when appropriate. The recipient of the concern will consider the issue, and when deemed necessary, seek additional information and convene the parties involved to form a response for the investigator or make necessary procedural or policy modifications, as warranted. In addition, the HRPP Administrator is available to address investigators' questions, concerns, and suggestions. Anyone with concerns may also report via the NJH Compliance Hotline or a confidential email.

Consistent with NJH policies, there will be no retaliation against any individual who reports concerns in good faith.

22. Sponsored Research

It is NJH policy that any sponsored research conducted under the auspices of the NJH is conducted in accordance with federal guidelines and ethical standards. This Section describes the procedures required to ensure that all sponsored research meets this requirement.

22.1 Definitions

Sponsor. Sponsor means the company, institution, individual donor, or organization responsible for the initiation, management or financing of a research study.

Sponsored research. Sponsored research means research funded by external entities (public, industry, or private) through a grant or contract that involves a specified statement of work (e.g., the research proposal), including clinical trials involving investigational drugs, devices or biologics.

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22.2 Responsibility

Sponsor grants, contracts, and other written agreements will be reviewed for the following by the Grants and Contracts office, with consultation with the NJH HRPP Office, as necessary:

1. All sponsor contracts have a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate.
2. In studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, the sponsor contracts have a written agreement with the Sponsor that the Sponsor promptly reports to the NJH findings that could affect the safety of participants or influence the conduct of the study.
3. When the Sponsor has the responsibility to conduct data and safety monitoring, the sponsor contracts have a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to the NJH.
4. Sponsor contracts have a written agreement with the Sponsor about plans for disseminating findings from the research and the roles that investigators and Sponsors will play in the publication or disclosure of results.
5. When participant safety could be directly affected by study results after the study has ended, the sponsor contracts have a written agreement with the Sponsor that the investigator or NJH will be notified of the results in order to consider informing participants
6. Payment in exchange for referrals of prospective participants from investigators (physicians) (finder's fees) is not permitted. Similarly, payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (bonus payments) are also not permitted.

23. Conflict of Interest in Research

It is NJH policy to preserve public trust in the integrity and quality of research by reducing actual or perceived conflict of interest in the conduct of research.

Conflicts of interest (COI) in research can be broadly described as any interest that competes with an organization's or individual's obligation to protect the rights and welfare of research subjects, the integrity of a research study, or the credibility of the research program. Conflicts of interest can be financial or non-financial.

In the environment of research, openness and honesty are indicators of integrity and responsibility, characteristics that promote quality research and strengthen the research process. Therefore, conflicts of interest should be eliminated when possible and effectively managed and disclosed when they cannot be eliminated.

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23.1 Researcher Conflicts of Interest

NJH relies upon a COI Institutional Official who will collaborate with the HRPP Office and IRB of record to ensure that COI of investigators and research team members (investigators) are identified and managed before the IRB completes its review of any research application.

23.1.1 Procedures

23.1.1.1 Disclosure of Researcher COI

The Compliance Office maintains a list of individuals who have declared financial interests following the NJH annual disclosure process, along with the Compliance Office's determination of whether or not they constitute significant financial interests (i.e., related to their institutional responsibilities).

All human subject research conducted under the auspices of NJH must include completed NJH Human Research Financial Interest Forms for each study team member. These forms are required:

1. At initial review (for exempt research) or at the time of study registration (for external research)
2. When a new study team member is added to the research
3. When a study team member discloses a new or updated financial interest related to the research

The Compliance Office is notified whenever a financial interest related to a research study is disclosed. The Compliance Office reviews the disclosure against the study sponsor and other details and either notifies the HRPP Administrator that no investigator COI was identified or that one or more investigators has a Significant Financial Interest (SFI) that constitutes a financial conflict of interest. In the latter case, the Compliance Office provides a Conflict Management Plan (CMP) to the HRPP Administrator who ensures submission to the IRB of record for their evaluation in accordance with their policies and procedures

23.1.1.2 Management of COI

The IRB has final authority to determine whether the research, the COI, and the CMP, if any, allow the research to be approved. With regard to the CMP issued by the Compliance Office, the IRB shall either affirm or request changes to strengthen it. The IRB can require additional measures to manage a COI so that the research may be approved. However, the IRB cannot weaken a CMP approved by the Compliance Office.

For example, in addition to the CMP, the IRB may require:

1. Disclosure of the COI to subjects through the consent process;
2. Modification of the research plan or safety monitoring plan;
3. Monitoring of research by a third party;

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4. Disqualification of the conflicted party from participation in all or a portion of the research;
5. Appointment of a non-conflicted PI;
6. Divestiture of significant financial interests; and/or
7. Severance of relationships that create actual or potential conflicts.

In the event the conflict cannot be effectively managed, the IRB may disapprove the research.

23.2 Institutional Conflict of Interest

As an organization that conducts and reviews research involving human subjects, NJH recognizes its obligation to protect the rights and welfare of those subjects, and ensure the integrity of the research and the HRPP. Toward this end, the financial interests of NJH or senior administrative officials must be identified, evaluated, managed, and minimized or eliminated in order to ensure that meeting that obligation is not jeopardized.

23.2.1 Definition of Institutional Financial Conflicts of Interest

An “Institutional Financial Conflict of Interest” arises in human subjects’ research when a financial interest of NJH may affect or appear to affect the design, conduct, reporting, review, or oversight of the human subjects’ research. Institutional financial conflicts of interest are of significant concern when they create the potential for inappropriate influence over a human subjects’ research project, particularly to the integrity of the research and the rights and welfare of subjects enrolled in the research. All forms of potential Institutional Financial Conflicts of Interest in human subjects’ research require disclosure, evaluation, and either management or elimination under this Policy.

An “Institutional Financial Conflict of Interest” (IFCOI) exists when:

1. The NJH receives or might reasonably be expected to receive royalty income from the sale of a product covered by any patent, license or copyright, whether issued or pending, held by, and is proposed to be used in human subjects’ research projects, at NJH;
2. The NJH holds or proposes to hold, directly or indirectly, any equity interests of any amount (or entitlement to the same), in research sponsors of human subjects’ research projects, whether such research sponsor is public or non-public, through its technology licensing activities or investments related to such activities;
3. The NJH has received substantial gifts (including gifts in kind) from a potential commercial sponsor of human subjects research or a company that owns or controls products being studied or tested in human subjects research; and/or
4. Senior Administrative Officials with direct responsibility for human subject research (or their spouse, dependent children), as defined in Section 23.2.2 below:
 - a. Hold positions such as an officer, trustee, director, employee or consultant in

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commercial research sponsors, or any company that owns or controls products being studied or tested in human subjects

- b. Receive remuneration from commercial research sponsors, or any company that owns or controls products being studied or tested in human subjects. Remuneration includes salary and any payment for services not otherwise identified as salary (e.g., consulting fees, honoraria, paid authorship);
- c. Hold any equity interest (e.g., stock, stock option, or other ownership interest) in commercial research sponsors, or any company that owns or controls products being studied or tested in human subjects
- d. Hold Intellectual property rights and interests (e.g., patents, copyrights), royalties from such rights, etc. relating to products being studied or tested in human subjects

23.2.2 Review and Evaluation

IRB proposals submitted to the HRPP Office in advance of IRB review and approval will be assessed by the Compliance Office for potential IFCOI by assessing applicability of information contained within the reports referred to above. In order for a study involving IFCOI to be permitted at NJH, the Institutional Review Board, in consultation as deemed necessary with the Compliance Office, determines that:

- Circumstances exist to justify NJH's participation in the project while still maintaining the protection of human subjects, and
- A conflict management plan is adopted to maintain research integrity and serve the best interests of subjects enrolled in the research. These circumstances and conflict management plans will be documented.

23.2.3 Conflict Management Plan

If NJH's participation in a project is permitted notwithstanding the IFCOI, NJH's participation will be subject to a CMP developed by the Compliance Office, and reviewed by the IRB of record as above. In the case of senior administrative officials, the conflict management plan shall be agreed to by the conflicted individual. The IRB has the final authority to determine whether any IFCOI and its management allows the research to be approved. Options for managing institutional conflict of interest, include but are not limited to the following:

- Disclosing the institutional conflict of interest to research subjects in the consent process and documents
- Disclosing the institutional conflict of interest to any journals or other publications for which the results of the research will be submitted
- Recusing of conflicted senior administrative officials from scientific merit,

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resource, or any other review of human research

- Having an external, independent IRB review the research in question
- Monitoring of research by independent reviewers
- Divestiture of financial conflicts of interests
- Severance of relationships that create actual or potential conflicts
- Prohibition of the conduct of the research at the NJH

23.2.4 Timing

The review, evaluation, and where applicable, IRB approval of an IFCOI management plan shall be completed prior to the account establishment of an award for the human subjects' research project or any commencement of the project (including enrollment of any research subjects), whichever comes first.

23.3 Recruitment Incentives

Payment arrangements between or among sponsors, organizations, investigators, research personnel, and those referring research participants present a conflict of interest and may place participants at risk of coercion or undue influence or cause inequitable selection. Payment in exchange for referrals of prospective participants (finder's fees) is not permitted. Similarly, payments designed to accelerate recruitment that is tied to the rate or timing of enrollment (bonus payments) are also not permitted. Bonus payments do not include payments for bona fide items or services.

24. Health Insurance Portability and Accountability Act (HIPAA)

The *Health Insurance Portability and Accountability Act of 1996* (HIPAA) required the creation of a Privacy Rule for identifiable health information. While the primary impact of the Privacy Rule is on the routine provision of and billing for health care, the Rule also affects the conduct and oversight of research.

The Privacy Rule defines individually identifiable health information transmitted or maintained by a covered entity in any form (electronic, written or oral) as "protected health information" (PHI) and establishes the conditions under which investigators may access and use this information in the conduct of research.

Except as otherwise permitted, the Privacy Rule requires that a research subject "authorize" the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject's consent to participate in research, which is required if the research is subject to the Common Rule, FDA regulations, and/or state laws that provide additional protection for research involving certain categories of health information (such as information derived from HIV/AIDS testing, genetic testing, and mental health records). When research consent is not required by regulation or law (e.g., for exempt research) or the requirement for research consent has been waived by an IRB, the requirements for authorization still apply unless an IRB or Privacy Board has determined that the criteria for a waiver of the authorization requirement are satisfied.

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24.1 Definitions

Access. Access is the mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

Accounting of Disclosures. Information that describes a covered entity's disclosures of PHI other than for treatment, payment, and health care operations; disclosures made with Authorization; and certain other limited disclosures. For those categories of disclosures that need to be in the accounting, the accounting must include disclosures that have occurred during the 6 years (or a shorter time period at the request of the individual) prior to the date of the request for an accounting.

Authorization. An individual's written permission to allow a covered entity to use or disclose specified PHI for a particular purpose. Except as otherwise permitted by the Privacy Rule, a covered entity may not use or disclose PHI for research purposes without a valid Authorization that includes all of the required elements under the Privacy Rule.

Covered entity. A health plan, a health care clearinghouse, or a health care provider who or that transmits health information in electronic form in connection with a transaction for which DHHS has adopted a standard.

Data Use Agreement. An agreement into which the covered entity enters with the intended recipient of a data set that establishes the ways in which the information in the data set may be used and disclosed and how it will be protected.

De-identified. Data are considered [de-identified under HIPAA](#) when they do not identify an individual, and there is no reasonable basis to believe that the data can be used to identify an individual. The Privacy Rule defines two methods for de-identifying PHI: (1) when the PHI is stripped of all 18 HIPAA-defined identifying elements and the covered entity does not have [actual knowledge](#) that the information could be used alone or in combination with other information to identify an individual who is a subject of the information (Safe Harbor method); or (2) when an appropriate expert determines that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual who is a subject of the information (Expert Determination method).

Designated Record Set. A group of records maintained by or for a covered entity that includes (1) medical and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) used, in whole or in part, by or for the covered entity to make decisions about individuals. A record is any item, collection, or grouping of information that includes PHI and is maintained, collected, used, or disseminated by or for a covered entity.

Disclosure. The release, transfer, provision of access to, or divulging in any manner, of information outside the entity holding the information.

Genetic Information. Genetic information means, with respect to an individual, information about: (1) The individual's genetic tests; (2) The genetic tests of family members of the individual; (3) The manifestation of a

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disease or disorder in family members of such individual; or iv) Any request for, or receipt of, genetic services, or participation in clinical research which includes genetic services, by the individual or any family member of the individual.

Genetic information concerning an individual or family member of an individual includes the genetic information of (1) A fetus carried by the individual or family member who is a pregnant woman; and (2) Any embryo legally held by an individual or family member utilizing an assisted reproductive technology. Genetic information excludes information about the sex or age of any individual.

Genetic services. A genetic test; genetic counseling (including obtaining, interpreting, or assessing genetic information); or genetic education.

Genetic test means an analysis of human DNA, RNA, chromosomes, proteins, or metabolites, if the analysis detects genotypes, mutations, or chromosomal changes. Genetic test does not include an analysis of proteins or metabolites that is directly related to a manifested disease, disorder, or pathological condition.

Health Information. Health Information means any information, including genetic information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.

Individually Identifiable Health Information. Information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

Limited Data Set. Refers to data sets that exclude 16 categories of direct identifiers that are specified in the Privacy Rule. Limited Data Sets may be used or disclosed, for purposes of research, public health, or health care operations, without obtaining either an individual's Authorization or a waiver or an alteration of Authorization for its use and disclosure, only if the covered entity obtains satisfactory assurances in the form of a Data Use Agreement. Limited Data Sets are not de-identified information under the Privacy Rule.

Minimum Necessary. The least PHI reasonably necessary to accomplish the intended purpose of the use, disclosure, or request. Unless an exception applies, this standard applies to a covered entity when using or disclosing PHI or when requesting PHI from another covered entity. A covered entity that is using or disclosing PHI for research without Authorization must make reasonable efforts to limit PHI to the minimum necessary. A covered entity may rely, if reasonable under the circumstances, on documentation of IRB or Privacy Board approval or other appropriate representations and documentation under Section 164.512(i) as establishing that the request for

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PHI for the research meets the minimum necessary requirements.

Privacy Board. A board that is established to review and approve requests for waivers or alterations of Authorization in connection with a use or disclosure of PHI as an alternative to obtaining such waivers or alterations from an IRB. A Privacy Board consists of members with varying backgrounds and appropriate professional competencies as necessary to review the effect of the research protocol on an individual's privacy rights and related interests. The board must include at least one member who is not affiliated with the covered entity, is not affiliated with any entity conducting or sponsoring the research, and is not related to any person who is affiliated with any such entities. A Privacy Board cannot have any member participating in a review of any project in which the member has a conflict of interest.

Protected Health Information. Protected Health Information (PHI) means individually identifiable health information that is transmitted by electronic media; maintained in electronic media; or transmitted or maintained in any other form or medium. PHI excludes individually identifiable health information in education records covered by the Family Educational Rights and Privacy Act (FERPA), as amended, [20 U.S.C. 1232g](#); in records described at 20 U.S.C. 1232g(a)(4)(B)(iv); in employment records held by a covered entity in its role as employer; and regarding a person who has been deceased for more than 50 years.

Psychotherapy Notes. Psychotherapy notes means notes recorded (in any medium) by a health care provider who is a mental health professional documenting or analyzing the contents of conversation during a private counseling session or a group, joint, or family counseling session and that are separated from the rest of the individual's medical record. Psychotherapy notes excludes medication prescription and monitoring, counseling session start and stop times, the modalities and frequencies of treatment furnished, results of clinical tests, and any summary of the following items: Diagnosis, functional status, the treatment plan, symptoms, prognosis, and progress to date.

Research. A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. This includes the development of research repositories and databases for research.

Use. With respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within the covered entity or health care component (for hybrid entities) that maintains such information.

Waiver or Alteration of Authorization. The documentation that the covered entity obtains from a researcher or an IRB or a Privacy Board that states that the IRB or Privacy Board has waived or altered the Privacy Rule's requirement that an individual must authorize a covered entity to use or disclose the individual's PHI for research purposes.

Workforce. Employees, volunteers, trainees, and other persons whose conduct, in the performance of work for a covered entity, is under the direct control of the covered entity, whether or not they are paid by the covered entity.

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24.2 The IRB's Role under the Privacy Rule

Under the Privacy Rule, IRBs have authority to consider, and act upon, requests for a partial or complete waiver or alteration of the Privacy Rule's Authorization requirement for uses and disclosures of PHI for research. Although the Common Rule and FDA regulations include protections to help ensure the privacy of subjects and the confidentiality of information (as applicable, to research activities that are regulated under those sets of regulations), the Privacy Rule supplements these protections where HIPAA is applicable, by requiring covered entities to implement specific measures to safeguard the privacy of PHI. If certain conditions are met, an IRB may grant a waiver or an alteration of the Authorization requirement for research uses or disclosures of PHI.

BRANY IRB fulfills the functions of NJH's Privacy Board for human subject research.

BRANY IRB documentation of approval of a waiver or alteration of the authorization requirement includes:

1. The identity of the approving IRB;
2. The date on which the waiver or alteration was approved;
3. A statement that the IRB has determined that the alteration or waiver or authorization, in whole or in part, satisfies the three criteria in the Rule;
4. A brief description of the PHI for which use or access has been determined to be necessary by the IRB;
5. A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures; and

NJH will not release PHI to investigators or other third parties without individual authorization or proper documentation of BRANY IRB's approval of a waiver or alteration of the requirement.

24.3 Authorization

Except as otherwise permitted, the Privacy Rule requires that a research subject "authorize" the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject's consent to participate in research, which is required for research to which the Common Rule, FDA regulations, and/or state laws regarding certain categories of health information apply (although certain research that is subject to the Privacy Rule may be exempt from Common Rule requirements). Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must be written in plain language and contain certain statements and core elements [[45 CFR 164.508.6\(c\)](#)].

At NJH, the HIPAA authorization is contained within the consent document, and is reviewed by the IRB, in consultation with the privacy officer as needed. As with the DHHS consent process, a signed copy of the combined consent/authorization must be provided to the research subject. Signed consents containing authorizations must be retained by NJH for 6 years from the date of creation or the date it was last in effect, whichever is later.

A research subject has the right to revoke their authorization at any time. See below for more information regarding an individual's right to revoke, procedures, and exceptions.

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When an Authorization permits disclosure of PHI to a person or organization that is not a covered entity (such as a sponsor or funding source), the Privacy Rule does not continue to protect the PHI disclosed to such entity. However, other federal and state laws and agreements between the covered entity and recipient such as a Business Associate Agreement (BAA) or Confidentiality Agreement may establish continuing protections for the disclosed information. Under the Common Rule or FDA regulations, an IRB may impose further restrictions on the use or disclosure of research information to protect subjects.

Authorization Core Elements:

1. A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner;
2. The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure;
3. The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure;
4. A description of each purpose of the requested use or disclosure;
5. Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure (A statement that there is “no expiration date or event” or that authorization expires at the “end of the research study” or “unless and until revoked” by the individual are permissible for research, including authorizations for future research); and
6. The signature of the individual and date. If the individual’s legally authorized representative signs the Authorization, a description of the representative’s authority to act for the individual must also be provided.

Authorization Required Statements:

1. A statement of the individual’s right to revoke his/her Authorization and how to do so, and, if applicable, the exceptions to the right to revoke his/her Authorization or reference to the corresponding section of the covered entity’s notice of privacy practices;
2. Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization (if such conditioning is permitted under the Privacy Rule), including research-related treatment and consequences of refusing to sign the Authorization; and
3. A statement of the potential risk that PHI will be re-disclosed by the recipient. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

24.4 Waiver or Alteration of the Authorization Requirement

Obtaining signed authorization to access and use PHI for research is not always feasible. The Privacy

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Rule contains criteria for waiver or alterations of authorization. If a covered entity has used or disclosed PHI for research pursuant to a waiver or alteration of authorization, documentation of the approval of the waiver or alteration must be retained for 6 years from the date of its creation or the date it was last in effect, whichever is later. This is in addition to any other documentation requirements that might apply.

For research uses and disclosures of PHI, an IRB or Privacy Board may approve a waiver or an alteration of the authorization requirement in whole or in part. A complete waiver occurs when the IRB or Privacy Board determines that no authorization will be required for a covered entity to use and disclose the PHI contemplated to be used or disclosed for that particular research project. A partial waiver of authorization occurs when the IRB or Privacy Board determines that a covered entity does not need authorization for all PHI uses and disclosures for some defined group of research purposes, such as accessing PHI for research recruitment purposes. An IRB or Privacy Board may also approve a request that removes some, but not all, required elements or statements of an authorization (an alteration).

In order for an IRB or Privacy Board to waive or alter authorization, the Privacy Rule ([45 CFR 164.512\(i\)\(2\)\(ii\)](#)) requires the IRB or Privacy Board to determine the following:

1. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
 - a. An adequate plan to protect health information identifiers from improper use and disclosure;
 - b. An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
 - c. Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule;
2. The research could not practicably be conducted without the waiver or alteration; and
3. The research could not practicably be conducted without access to and use of the PHI.

24.5 Activities Preparatory to Research

Under the preparatory to research provision of the Privacy Rule, a covered entity may permit an NJH researcher to use PHI for purposes preparatory to research such as assessing the feasibility of conducting a research project, developing a grant application or protocol, or identifying potential subjects.

The NJH Compliance Office must obtain from the investigator a completed HIPAA Preparatory to Research Form that indicates that (1) the use or disclosure of the PHI is solely to prepare a research protocol or for similar purposes preparatory to research, (2) that the investigator will not remove any PHI from the covered entity (e.g., physically taken out of a facility, or downloaded and retained on

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the investigator's device) in the course of the review, and (3) the PHI for which access is sought is necessary for the research purpose. [45 CFR 164.512(i)(1)(ii)]

Federal guidance has drawn a distinction between activities that may be undertaken by a researcher who is a member of the covered entity's workforce, e.g., an employee of the covered entity, and a researcher who is not part of the covered entity's workforce. This guidance indicates that researchers may use PHI under the preparatory to research provision to *identify* potential study participants, so long as no PHI is removed from the covered entity and the remaining two representations set forth above can be made. However, the guidance also indicates that researchers may not use PHI obtained pursuant to the "preparatory to research" provision to *contact* potential study subjects unless (i) the researcher is a member of the covered entity's workforce, or (ii) the researcher enters into a BAA with the covered entity. NJH requires, however, that access to NJH PHI may only be permitted for activities involving researchers outside the NJH covered entity if that research is part of a confirmed collaboration (e.g., via a grant subaward, an IRB approved submission, etc.) with an NJH researcher, and the NJH would access the PHI on behalf of the collaboration.

NJH further requires that first contact with a patient for recruitment into a study must always be via an NJH individual who has a treatment relationship with that patient. These details, along with approved recruitment tools (e.g., script or flyer etc.) to be used by the individual with the treatment relationship, must be provided in the IRB submission.

An NJH clinician who is not the researcher may approach a patient about participation in another researcher's study. The NJH clinician or his/her staff must document the communication. If the patient agrees to a referral to the researcher, suggested language is as follows:

"I discussed the referral of the patient to [team or doctor] for [describe research study]. The patient agreed to the referral, including sharing information about the patient's condition."

24.6 Research Using Decedent's Information

The HIPAA Privacy Rule protects the individually identifiable health information about a decedent for 50 years following the date of death of the individual. When a researcher seeks to use PHI from decedents for a research protocol, the researcher must (1) obtain authorization from the personal representative of the decedent (i.e., the person under applicable law with authority to act on behalf of the decedent or the decedent's estate), (2) obtain a waiver of the requirement to obtain authorization from an IRB or Privacy Board, or (3) attest to the covered entity holding the PHI that the use or disclosure is solely for research on the PHI of decedents, that the PHI being sought is necessary for the research, and, if requested by the covered entity, provide documentation of the death of the individuals about whom information is being sought.

At NJH, the attestation option referenced above is accomplished by the investigator submitting a Research Use of Decedents' PHI Form to the Privacy Officer.

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24.7 Storage and Use of PHI for Future Research

The Privacy Rule recognizes the creation of a research database or a specimen repository to be a research activity if the data/specimens to be stored contain PHI. When researchers establish a database or repository containing PHI for the purposes of future research, or intend to maintain PHI following completion of a primary study for potential future research use, individual authorization for the storage of PHI for such future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied.

An authorization for use and/or disclosure of the stored PHI for future research must describe the future research uses and/or disclosures in sufficient detail to allow the potential subject to make an informed decision. The Rule does not require that an authorization describe each specific future study if the particular studies to be conducted are not yet determined. Instead, the authorization must adequately describe future purposes such that it would be reasonable for the subject to expect that their PHI could be used or disclosed for such research. When developing the description of potential future research uses, the investigator should be cognizant of uses of information/specimens that the community may consider particularly sensitive, such as genetics, mental health, studies of origin, and use of tissues that may have cultural significance, including whether any state laws may impose additional consent requirements with respect to any of these sensitive categories of information.

The authorization for future research is to be presented within the consent form that contains the authorization for the establishment of the database or repository or for the primary study (unless the research involves the use or disclosure of psychotherapy notes, in which case, such the use or disclosure can only be combined with *another* authorization for a use or disclosure of psychotherapy notes). However, there must be clear differentiation between the authorization for the primary study and the authorization for the unspecified future research activities, with specific allowance for the subject to opt-in to the future research. Opt-outs for future research are not permitted under the Privacy Rule because an opt-out process does not provide individuals with a clear ability to authorize the use of their information/specimens for future research, and may be viewed as coercive.

It is important to note that securing a HIPAA authorization for unspecified future research activities may not, by itself, satisfy all applicable legal consent requirements. The Common Rule, FDA regulations, and state laws also must be considered, as applicable, in evaluating whether the information (including PHI) or identifiable biospecimens may be used for future research projects.

24.8 Corollary and Sub-studies

Consistent with the discussion above relating to future uses of research databases or repositories, the Privacy Rule mandates that subject participation in corollary or sub-studies not essential to the primary aims of the research, such as when PHI from an interventional clinical trial is used to create or to contribute to a central research repository, must be on a voluntary, “opt-in” basis. This is particularly important when the primary research offers a potential direct benefit to the research subject, such as treatment, that might compel the potential subject to

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agree to an ancillary study, even if the subject would prefer not to do so.

HIPAA reinforces this ethical principle by explicitly stating that authorization for “unconditioned” activities, for which there is no associated treatment, benefit or other effect on the individual subject associated with participation, cannot be required. The published preamble to HIPAA Omnibus clarifies the basis for this position, and the requirement that authorization for unconditioned activities involve a clear opt-in mechanism, stating:

“This limitation on certain compound authorizations was intended to help ensure that individuals understand that they may decline the activity described in the unconditioned authorization yet still receive treatment or other benefits or services by agreeing to the conditioned authorization.” and “an opt out option does not provide individuals with a clear ability to authorize the optional research activity, and may be viewed as coercive by individuals.”

As with authorization for future research (which is one form of “unconditioned activity”), it is acceptable to combine in a single document the authorization for a conditioned activity, such as a clinical trial, with authorization for other forms of unconditioned activities such as a corollary or sub-study that does not directly benefit or affect the individual participant, **provided that**:

1. The authorization clearly differentiates between the conditioned and unconditioned research activities;
2. The authorization clearly allows the individual the option to opt in to the unconditioned research activities; and
3. Sufficient information is provided for the individual to be able to make an informed choice about both the conditioned and unconditioned activities.

Separate authorization must be obtained for research activity that involves the use and disclosure of psychotherapy notes. For example, authorization for the use and disclosure of psychotherapy notes for a clinical trial cannot be combined with an authorization for the use and disclosure of those psychotherapy notes for a corollary research activity.

24.9 De-identification of PHI under the Privacy Rule

Covered entities may use or disclose health information that is de-identified without restriction under the Privacy Rule, because information that has been de-identified consistent with the Privacy Rule requirements is not considered individually identifiable health information. The “Safe Harbor” method permits a covered entity to de-identify data by removing all 18 data elements specified in the Privacy Rule that could be used to identify the individual who is the subject of the information or the individual’s relatives, employers, or household members. To satisfy the Safe Harbor method of de-identification, the covered entity also must have no [actual knowledge](#) that the remaining information could be used alone or in combination with other information to identify individuals. Under this method, the identifiers of the individual or his or her relatives, employers, or household members that must be removed are the following:

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1. Names;
2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
 - a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people;
 - b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
4. Telephone numbers;
5. Facsimile numbers;
6. Electronic mail addresses;
7. Social security numbers;
8. Medical record numbers;
9. Health plan beneficiary numbers;
10. Account numbers;
11. Certificate/license numbers;
12. Vehicle identifiers and serial numbers, including license plate numbers;
13. Device identifiers and serial numbers;
14. Web universal resource locators (URLs);
15. Internet Protocol (IP) address numbers;
16. Biometric identifiers, including fingerprints and voiceprints;
17. Full-face photographic images and any comparable images; and
18. Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

Alternatively, consistent with requirements outlined in [45 CFR § 164.514\(b\)](#), a qualified statistician may certify that the risk is very small that the health information could be used, alone or in combination with other reasonably available information, to identify individuals. The qualified statistician must document the methods and results of the analysis that justify such a determination. This analysis must be retained by the covered entity for 6 years from the date of its creation or when

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it was last acted on, whichever is later.

The Privacy Rule permits a covered entity to assign to, and retain with, the de-identified health information, a code or other means of record re-identification if that code **is not** derived from or related to the information about the individual and is not otherwise capable of being translated to identify the individual. The covered entity may not use or disclose the code or other means of record identification for any other purpose and may not disclose its method of re-identifying the information.

NOTE: Data that are considered de-identified under HIPAA may still be considered human subject data under the Common Rule and may require IRB review and approval. Removal of HIPAA-identifying elements does not necessarily mean that the identity of the subject is not or may not readily be ascertained by the investigator or associated with the information and thus be considered identifiable private information under the Common Rule. The reverse can also be true (and, in practice, is more likely to occur): information may not be “identifiable” under the Common Rule but, because it contains certain HIPAA identifiers, it is considered identifiable under HIPAA.

24.10 Limited Data Sets and Data Use Agreements

Limited data sets are data sets stripped of certain direct identifiers. Limited data sets may be used or disclosed only for public health, research, or health care operations purposes. Because limited data sets may contain identifiable information, they are still PHI and as such are not considered de-identified under the Privacy Rule. Unlike de-identified data, Protected Health Information in limited data sets may include: addresses other than street name or street address or post office boxes, all elements of dates (such as admission and discharge dates) and unique codes or identifiers not listed as direct identifiers. The following direct identifiers must be removed for PHI to qualify as a limited data set:

1. Names;
2. Postal address information, other than town or city, state, and ZIP code;
3. Telephone numbers;
4. Fax numbers;
5. Email addresses;
6. Social Security numbers;
7. Medical Record numbers;
8. Health Plan Beneficiary numbers;
9. Account numbers;
10. Certificate or license numbers;
11. Vehicle identifiers and license plate numbers;
12. Device identifiers and serial numbers;

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13. URLs;
14. IP addresses;
15. Biometric identifiers; and
16. Full-face photographs and any comparable images.

Before disclosing a data set, a covered entity must enter into a Data Use Agreement (DUA) with the recipient, even when the recipient is a member of its workforce. The DUA establishes the parameters around the proposed uses and disclosures of the data, who is permitted to have access to the data, and stipulates that no other use or disclosure will be made other than as permitted by the DUA or as otherwise required by law, no attempt will be made to identify or contact individuals whose data are included in the limited data set, that appropriate safeguards are in place to protect the data from unauthorized use or disclosure, that any agents, including subcontractors, to whom the recipient provides the data will agree to the same restrictions and conditions that apply to the recipient, and that the recipient will report any uses or disclosures of the information that they become aware of that are not in keeping with the terms of the DUA. Data Use Agreements for the purposes of research are available from the NJH Privacy Office.

24.11 Research Subject Access to PHI

With few exceptions, the Privacy Rule guarantees individuals access to their medical records and other types of health information. One exception is during a clinical trial, when the subject's right of access can be suspended while the research is in progress. The subject must have been notified of and agreed to the temporary denial of access when providing consent and authorization. Any such notice must also inform the individual that the right to access will be restored upon conclusion of the clinical trial. Language accommodating this exclusion is included in the authorization section of the IRB consent template.

24.12 Revoking Authorization

The Privacy Rule establishes the right for an individual to revoke their authorization for uses and disclosures of PHI for research, in writing, at any time, except to the extent that the covered entity has taken action in reliance on the authorization. [45 CFR 164.508(b)(5)] However, individuals providing authorization should be made aware that revoking authorization does not mean that the individual's PHI may no longer be used in the research or be used or disclosed for other purposes.

At NJH, individuals may revoke authorization by notifying the Principal Investigator in writing. The Principal Investigator, in turn, should inform the Privacy Officer as well as the HRPP Office by either e-mail or by phone.

A covered entity may continue to use and disclose PHI that was obtained **before** the individual revoked authorization to the extent that the entity has taken action in reliance on the authorization. When the research is being conducted by the covered entity, the covered entity is permitted to continuing using or disclosing the **already obtained** PHI to the extent necessary to

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maintain the integrity of the research (e.g., to account for a subject's withdrawal from a study, to report adverse events, or to conduct an investigation of misconduct). A covered entity may also continue to use the PHI for other activities that are permitted under the Rule without authorization (e.g., health care operations such as QA/QI). Additionally, revoking an authorization does not prevent the continued use or disclosure of PHI by a non-covered entity that had **already received** it pursuant to the authorization.

24.13 Accounting of Disclosures

The Privacy Rule generally grants individuals the right to a written "Accounting of Disclosures" of their Protected Health Information made by a covered entity without the individual's authorization in the six years prior to their request for an Accounting. A covered entity must therefore keep records of such PHI disclosures for 6 years.

It is important to understand the difference between a use and a disclosure of PHI. In general, the use of PHI means use of that information within the covered entity. A disclosure of PHI means "the release, transfer, provision of access to, or divulging in any manner of information outside of the entity holding the information." The Privacy Rule restricts both uses and disclosures of PHI, but it requires an accounting only for certain PHI disclosures.

Generally, an Accounting of Disclosures is required for:

1. Routinely Permitted Disclosures (e.g., under public health authority, to regulatory agencies, to persons with FDA-related responsibilities) with limited exceptions (e.g., law enforcement, national security, etc.);
2. Disclosures made pursuant to:
 - a. Waiver of Authorization;
 - b. Research on Decedents' Information; or
 - c. Reviews Preparatory to Research.

An accounting is not needed when the PHI disclosure is made:

1. For treatment, payment, or health care operations;
2. Under an Authorization for the disclosure;
3. To an individual about himself or herself; or
4. As part of a limited data set under a data use agreement.

The Privacy Rule allows three methods for accounting for research-related disclosures that are made without the individual's Authorization or other than a limited data set: (1) A standard approach, (2) a multiple-disclosures approach, and (3) an alternative for disclosures involving 50 or more individuals. Whatever approach is selected, the accounting is made in writing and provided to the requesting individual. Accounting reports to individuals may include results from more than one accounting method.

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The administration and completion of the Accounting process will follow the NJH Policy and Procedure: "Patient Right to Request an Accounting of Disclosures of Protected Health Information".

24.14 Breach/Unauthorized Disclosure Notification and Reporting

Any unauthorized disclosures and breaches should be considered a noncompliance event that must be reported the HRPP Office within 2 business days. The HRPP Office will contact the Privacy Officer immediately thereafter.

25. Special Topics

25.1 Mandatory Reporting

While any person may make a report if they have reasonable cause to believe that a child or elder was abused or neglected, Colorado State law mandates that certain persons who suspect child or elder abuse or neglect report this to the county department or local law enforcement agency.

NJH requires the solicitation of informed consent from all adult research subjects and assent from children involved as research subjects, in addition to the consent of their parents. In situations where conditions of abuse or neglect might be revealed, mandated reporters should make themselves known as such to parents of children under age 18, to subjects who are children, and to subjects who are potential victims of elder abuse or neglect.

The Colorado Child Protection Act, 19-3-304 et seq., requires any physician, surgeon, physician in training, child health associate, medical examiner, coroner, dentist, osteopath, optometrist, chiropractor, chiropodist, podiatrist, registered nurse, licensed practitioner nurse, hospital personnel engaged in the admission, care, or treatment of patients, Christian Science practitioner, school official or employee, social worker, mental health professional, dental hygienist, psychologist, physical therapist, veterinarian, peace officer, pharmacist, victim's advocate, licensed professional counselor, licensed marriage and family therapist, unlicensed psychotherapist, and clergy member who has reasonable cause to know or suspect that a child has been subjected to circumstances or conditions which would reasonably result in abuse or neglect to report or cause a report to be made to the county department or local law enforcement agency.

Colorado's Protective Services For Adults Act, C.R.S. 26-3.1-101 et seq., encourages any physician, surgeon, physicians' assistant, osteopath, physician in training, medical examiner, coroner, registered nurse, licensed practitioner nurse, hospital or nursing home personnel engaged in the admission, care, or treatment of patients, psychologists, mental health professionals, social work practitioners, dentists, law enforcement officials, court-appointed guardians, pharmacists, and employees of a licensed care facility who have observed the mistreatment or self-neglect of an at-risk adult or who have reasonable cause to believe that an at-risk adult has been mistreated to report or cause a report to be made to the county department or local law enforcement agency.

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25.2 Certificates of Confidentiality

Certificates of Confidentiality (CoC) protect research information by prohibiting certain disclosures and conditioning others upon consent from the subject. The protections and requirements of CoCs are outlined in [42 U.S.C. 241\(d\)](#) and in written policies and requirements of certain Federal agencies such as [NIH](#) and [CDC](#), and summarized below.

CoC's are obtained as follows:

- CoCs are issued automatically when research is conducted or supported by NIH and falls within the scope of the NIH policy.
- CoCs are issued automatically when research is conducted or supported by the CDC and involves the collection of identifiable, sensitive information.
- CoCs are issued automatically when research is funded by the FDA in whole or in part and involves the collection or use of identifiable, sensitive information as defined in [42 U.S.C. 241\(d\)](#).
- Research that is not funded by NIH, CDC, or FDA may still have the protections afforded by CoCs through successful application to the NIH, FDA, HRSA, SAMHSA, or other authorized Federal agencies or departments.

Additional information about CoCs and the application process for non-NIH research is available on the [NIH CoC Website](#).

25.2.1 Definitions

Identifiable, sensitive information means information that is about an individual and that is gathered or used during the course of biomedical, behavioral, clinical, or other research and

1. Through which an individual is identified; or
2. For which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

25.2.2 Protections and Requirements

When a CoC is issued, whether automatically or under an approved application, the person(s) engaged in the research must not disclose or provide the name of a subject or any information, document, or biospecimen that contains identifiable, sensitive information about the subject and that was compiled for the purposes of the research:

1. In any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, unless the disclosure is made with the consent of the individual to whom the information, document, or biospecimen pertains; or

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2. To any other person not connected with the research, unless:
 - a. Required by Federal, State, or local laws (e.g., adverse event reporting to the FDA, transmissible disease reporting required under State law), but excluding proceedings as described in “1” above;
 - b. Necessary for the medical treatment of the subject to whom the information, document, or biospecimen pertains and made with the consent of the subject;
 - c. Made with the consent of the individual to whom the information, document, or biospecimens pertains; or
 - d. Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

25.2.3 Additional Protections

Identifiable, sensitive information protected under a CoC, and all copies thereof, are immune from the legal process, and shall not, without the consent of the individual to whom the information pertains, be admissible as evidence or used in any action, suit, or other judicial, legislative, or administrative proceeding.

Identifiable, sensitive information that has been collected under a CoC, and all copies thereof, are protected for perpetuity. If identifiable, sensitive information covered by a CoC is shared with other researchers or organizations, the researchers or organizations must be informed that the information is covered by a CoC and of their responsibility to protect the information accordingly.

Nothing in the Rule (42 U.S.C. 241(d)) may be construed to limit the access of a subject to information about himself or herself collected during the research.

When consent is obtained, the consent should inform subjects that a CoC is in place and describe the protections and limitations.

25.2.4 NIH and CDC

The [NIH Policy on CoCs](#) applies to *“all biomedical, behavioral, clinical, or other research funded wholly or in part by the NIH, whether supported through grants, cooperative agreements, contracts, other transaction awards, or conducted by the NIH Intramural Research Program, that collects or uses identifiable, sensitive information”* that was commenced or ongoing on or after December 13, 2016.

The [CDC requirements for CoCs](#) apply to *“CDC supported research commenced or ongoing after December 13, 2016 and in which identifiable, sensitive information is collected, as defined by Section 301(d).”*

CoCs are automatically granted, and the requirements of such must be complied with,

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whenever a NIH or CDC- funded activity falls within the scope of the NIH policy or CDC's requirements. Investigators and institutions are responsible for determining when research with NIH or CDC support are covered by a CoC.

NIH and CDC expands upon 42 U.S.C. 241(d) by explaining that NIH and CDC consider research in which identifiable, sensitive information is collected or used, to include:

- Human subjects research as defined in 45 CFR 46, including research determined to be exempt (except for exempt research when the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects);
- Research involving the collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual;
- Research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained; or
- Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual, as defined in subsection 301(d) of the Public Health Service Act.

25.2.5 FDA

The FDA requires, as a [term and condition](#) of all FDA funding and grant awards, compliance with the requirements of [42 U.S.C. 241\(d\)](#) when research is funded in whole or in part by the FDA and involves the use or collection of identifiable, sensitive information. Certificates are deemed issued through FDA funding/award terms and conditions and are not issued as a separate document.

Investigators and institutions are responsible for determining when research with FDA support is covered by a CoC and for ensuring compliance with the requirements of 42 U.S.C. 241(d). Awardees are expected to ensure that any investigator or institution not funded by FDA who receives a copy of identifiable, sensitive information protected by these requirements, understand they are also subject to the requirements of 42 U.S.C. 241(d). Awardees are also responsible for ensuring that any subrecipient that receives funds to carry out part of the FDA award involving a copy of identifiable, sensitive information protected by these requirements understand they are also subject to subsection 42 U.S.C. 241(d).

When research is not funded by the FDA but involves “the use or study of a product subject to FDA’s

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jurisdiction and subject to FDA's regulatory authority" (e.g., a clinical investigation of a drug, device, or biologic), the sponsor or sponsor-investigator can [request a discretionary CoC from the FDA](#). Information about discretionary CoC's issued by FDA is available in the FDA guidance document: [Certificates of Confidentiality](#).

25.2.6 NIH, CDC and FDA CoC Policy Determination

At NJH, Grants and Contract Office (GCO) staff will, in consultation with the investigator(s) (or Program or Project Director, if applicable), determine if the NIH policy or CDC or FDA requirements applies to research with NIH, CDC, or FDA involvement or support. The questions outlined in the NIH policy and CDC requirements will be used to guide the analysis for research conducted or supported by NIH and CDC. The definitions and text of 42 U.S.C. 241(d) will be used to guide the analysis for research supported by FDA funding/awards. When it has been determined that the NIH policy or CDC or FDA requirements do not apply, investigators are responsible for consulting with GCO whenever they are proposing changes to the supported activity that may impact or change the analysis.

The NIH policy and CDC requirements include additional responsibilities and requirements for internal controls and for ensuring that recipients of identifiable, sensitive information protected by a CoC understand that they are also subject to the requirements of subsection 301(d) of the Public Health Service Act. Likewise, FDA requires awardees ensure that recipients of identifiable, sensitive information protected by an FDA CoC understand that they are also subject to the requirements of 42 U.S.C. 241(d).

25.2.7 Application Procedures for Research Not Automatically Issued a CoC

Any person engaged in human subjects research that collects or uses identifiable, sensitive information may apply for a CoC. For most research, CoCs are obtained from NIH, an investigator may apply for a CoC through the NIH Institute or Center funding research in a scientific area similar to the project.

If the research is conducting a sensitive research project that is covered by the Agency for Healthcare Research and Quality (AHRQ) confidentiality statute ([42 U.S.C. section 299c-3\(c\)](#)), a CoC is not needed ([AHRQ notice NOT-HS-18-012](#)). While the AHRQ statute does not define "identifiable", AHRQ applies the PHS Act definition of "identifiable, sensitive information". Investigators should consult with AHRQ when they believe that data might be considered "non-identifiable" or when otherwise uncertain whether a research project falls within the scope of the statute.

When a researcher is conducting a research project that is covered by the Department of Justice (DoJ) confidentiality statute, 28 CFR 22, and/or a NIJ Privacy Certificate, a CoC may not be needed. Investigators should consult with DoJ/NIJ to determine whether a CoC should be obtained.

If there is an Investigational New Drug Application (IND) or an Investigational Device

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Exemption (IDE), the sponsor can request a CoC from the FDA. When FDA funds or conducts research, a CoC is automatically issued.

CoCs may also be issued by other Federal agencies and departments, such as SAMSHA, or HRSA. For more information, see the [NIH CoC Website](#).

25.2.8 IRB Review

Investigators are responsible for clearly representing in the IRB submission that a CoC is in place, or that an application for CoC has been submitted. When the CoC application is in process or pending, the IRB may condition final approval upon its receipt.

For studies that are already underway, investigators must submit a Modification Request to the IRB, along with updated consent language (if applicable), when a CoC is applied for, or when automatically issued under the NIH policy.

When reviewing research under a CoC, the BRANY IRB will evaluate whether the research plan is consistent with the obligations to protect information and specimens under a CoC and whether the consent language, if applicable, discloses the CoC and appropriately describes the associated protections and limitations. Sample consent language is available on the [NIH CoC Website](#) and in the template consent forms available on NJH's HRPP website.

When non-NIH research is not under a CoC, the IRB may require an investigator to apply for a CoC if the research includes identifiable, sensitive information and the IRB determines that a CoC is necessary to minimize risks and adequately protect subjects' privacy and the confidentiality of subjects' information or specimens.

25.3 Case Reports

Federal regulations at [45 CFR 46.102\(d\)](#) and [45 CFR 164.501](#) define research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. A **case report** is a detailed report of the diagnosis, treatment, response to treatment, and follow-up after treatment of an individual patient. A **case series** is a group of case reports involving patients who were given similar treatment. Case reports and case series usually contain demographic information about the patient(s), for example, age, gender, ethnic origin.

NJH regards case report preparations as an educational activity, not research, and thus it is permissible under the Privacy Rule (HIPAA) as a part of health care operations ([45 CFR 164.501](#)).

However, when information on more than three patients is included, NJH considers the case series to be a systematic investigation designed to contribute to generalizable knowledge (i.e., research), and therefore a submission to the HRPP/IRB is required. In addition, if PHI is accessed, used, or disclosed, authorization (or a waiver of authorization from an IRB/Privacy Board) is required.

As always, anyone who is unsure whether a project requires IRB review should contact the HRPP Office for assistance.

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A copy of this policy can be provided to journal editors or others who request confirmation of IRB review or waiver.

25.4 Databases, Registries, & Repositories

Databases, registries, and biospecimen repositories (all referred to as repositories throughout this Section) are used to store data and/or biospecimens for future use.

There are two type of repositories:

- Non-research repositories created and maintained for purposes that are unrelated to research. Such purposes may include diagnosis, treatment, billing, marketing, quality control, and public health surveillance.
- Research repositories created and maintained specifically for research purposes. Such purposes may include databases to identify prospective subjects, patient outcome information to evaluate treatment effectiveness, and tissues samples for future research. Non-research repositories that are altered to facilitate research (e.g., through the addition of data fields not necessary for the core purpose of the repository) are considered research repositories.

25.4.1 Non-research Repositories

Even though repositories were not created for research purposes, they may contain information that is of great interest to researchers. The creation (or operation) of non-research databases or repositories does not involve human subject research and does not require IRB oversight. However, IRB approval is required for the research use of identifiable private information or identifiable human specimens from non-research repositories, and, regardless of identifiability, when specimens will be used to evaluate the safety or effectiveness of a medical device. Research under the auspices of National Jewish Health that includes the use of coded private information or specimens, must either be submitted for IRB review or for a “Human Subjects Research Determination” (See Section 4).

Researchers submitting an application for research using data or specimens from non-research repositories must describe the source of the data/specimens and any terms, conditions, or restrictions on use. Data/specimens cannot be used for research if the person from whom the data/specimens originated objected to its use for research. Informed consent and HIPAA authorization (when applicable) must be obtained unless the IRB determines that the criteria for a waiver are satisfied.

25.4.2 Research Repositories

Research repositories involve three distinct activities:

1. Collection of data/specimens;

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2. Storage and management of data/specimens; and
3. Distribution of data/specimens.

NJH developed and maintains a **Research Database** and institutional **Biobank**. The Research Database provides access to data on patients and research subjects in a single, searchable repository. The database can also be used to find clinical data linked to samples in the NJH Biobank. With these resources available to researchers, NJH limits the scope of individual data repositories and prohibits the creation of individual (lab, investigator, or research group) specimen biorepositories.

NJH researchers may create their own data repositories, however the data may not be linked to samples in the NJH Biobank, appropriate security/confidentiality controls in place, and HRPP/IRB review is required.

NJH researchers are not permitted to create their own specimen biorepositories. Specimens collected for a specific research project must be destroyed after the study is completed or absorbed into the NJH Biobank for future use with appropriate permissions and consent.

25.4.3 IRB Oversight

Separate HRPP/IRB approval is required for the use of data/specimens from NJH's Biobank and/or Research Database. Requests for deidentified, coded, or brokered data/specimens must be submitted to NJH HRPP via the "Request for Human Subjects Research Determination" xForm in IRB Manager (See Section 4). Requests for identifiable data/specimens, or when specimens will be used to evaluate the safety or effectiveness of a medical device, must be reviewed by BRANY IRB unless the project qualifies for exemption.

25.5 Research Involving or Generating Genetic Information

Research that generates or uses genetic information may create special risks to human subjects and their relatives. These involve medical, psychosocial, legal and economic risks, such as the possible loss of privacy, insurability, and employability, and may result in stigmatization and discrimination. Information about one's own genetic make-up may also provide information about family members.

In studies involving genetic testing or analysis of genetic information, several questions should be addressed to ensure that potential risks are well understood and that the rights and interests of subjects and their family members are carefully considered and planned for. For example:

1. Is the testing intrinsic to the study? If not, has participation in the genetic testing component been provided as an opt-in?
2. Will test results be given? Is there an appropriate plan for return of results?
3. Will the subject or family member be provided the option to receive or not receive results? How will this decision be recorded?

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4. Could the results provide information about individual disease risk? Disease risk for family members?
5. Could other clinically relevant information or incidental findings be uncovered by the study? Is there a plan for the management of such findings?
6. Will testing that could produce clinically relevant information occur in a CLIA-certified lab? If not, are there tests available that could validate or support findings?
7. Could a change in a family relationship be disclosed, such as mistaken paternity?
8. Could/will the research provide information about the origins, ancestry, or natural history of families, indigenous peoples, tribal populations, or other populations? What are the possible risks?
9. Could/will the research generate information that could place subjects or family members at risk or be stigmatizing?
10. Could/will the research generate information of other value or importance to subjects/families?
11. Do any practical limitations exist on the subject's right to withdraw from the research, withdraw data, and/or withdraw biological materials (e.g., specimens, cell lines, extracted genomic DNA)?
12. How will the information and/or biological materials be protected and who will have access?
13. What is the potential for re-identification of individual subjects (e.g., through the combination of their genetic information and/or materials with other sources of information (e.g., public records))? What measures can be taken to mitigate these risks?
14. Is a Certificate of Confidentiality (CoC) in place or should one be considered? (See Section 26.2)
15. Will the specimens, cell lines, or genetic information be stored and/or made available for future research? Is this provided as an opt-in when not intrinsic to the study?

Investigators should carefully consider the above and other factors relevant to their specific study when developing the protocol, consent process, and consent form. The President's Bioethics Commission, the National Academies of Sciences, Engineering, and Medicine, and others have produced reports, recommendations, and materials that investigators and the IRB may find helpful in protocol development and review, including:

- [Returning Individual Research Results to Participants: Guidance for a New Research Paradigm](#)
- [Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts](#)
- [Privacy and Progress in Whole Genome Sequencing](#)
- [Genetics Research and American Indian and Alaska Native Communities](#)
- National Human Genome Research Institute:
 - [Human Subjects Research in Genomics](#)
 - [Return of Research Results](#)
 - [Data Sharing and Privacy](#)
 - [Informed Consent for Genomics Research](#)

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In addition to the ethical considerations, investigators must ensure that research involving genetic testing or use of genetic information is consistent with applicable law (e.g., GINA, HIPAA, EU GDPR, state law) and policy (e.g., NIH).

25.5.1 Genetic Information Nondiscrimination Act (GINA)

GINA generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against individuals based on their genetic information.

This law protects individuals, including research subjects, in the following ways:

- Health insurance companies and health plans are generally prohibited from requesting or requiring genetic information of an individual or their family members, including genetic information generated from research;
- If health insurance companies and health plans do receive such genetic information, they may not use it to make decisions regarding coverage, rates, or preexisting conditions; and
- Employers with 15 or more employees generally may not use genetic information for hiring, firing, promotion, or other decisions regarding terms of employment.

GINA's protections do not extend to life insurance, disability insurance, or long-term care insurance. GINA defines genetic information as information about:

- An individual's genetic tests;
- Genetic tests of an individual's family members;
- Genetic tests of any fetus of an individual or family member who is a pregnant woman, and genetic tests of any embryo legally held by an individual or family member utilizing assisted reproductive technology;
- The manifestation of a disease or disorder in an individual's family members (family history); or
- Any request for, or receipt of, genetic services or participation in clinical research that includes genetic services (genetic testing, counseling, or education) by an individual or an individual's family members.

GINA includes a "research exception" that allows health insurers and health plans who are engaged in research to request, but not require, that an individual undergo a genetic test so long as certain requirements are satisfied. Additional information on GINA and this exception are available on this [OHRP website](#).

The IRB will consider the protections and limitations of GINA when it assesses the risks of research generating or using genetic information and the adequacy of the measures to protect privacy and maintain confidentiality. Generally, the IRB will also require that the protections and limitations of GINA are disclosed in the consent process when applicable. Sample language for GINA is provided in NJH's template consent form.

25.6 Genomic Data Sharing

NJH complies with the [NIH GDS Policy](#), which allows for "broad and responsible sharing of genomic

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research data”, via submission of said data into an NIH-designated data repository. The intent of NIH’s policy is to speed discoveries to diagnose, treat, and prevent disease. To ensure consistency in the protection of human subjects, NJH applies the NIH principles for informed consent and for a genomic data sharing plan to all research that involves or contemplates genomic data sharing.

The NIH policy applies to grant activities requesting support from NIH for research involving the generation of large-scale human (and/or non-human) genomic data, regardless of funding level, such as:

- Research project grants (Rs);
- Program projects (Ps) and SCORs (Ss);
- Cooperative agreements for research (Us);
- Individual career development awards (Ks) that include a research component;
- S activities that include a research component; and
- All other activities that include a research component.

Also covered under this policy is research involving data derived from these activities for subsequent research. All basic and clinical research, including clinical trials, supported by NIH that involves the generation or use of large- scale genomic data fall within the scope of the policy.

The policy does not apply to:

- Institutional training grants (T32s, T34s, T35s, and TL2s);
- K12 career development awards (KL2s);
- Individual fellowships (Fs);
- Resource grants and contracts (Ss);
- Linked awards derived from previously reviewed applications (KL1, KL2, RL1, RL2, RL5, RL9, TL1, UL1);
- Facilities or coordinating centers funded through related initiatives to provide genotyping, sequencing, or other core services in support of GDS.

Because of the potential for re-identification of genomic data, Certificates of Confidentiality (CoCs) are automatically issued by the NIH for any research it supports, in part or in whole, that involves *“the generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained as defined in the Federal Policy for the Protection of Human Subjects (45 CFR 46).”*

Research covered by the [NIH policy](#) and/or the underlying [PHS Act](#) is protected by the CoC in perpetuity; as such any downstream recipients of such information must comply with the requirements of the PHS Act.

Investigators without NIH support who intend to submit genomic data to a NIH repository are encouraged to obtain a CoC. Investigators conducting research generating or using genomic data are encouraged to obtain a CoC when one is not already in place (e.g., for downstream use of data that was collected under a CoC).

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For more information on CoCs, see Section 26.2.

25.6.1 Definitions

Genomic data: information derived from study of an organism’s genome, i.e., the set of DNA (including all the genes within) in every cell that provides all of the information needed to build and maintain that organism.

Genomic Summary Results (GSR): GSR (also referred to as “aggregate genomic data” or “genomic summary statistics”) are results from primary analyses of genomic research that convey information relevant to genomic associations with traits or diseases across datasets rather than associations specific to any one individual research participant (e.g., genotype counts and frequencies; allele counts and frequencies; effect size estimates and standard errors; likelihood; and p-values).

Sensitive GSR refers to GSR where the privacy risks may be heightened for study populations (e.g., populations from isolated geographic regions or with rare traits) or the study populations may be more vulnerable to group harm (e.g., because the data includes potentially stigmatizing traits). Information regarding NIH’s updated policy on the access, use, and management of GSR may be found here: <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-023.html>

Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data. Examples of genomic research projects that are subject to the Policy and the timeline for submission and sharing of data from such projects may be found here: https://osp.od.nih.gov/wp-content/uploads/Supplemental_Info_GDS_Policy.pdf

NIH-Designated Data Repository: any data repository maintained or supported by NIH either directly or through collaboration. Examples of such repositories is available here: <https://osp.od.nih.gov/scientific-sharing/data-repositories-and-trusted-partners/>. Data may be unrestricted or controlled access:

- **Unrestricted-Access (“Open Access”):** data are publicly available to anyone (e.g., The 1000 Genomes Project). Non-sensitive GSR are made available through unrestricted access.
- **Controlled-Access:** the data are available to an investigator for a specific project only after the investigators and institution certify to abide by specified terms and conditions and NIH has approved the use. Sensitive GSR are made available through controlled access.

25.6.2 Procedures

IRB Submissions and GDS

For any cell lines created or specimens to be collected, analyzed, and shared subject to the

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GDS Policy, the IRB expects that informed consent will be obtained from the research subject for the future research uses and broad sharing of data required under the policy. **This is the case even if the specimens or cell lines are de-identified.** If there are compelling scientific or legal reasons that necessitate the use of genomic data from cell lines or clinical specimens that lack consent for research use and data sharing, investigators will need to provide a justification in the funding request to NIH for their use. The funding NIH institute/center will review the justification and decide whether to make an exception to the consent expectation. Exceptions from the NIH are not required only some participants decline to consent to broad sharing, rather an exception request must be granted by NIH for research when consent for broad sharing has not or will not be sought.

Subjects asked to allow for future research uses and broad sharing of their genomic data have the ability to decline and still remain in the research (however their data cannot be placed into a repository or otherwise broadly shared). The only exception to this is when sharing of the data is intrinsic to the study (e.g., the purpose of the study is to establish a repository for sharing biological specimens and/or data for future research).

Sample consent language for studies subject to GDS is available in the consent template, from the HRP Office. [NIH](#) and [NHGRI](#) also provides guidance and resources to assist in the development of appropriate consent forms for research involving or generating genetic or genomic data.

Applications to BRANY IRB should include information about the proposed generation or use of genomic data including, as per their SOPs, e.g.:

- Whether the research will generate or use data subject to the NIH GDS policy;
- The name of the [NIH data repository/database](#), or other repository or database, that data will be submitted to or acquired from;
- Whether the data is restricted access or unrestricted access;
- Whether there are any data use limitations or modifiers (e.g., use limited to a specific disease, restricted to not-for-profit organizations, IRB approval requirement, etc.);
- The plan for informed consent and the proposed consent language; and
- A copy of the genomic data sharing plan.

The IRB will review the proposal for genomic data sharing or subsequent use of such genomic data in accordance with the criteria for approval of research and the [guidelines for IRBs](#) provided by NIH.

When NJH is responsible for NIH Institutional Certification (see below), the IRB review will specifically address the required assurances outlined on the [Extramural Institutional Certification](#). When appropriate, if the IRB is unable to confirm that a certification element is satisfied (e.g., because the IRB has not yet granted final approval), [Provisional Institutional Certification](#) will be provided.

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Grant Applications and GDS

Investigators planning to apply to NIH for research that will generate large-scale human genomic data as defined above should contact the appropriate NIH Program/Project officials to discuss expectations and timelines for complying with this policy. Along with the grant, the following will need to be submitted:

- **Notification in a cover letter** of the intent to generate large-scale human genomic data
- **A genomic data sharing plan**, within the grant's resource sharing plan section (NIH guidance on these plans is available here: https://osp.od.nih.gov/wp-content/uploads/NIH_Guidance_Developing-GDS_Plans.pdf)
- **Institutional Certification** from the Office of Sponsored Programs (templates available here: <https://osp.od.nih.gov/scientific-sharing/institutional-certifications/>). Certification must be provided for all sites contributing samples. If more than one site is contributing samples, the primary site may submit one certification on behalf of all collaborating sites (or each site may provide their own certification if this is the site's preference). This certification assures that:
 - The data submission is consistent with applicable national, tribal, and state laws and regulations, and institutional policies;
 - Any limitations on the research use of the data, as expressed in the informed consent documents, are delineated within the certification;
 - The identities of research participants will not be disclosed to the repositories;
 - An IRB and/or Privacy Board has reviewed the investigator's proposal for data submission and assures that:
 - the protocol for the collection of genomic and phenotypic data is consistent with human subjects regulations;
 - data submission and subsequent data sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained;
 - consideration was given to the risks to participants and their families, and, to the extent relevant and possible, to groups or populations associated with the submission and subsequent sharing of the data; and
 - the investigator's plan for de-identifying datasets is consistent with the standards outlined in the [NIH Genomic Data Sharing \(GDS\) Policy](#)
- **In situations where the sharing of human data is not possible** (i.e., the Institutional Certification criteria cannot be met), a justification is required to explain why these data cannot be shared, and an alternative data sharing plan will need to be provided. Exceptions to NIH expectations for data submission to an NIH-designated data

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repository will be considered on a case-by-case basis by the NIH funding Institute or Center (IC).

Investigators who wish to use controlled-access human genomic data from NIH-designated data repositories (e.g., dbGaP) should briefly address their plans for requesting access to the data and state their intention to abide by the NIH Genomic Data User Code of Conduct in the Research Plan of the application. The code of conduct is available here:

https://osp.od.nih.gov/wp-content/uploads/Genomic_Data_User_Code_of_Conduct.pdf .

Access to controlled-access data is dependent on an approval process that involves the relevant NIH Data Access Committee(s). Applicants may wish to secure access to the data prior to submitting their application for NIH support. Secondary users of controlled-access data are not expected to deposit their findings into NIH-designated data repositories, unless appropriate.

Investigators who wish to use/download data from NIH unrestricted-access repositories, including non-sensitive GSR:

- Should use the data to promote scientific research or health;
- Should not use the data to re-identify individuals or generate information that could allow participant's identities to be readily ascertained; and
- In all oral and written presentations, disclosures, or publications, acknowledge the specific dataset or accession numbers and the repository through which the data were accessed.

Procedures for submitting data into, or requesting access for data from an NIH-designated repository, are available here: <https://osp.od.nih.gov/scientific-sharing/researchers-institutional-certifications/>.

25.7 Department of Defense

NOTE: See BRANY IRB SOPs for additional details regarding compliant IRB review of DoD Research, including additional protections for vulnerable subjects (additionally including military personnel and DoD Civilians).

The U.S. Department of Defense (DoD) is a signatory to the Common Rule with regulations equivalent to 45 CFR 46 published under [32 CFR 219](#). Research conducted or supported by DoD is subject to additional requirements for investigators and for reviewing IRBs. These requirements are outlined in this section.

DoD support of a study includes funds or assistance by the DoD through a grant, contract, or similar agreement, and also includes provision of assistance such as facilities, equipment, personnel (investigators or other personnel performing tasks identified in the research protocol), access to or information about DoD-affiliated personnel for recruitment, or data or specimens.

NJH assures that DoD supported research will be conducted in compliance with all relevant DoD

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human subjects protection requirements, including but not limited to:

- [DoD Instruction \(DoDI\) 3216.02](#), “Protection of Human Subjects and Adherence to Ethical Standards in DoD-supported Research”
- Subparts B, C, and D of 45 CFR 46 with modifications as described in DoDI 3216.02 (see Section 28.9.7 below for details)
- Title 10 United States Code Section 980 ([10 U.S.C. 980](#)), “Limitation on Use of Humans as Experimental Subjects”
- [DoDI 3210.7](#), “Research Integrity and Misconduct”
- [DoDI 6200.2](#), “Application of Food and Drug (FDA) Rules to Department of Defense Force Health Protection Programs”
- Any additional applicable requirements from the respective DoD component (e.g., [Army](#), [Navy](#), [Air Force](#), [Marine Corps](#), Defense Intelligence Agency, National Security Agency, etc.)

It is the responsibility of the PI to ensure compliance with DoD requirements for human subject protection.

25.7.1 Activities Not Considered Human Subjects Research (‘excluded activities’)

In addition to the activities deemed “Not Research” in the 2018 Common Rule, the following activities conducted or supported by the DoD are not considered Human Subjects Research (HSR):

- Activities carried out solely for purposes of diagnosis, treatment, or prevention of injury and disease under force health protection programs of DoD, including health surveillance pursuant to 10 U.S.C. 1074f, and the use of medical products consistent with DoDI 6200.02.
- Health and medical activities as part of the reasonable practice of medicine or other health professions undertaken for the sole purpose of diagnosis, cure, mitigation, treatment, or prevention of disease in a patient.
- Activities performed for the sole purpose of medical quality assurance (see 10 U.S.C. 1102, and DoDI 6025.13).
- Activities that meet the definition of operational test and evaluation as defined in 10 U.S.C 139(a)(2)(A).
- Activities performed solely for assessing compliance, including occupational drug testing, occupational health and safety reviews, network monitoring, and monitoring for compliance with requirements for protection of classified information.
- Activities, including program evaluation and surveys, user surveys, outcome reviews, and other methods, designed solely to assess the performance of DoD programs where the results are only for the use of government officials responsible for the operation or oversight of the program being evaluated.

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25.7.2 Single (sIRB) Mandate

Effective 20 January 2020, any institution located in the U.S. that is engaged in multi-site cooperative human subjects research must rely upon approval by a single IRB for that portion of the research that is conducted in the U.S. unless the relevant DoD Component Office of Human Research Protections (COHRP) determines and documents that use of a single IRB is not appropriate for the particular context of the proposed research. Studies already in progress before January 20, 2020 are not required to transition to a single IRB.

When any institution relies upon another institution's IRB for DoD research, there must be a written agreement defining the responsibilities and authorities of each organization in complying with the terms of each institution's Federal Assurance and DoDD 3216.02. When appropriate, the lead institution or reviewing IRB may take responsibility for required DoD reporting.

The primary awardee (lead institution) of a DoD-conducted or supported research proposal that includes a multi-site, cooperative effort is responsible for developing a plan for coordinating all collaborating sites' reliance on a single IRB for DoD-supported multi-site cooperative research.

25.7.3 Education and Training

All personnel involved in the conduct of DoD research must complete initial and continuing education in the protection of human subjects as described in this manual (see Section 3) and relevant sections of BRANY IRB SOPs. Personnel must also familiarize themselves with DoD's specific requirements by reviewing these SOPs, DoDI 3216.02, and any relevant materials specific to the DoD component. The DoD component may require additional education and/or certification to ensure that personnel are qualified to perform the research.

25.7.4 Selection of Subjects

The selection of human subjects in DoD-conducted or supported research must comply with Section 252 (Inclusion of Women and Minorities in Clinical Research Projects) of the [National Defense Authorization Act for Fiscal Year 1994](#) (Public Law 103-160), with respect to gender, minority participation, and membership in the Armed Services unless this requirement is waived by the Secretary of Defense, or, when delegated, by the relevant DoD Component.

25.7.5 Evaluating Risk

Minimal Risk is defined in the Common Rule (at 32 CFR 219) as meaning that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

However, per DoDI 3216.02, this definition may not be interpreted to include the inherent occupational risks that certain subjects face in their everyday life, such as those:

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- Encountered by Service members, law enforcement, or first responders while on duty.
- Resulting from or associated with high-risk behaviors or pursuits.
- Experienced by individuals whose medical conditions involve frequent tests or constant pain.

25.7.6 Informed Consent/HIPAA Authorization

25.7.6.1 Additional Consent/Authorization Elements

When consent is to be obtained from subjects in DoD-conducted or supported research, the following additional information should be provided to potential subjects in the consent document when applicable unless the requirement is waived by the DoD:

- A statement that the DoD or DoD component is conducting or supporting the research.
- A statement that representatives of the DoD are authorized to review research records.
- If the research involves DoD-affiliated personnel as subjects and includes any risks to their fitness for duty (e.g., health, availability to perform job, data breach), the consent must inform DoD-affiliated personnel about these risks and that they should seek command or Component guidance before participating.
- If the research involves DoD-affiliated personnel as subjects, the consent must include, if applicable, potential risks for the revocation of clearance, credentials, or other privileged access or duty.
- If a Certificate of Confidentiality (CoC) is in place, exceptions to the CoC must be listed.
- If the research is greater than minimal risk and is conducted by the DoD, the explanation regarding the availability of compensation and medical treatments for research-related injuries must include a statement that subjects may, for the duration of the study, be eligible for health care services for research-related injuries at a military treatment facility, in accordance with 32 CFR 108. This eligibility for health care services extends beyond subjects' participation in the study to such time after the study has ended.

When HIPAA authorization is to be obtained, the authorization should include a statement that protected health information may be disclosed to representatives of the DoD.

25.7.6.2 Limitation of Waivers and Alterations of Informed Consent

10 U.S.C. 980 addresses requirements related to informed consent, or the waiver thereof, for research supported by DoD funds that involves a human being as an experimental subject.

Per DoDI 3216.02, research involving a human being as an experimental subject is defined as:

“An activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human

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subjects.”

This definition relates only to the application of 10 U.S.C. 980 (see above); it does not affect the application of the Common Rule at 32 CFR 219.

When non-exempt research involving a human being as an experimental subject is supported or conducted by the DoD, informed consent must be obtained in advance from the experimental subject or their LAR if the subject cannot consent. If consent is to be obtained from a LAR, the research must be intended to be beneficial to the subject.

The requirement for advanced informed consent may be waived by the DoD Office for Human Research Protections (DOHRP) or its delegate if the following conditions are met:

- The research is to advance the development of a medical product necessary to the DoD;
- The research may directly benefit the individual experimental subject; and
- The research is conducted in compliance with all other applicable laws and regulations.

If the research involves no more than minimal risk, an IRB may alter or waive other required elements of informed consent so long as it still preserves informed consent of the subject (i.e., the consent indicates the subject’s participation in the research is completely voluntary and includes the requirement that the subject is informed of research risks).

25.7.6.3 Posting of Clinical Trial Informed Consent Forms

When DoD-conducted or supported research is a clinical trial as defined at 32 CFR 219.02(b), the DoD Component Office for Human Research Protections (COHRP) has the authority to review and determine appropriate redactions prior to posting informed consent forms pursuant to 32 CFR 219.116(h).

25.7.7 Additional Protections for Human Subjects

25.7.7.1 Pregnant Women, Fetuses, or Neonates as Subjects

Non-exempt research involving pregnant women, fetuses, or neonates as subjects must meet the requirements of Subpart B of 45 CFR 46, with the following modifications:

- The applicability of Subpart B is limited to research involving pregnant women in research that is greater than minimal risk and that includes interventions or invasive procedures involving
 - o The woman or the fetus; or
 - o Fetuses or neonates as subjects.
- For purposes of applying Subpart B, the phrase “biomedical knowledge” is replaced with “generalizable knowledge.”
- Research using fetal tissue must comply with 42 U.S.C 289g – 289g-2.

Explicit written approval is required from the DOHRP before the research begins for research that would not otherwise be approvable under Subpart B but presents an opportunity to understand,

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prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

25.7.7.2 Prisoners as Subjects

Research involving prisoners as subjects must meet the requirements of Subpart C of 45 CFR 46, with the following modifications:

- In addition to the four allowable categories of research involving prisoners in Subpart C, two additional categories are allowable:
 - o Certain epidemiological research in accordance with the HHS waiver published in Federal Register, Volume 68 pages 36929-36931 that meets the requirements of 45 CFR 46 Subpart C, DoDD 3216.02, and other applicable requirements.
 - o Research that would meet the criteria for exemption described at 32 CFR 219.104, but such research must first be approved by an IRB and meet the requirements of 45 CFR 46 Subpart C, DoDD 3216.02, and other applicable requirements.
- When a previously enrolled human subject becomes a prisoner, and the research was not previously approved for the inclusion of prisoners:
 - o The PI must promptly notify the IRB, and
 - o The Institution must notify the HRPO and other federal agencies (if required).

25.7.7.3 Children as Subjects

Research involving children as subjects must meet the requirements of Subpart D of 45 CFR 46 and 21 CFR 50.54, if applicable.

25.7.7.4 Detainees or Prisoners of War

Research involving a detainee or a prisoner of war as a human subject is prohibited.

This prohibition does not apply to activities covered by the IND or IDE provisions of the FDA regulations at Title 21, CFR, when the purpose is for diagnosis or treatment of a medical condition in a patient. Such treatment may be offered to detainees or prisoners of war with their informed consent when the medical products are subject to Title 21, CFR, and only when the same product may be available to DoD-affiliated personnel consistent with established medical practices.

25.7.7.5 DoD-Affiliated Personnel as Subjects

The recruitment and inclusion of DoD-affiliated personnel (i.e., Service members, Reserve Service members, National Guard members, DoD civilians, and DoD contractors) in research must be approached with care and in accordance with the requirements of DoDI 3216.02 and any applicable DoD-component requirements.

Researchers who intend to recruit DoD-affiliated personnel are advised to seek collaboration with a military investigator who will be familiar with DoD and service-specific requirements. A letter of

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support from Commanders of military facilities or units in which recruitment will occur or the study will be conducted may be required by the HRPO. Some military sites may also require that personnel seek written permission from their supervisor prior to participation in research.

Specific requirements of DoDI 3216.02 include the following:

- If the research involves DoD-affiliated personnel as subjects, and the research includes any risks to their fitness for duty (e.g., health, availability to perform job, data breach), the informed consent document must inform DoD-affiliated personnel about these risks and that they should seek command or Component guidance before participating.
- If the research involves DoD-affiliated personnel, the key investigator (the person leading the performance of the research) must receive command or Component approval to execute the research.
- Military and civilian supervisors, officers, and others in the chain of command are prohibited from influencing their subordinates to participate in research.
- Military and civilian supervisors, officers, and others in the chain of command must not be present at any recruitment sessions or during the consent process for DoD-affiliated personnel. Excluded supervisors or those in the chain of command may participate in separate recruitment sessions, if applicable.
- Service members and all Reserve Component and National Guard members in a federal duty status are considered for purposes of DoDI 3216.02, to be adults. If a Service member, Reserve Component or National Guard member in federal duty status, student at a Service Academy, or trainee is under 18 years of age, the IRB must carefully consider the recruitment process and the necessity of including such member as a human subject.
- In order to approve research involving DoD-affiliated personnel as human subjects, the IRB or HRPO must determine whether the following requirements have been satisfied:
 - The consent documentation must include, if applicable, potential risks for the revocation of clearance, credentials, or other privileged access or duty.
 - For research involving recruitment of DoD-affiliated personnel in greater than minimal risk research, and when recruitment occurs in a group setting, the IRB must appoint an ombudsperson. The ombudsperson:
 - Must not have a conflict of interest with the research or be a part of the research team.
 - Must be present during recruitment, monitoring that the recruitment and informed consent explain that participation is voluntary and that the information provided about the research is consistent with the IRB-approved script and materials, including digitally provided materials.
 - Should be available to address DoD-affiliated personnel's concerns about participation.

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- Compensation, including non-monetary compensation, to DoD-affiliated personnel for participation in research while on duty is prohibited other than compensation for blood draws (maximum of \$50 per blood draw) in accordance with 24 U.S.C. 30.

25.7.8 Research Involving Large Scale Genomic Data (LSGD) Collected on DoD-Affiliate Personnel

25.7.8.1 LSGD Definition

Data derived from genome-wide association studies; single nucleotide polymorphisms arrays; genome sequencing; transcriptomic, metagenomic, epigenomic analyses; and gene expression data; etc. Research involving LSGD may or may not also constitute human subjects research. Examples of research involving LSGD includes, but is not limited to, projects that involve generating the whole genome sequence data for more than one gene from more than 1,000 individuals or analyzing 100 or more genetic variants in more than 1,000 individuals.

25.7.8.2 Requirements for LSGD Research

DoD-conducted or supported research involving LSGD collected on DoD-affiliated personnel, or for which research the DoD provides assistance, is subject to the following additional requirements:

- The disclosure of DoD-affiliated personnel's genomic data may pose a risk to national security; accordingly, such research requires administrative, technical, and physical safeguards commensurate with risk, including the secondary use or sharing of de-identified data or specimens.
- All research involving LSGD collected from DoD-affiliated personnel must be covered by a Certificate of Confidentiality (CoC). Exceptions to the CoC must be listed in the informed consent form. For more information on CoC's see Section 28.3 of this manual.
- Research involving LSGD collected from DoD-affiliated personnel is subject to DoD Component security review to ensure the adequacy of the proposed administrative, technical, and physical safeguards, including the secondary use or sharing of de-identified data or specimens.

25.7.9 Chemical or Biological Agents

Human subjects research for the testing of chemical or biological agents is prohibited with exceptions for certain prophylactic, protective, or other peaceful purposes. Exceptions from the prohibition for such research must receive explicit written approval from the DOHRP.

25.7.10 International Research

When conducting human subjects research outside of the United States, the research must be conducted in accordance with U.S. federal and DoD regulatory requirements and the host nation's laws, as applicable. Host nation laws concerning human subjects research are not typically applicable to DoD-conducted research that only involves DoD-affiliated personnel as research subjects (unless also a citizen of that host nation). DoD Components will consult legal counsel to assess applicability of host nation laws for human subjects research. Where differences in applicable standards exist, the standard that is most

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protective of human subjects will be applied.

The key investigator must provide written notification to the U.S. Central, U.S. Africa, U.S. European, U.S. Indo-Pacific, and U.S. Southern Commands of human subjects research that is to be conducted or supported in their area of responsibility before the research may proceed. This does not apply to research performed within the U.S. or at DoD institutions overseas.

25.7.11 DoD HRPO Approval for Human Subjects Research

Written notification of approval from the relevant Component's Human Research Protection Official (HRPO) must be issued before research involving human subjects can begin. The HRPO provides administrative review and approval to confirm the research is compliant with federal and DoD requirements, including confirmation of local institution determinations of (a) research not involving human subjects; or (b) research involving human subjects that is exempt from the regulatory provisions of 32 CFR 219.

When a DoD IRB serves as the reviewing IRB, the DoD IRB approval will constitute the HRPO review; additional review by the HRPO is not required.

25.7.11.1 Non-Exempt Human Subjects Research (HSR)

For non-exempt HSR, the Institution will submit to the HRPO for the DoD Component conducting or supporting the research:

- Documentation that the DoD-supported HSR has been reviewed and approved by an IRB, including scientific merit, amendments, and additional reviews.
- Documentation of key investigators' human research protection training.
- IRB-approved protocol documents.
- Current FWA and IRB registration numbers.
- Any other information required by the Component.

25.7.11.2 NHSR and Exempt Human Subjects Research

For DoD-supported research that is exempt or does not involve human subjects, the Institution will submit to the HRPO documentation of the determination that the research is not HSR (NHSR), exempt HSR, or exempt HSR with limited IRB review to the HRPO. The submission will include all protocol documents (e.g., the protocol, consent form, subject materials, etc.).

25.7.12 Reporting Requirements

The Institution must promptly (i.e., no longer than within 30 days or as defined by the DoD Component) notify the HRPO of the following:

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- IRB-approved changes to research that involve:
 - I. changes to key investigators or institutions;
 - II. decreased benefit or increased risk to subjects in greater than minimal risk research;
 - III. addition of vulnerable populations, or DoD-affiliated personnel as subjects.

Note: Investigators should be aware that the DoD Component HRPO may require HRPO approval of IRB-approved changes to research before the changes are implemented.
- Transfer of IRB oversight to a different IRB.
- Notification by any federal body, State agency, official governing body of a Native American or Alaskan native tribe, other entity, or foreign government that the non-DoD institution's DoD-supported human subjects research is under investigation.
- Any problems involving risks to subjects or others, suspension or termination of IRB approval, or any serious or continuing noncompliance pertaining to DoD-supported research.
- The results of the IRB's continuing review, if required.
- Change in status when a previously enrolled human subject becomes pregnant, or when the researcher learns that a previously enrolled human subject is pregnant, and the protocol was not reviewed and approved by the IRB in accordance with Subpart B of 45 CFR 46.
- Change in status when a previously enrolled human subject becomes a prisoner, and the protocol was not reviewed and approved by the IRB in accordance with Subpart C of 45 CFR 46.
- A DoD-supported study's closure.

25.7.13 Addressing and Reporting Allegations of Noncompliance

NJH must respond to allegations of noncompliance with DoDI 3216.02 or other requirements and conduct an investigation in accordance with the agreement in place with relevant DoD component. Allegations of noncompliance must be promptly and properly investigated. Substantiated serious and/or continuing non-compliance findings must be promptly reported to the DoD Component via the Component HRPO. If the research is classified, substantiated allegations must be reported immediately.

25.7.14 Addressing and Reporting Allegations of Research Misconduct

NJH will adhere to the requirements of DoDI 3210.7 "Research Integrity and Misconduct", the requirements of the relevant DoD Component, and the terms of any DoD award, contract, or other agreement when allegations or findings of research misconduct arise.

25.7.15 Recordkeeping Requirements

The Common Rule requires all institutions engaged in DoD-conducted or supported human subjects research to retain records for at least 3 years after the completion of the research, or longer if required by DoD Manual 6025.18, the Privacy Act, FDA regulations, or other applicable requirements. Investigators should consult with

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the Component HRPO regarding record-keeping requirements for their research.

Records maintained by this institution that document compliance or noncompliance with DoD regulations must be accessible for inspection and copying by authorized representatives of the DoD.

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