



Human Research Protection Program &
Institutional Review Board
(HRPP/IRB)
Standard Operating Procedures

-January 2019-

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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Table of Contents

1	Human Research Protection Program	12
1.1	Mission	12
1.2	Organizational Authority	12
1.3	Definitions	12
1.4	Ethical Principles	16
1.5	Regulatory Compliance	16
1.5.1	Management of pre-existing studies once the revised Common Rule ('2018 Rule') goes into effect ...	16
1.6	International Conference on Harmonization-Good Clinical Practice (ICH-GCP)	17
1.7	Federalwide Assurance (FWA) and IRB Registration	17
1.8	Research Under the Auspices of National Jewish Health	17
1.9	Written Procedures	18
1.10	National Jewish Health HRPP Structure.....	19
1.10.1	Institutional Official.....	19
1.10.2	Director of Research Regulatory Affairs (RRA)	20
1.10.3	HRPP Staff.....	21
1.10.4	Institutional Review Board (IRB).....	21
1.10.5	Legal Counsel	22
1.10.6	Chief Compliance Officer (CCO):.....	22
1.10.7	Department Chairs and/or Organizational Leaders.....	22
1.10.8	Principal Investigators	22
1.10.9	Other Related Units.....	23
1.10.10	Relationship Among Components	24
1.10.11	Study-Specific Coordination	24
2	Quality Assurance	24
2.1	External Monitoring, Audit, and Inspection Reports	24
2.2	Investigator Compliance Reviews	25
2.3	IRB Compliance Reviews	26
2.4	HRPP Quality Assessment and Improvement.....	26

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.

3	Education & Training	27
3.1	Training / Ongoing Education of NJH IRB Co-Chairs, Members, and Staff	27
3.2	Training / Ongoing Education of Investigators and Research Team	28
3.2.1	Initial Education	28
3.2.2	Continuing Education	29
4	“Human Subjects” and “Research” Determinations	29
5	Exempt Determinations	30
5.1	Limitations on Exemptions	31
5.2	Categories of Exempt Research	31
5.3	FDA Exemptions	33
5.4	Procedures for Exemption Determination	34
6	Multi-site and Collaborative Research	35
7	Research Previously Approved By An External IRB	36
8	IRB Reliance Arrangements in Multi-Site Research	36
8.1	Reliance Agreements	36
8.2	NJH Serving as the Reviewing IRB.....	37
8.2.1	Factors Considered by the HRPP Office to have NJH provide IRB Services	37
8.2.2	Responsibilities when NJH is the Reviewing IRB	38
8.3	NJH Ceding IRB Review to an External IRB	39
8.3.1	Standing Reliance Agreements	39
8.3.2	Factors Considered by the HRPP Office in the decision to allow NJH to Cede to an External IRB	39
8.3.3	NJH, External IRB, and NJH Investigator Responsibilities When NJH Cedes Review	40
8.3.4	Institutional Registration Requirement:	40
8.3.5	Post-IRB Approval Requirements:	41
8.4	Exceptions to IRB vs. Local Site Responsibilities	41
9	NIH Single IRB (sIRB) for Multi-Site Research	42
9.1	Selection and Designation of a sIRB	42
9.2	Reliance Agreements for sIRB Studies	42
9.3	sIRB Responsibilities.....	43
9.4	Participating Site Responsibilities	43

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.

10 NJH Institutional Review Board	44
10.1 IRB Authority	44
10.2 Roles and Responsibilities	45
10.2.1 Co-Chairs of the IRB	45
10.2.2 IRB Members	45
10.2.3 Alternate IRB members	46
10.2.4 Subcommittees of the IRB	46
10.2.5 Composition of the IRB Membership.....	46
10.3 Appointment of Members to the IRB	47
10.4 Liability Coverage for IRB Members.....	48
10.5 Use of Consultants.....	48
10.6 Reporting and Investigation of Allegations of Undue Influence	48
11 IRB Actions, Failure to Respond, Appeals	48
11.1 IRB Actions	48
11.2 Failure to Respond.....	50
11.3 Reporting IRB Actions	50
11.4 Appeal of IRB Decisions	50
12 IRB Review Process	51
12.1 Expedited Review	51
12.1.1 Definitions	51
12.1.2 Categories of Research Eligible for Expedited Review	52
12.1.3 Expedited Review Procedures	54
12.1.4 Informing the IRB.....	55
12.2 Convened IRB Meetings.....	55
12.2.1 IRB Meeting Schedule.....	55
12.2.2 Preliminary Review	55
12.2.3 Primary and Secondary Reviewers.....	56
12.2.4 Materials received by the IRB	56
12.2.5 Quorum	57
12.2.6 Meeting Procedures	58

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.

12.2.7	Guests	58
12.3	Criteria for IRB Approval of Research	58
12.4	Risk/Benefit Assessment	59
12.5	Scientific or Scholarly Review	60
12.6	Equitable Selection of Subjects	60
12.7	Recruitment of Subjects	61
12.8	Informed Consent	61
12.9	Data and Safety Monitoring.....	61
12.10	Privacy and Confidentiality.....	62
12.10.1	Definitions	62
12.10.2	Privacy.....	63
12.10.3	Confidentiality.....	63
12.11	Vulnerable Populations.....	64
12.12	Additional Considerations	64
12.12.1	Determination of Risk Level	64
12.12.2	Period of Approval	64
12.12.3	Review More Often Than Annually	65
12.12.4	Independent Verification That No Material Changes Have Occurred.....	66
12.12.5	Consent Monitoring.....	67
12.12.6	Investigator Qualifications.....	68
12.12.7	Significant New Findings	68
12.12.8	Conflicts of Interest (COI)	68
12.12.9	Advertisements and Recruitment Materials.....	68
12.12.10	Payments and Reimbursements.....	69
12.12.11	Non-Monetary Gifts and Incentives.....	70
12.12.12	State and Local Laws	71
12.13	Continuing Review	71
12.13.1	Continuing Review Process	72
12.13.2	IRB Considerations for Continuing Review	73
12.13.3	Convened Board Review	73

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.

12.13.4	Expedited Review	73
12.13.5	Possible IRB Actions after Continuing Review	74
12.13.6	Lapses in Continuing Review	74
12.14	Modification of an Approved Protocol.....	75
12.14.1	Procedures.....	76
12.14.2	Possible IRB Actions after Modification Review	77
12.15	Protocol Exceptions	77
12.16	Closure of Research Studies.....	77
13	Suspensions and Terminations	78
13.1	Definitions	78
13.2	Protection of Currently Enrolled Participants.....	79
14	Documentation and Records.....	79
14.1	IRB Records.....	80
14.2	IRB Protocol Files	80
14.3	The IRB Minutes.....	82
14.4	IRB Membership Roster	83
14.5	Documentation of Exemptions.....	84
14.6	Documentation of Expedited Reviews.....	84
14.7	Access to IRB Records.....	85
14.8	Record Retention.....	85
15	Obtaining Informed Consent from Research Subjects	85
15.1	General Requirements	86
15.2	Additional Requirements.....	87
15.3	Legally Authorized Representative (LAR).....	87
15.4	Basic Elements of Informed Consent	88
15.5	Additional elements of informed consent to be applied, as appropriate:.....	89
15.6	NJH Requirements.....	90
15.7	Subject Withdrawal or Termination	90
15.8	Documentation of Informed Consent.....	91
15.9	Special Consent Circumstances.....	92

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.

15.9.1	Enrollment of persons with Limited English Proficiency.....	92
15.9.2	Braille consent.....	93
15.9.3	Consenting in American Sign Language (ASL)	93
15.9.4	Oral Consent	93
15.9.5	Physically-Challenged Subjects.....	93
15.10	Waiver or Alteration of Informed Consent.....	94
15.10.1	Screening, recruiting, or determining eligibility	95
15.11	Waiver of Documentation of Informed Consent.....	95
15.12	Waiver of Informed Consent for Planned Emergency Research	96
15.12.1	Definitions	96
15.12.2	Procedures.....	96
15.12.3	FDA-regulated Planned Emergency Research.....	98
15.12.4	Documentation and Reporting of Planned Emergency Research Not Subject to FDA Regulations	98
15.13	Posting of Clinical Trial Consent Forms.....	98
16	Vulnerable Subjects in Research	99
16.1	Definitions	99
16.2	Involvement of Vulnerable Populations in Research	100
16.3	Procedures.....	101
16.3.1	Initial Review of Research Proposal:.....	101
16.3.2	Modifications to Research.....	101
16.3.3	Continuing Review	102
16.4	Research Involving Pregnant Women, Human Fetuses and Neonates.....	102
16.4.1	Research Involving Pregnant Women or Fetuses.....	102
16.4.2	Research involving Neonates of Uncertain Viability or Nonviable Neonates.....	104
16.4.3	Viable Neonates	106
16.4.4	Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material	106
16.4.5	Research Not Otherwise Approvable	107
16.5	Research Involving Prisoners.....	107
16.5.1	Applicability	107

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.

16.5.2	Minimal Risk.....	108
16.5.3	Composition of the IRB.....	108
16.5.4	Review of Research Involving Prisoners	108
16.5.5	Additional Duties of the IRB	109
16.5.6	Certification to DHHS	110
16.6	Research Involving Children	111
16.6.1	Allowable Categories.....	111
16.6.2	Parental Permission and Assent.....	113
16.6.3	Documentation of Assent.....	115
16.6.4	Children Who are Wards	115
16.7	Adults with Impaired Decision Making Capacity	116
16.7.1	Informed Consent	116
16.7.2	Decision-Making Capacity	116
16.7.3	Inclusion of Adults with Impaired Decision-Making Capacity in Research	117
16.7.4	IRB Review	118
17	FDA-Regulated Research.....	119
17.1	Definitions	119
17.2	FDA Exemptions.....	121
17.3	Investigator Responsibilities.....	121
17.4	Dietary Supplements.....	123
17.5	Clinical Investigations of Articles Regulated as Drugs or Devices	123
17.5.1	IND/IDE Requirements	123
17.5.2	IND Exemptions.....	124
17.5.3	IDE Exemptions.....	126
17.5.4	Significant and Non-Significant Risk Device Studies.....	127
17.6	Diagnostic or Treatment Use of Humanitarian Use Devices	128
17.6.1	Definitions	128
17.6.2	IRB Review Requirements.....	128
17.6.3	Procedures.....	129
17.6.4	Emergency Uses of HUDs	130

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.

17.7	Expanded Access to Investigational Drugs, Biologics, and Devices	131
17.7.1	Expanded Access to Investigational Drugs and Biologics	131
17.7.2	Expanded Access to Investigational and Unapproved/Uncleared Medical Devices.....	134
17.7.3	Treatment Use of Investigational/Unapproved Medical Devices	136
17.8	Emergency Uses	137
17.8.1	Emergency Use of Investigational Drugs.....	137
17.8.2	Emergency Use of Investigational Devices	138
17.8.3	Emergency Exception from the Informed Consent Requirement.....	139
17.9	Charging Subjects for Investigational Products	140
17.9.1	Charging for Investigational Medical Devices and Radiological Health Products	140
17.9.2	Charging for Investigational Drugs and Biologics	140
18	Unanticipated Problems Involving Risks to Subjects or Others	140
18.1	Definitions	141
18.2	Procedures.....	141
18.2.1	Reporting	141
18.2.2	Review Procedures.....	143
19	Noncompliance.....	144
19.1	Definitions	144
19.2	Reporting	145
19.3	Review Procedures.....	145
20	Complaints	146
21	Other Reportable Information.....	147
21.1	Review Procedures	148
22	Reporting to Federal Agencies, Departments, and Organizational Officials	148
22.1	Procedures.....	148
23	Investigator Responsibilities	150
23.1	Responsibilities.....	150
23.2	Record Retention	152
23.3	Investigator Concerns	152
24	Sponsored Research.....	153

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.

24.1	Definitions	153
24.2	Responsibility	153
25	Conflict of Interest in Research.....	154
25.1	Researcher Conflicts of Interest	154
25.1.1	Procedures.....	154
25.2	IRB Member Conflict of Interest.....	155
25.3	Institutional Conflict of Interest	156
25.3.1	Definition of Institutional Financial Conflicts of Interest	156
25.3.2	Reporting	157
25.3.3	Review and Evaluation	158
25.3.4	Conflict Management Plan	158
25.3.5	Timing	158
25.4	Recruitment Incentives	159
26	Participant Outreach	159
26.1	Outreach Resources and Educational Materials.....	159
26.2	Evaluation	159
27	Health Insurance Portability and Accountability Act (HIPAA).....	160
27.1	Definitions	160
27.2	The IRB's Role under the Privacy Rule	163
27.3	Authorization	164
27.4	Waiver or Alteration of the Authorization Requirement.....	165
27.5	Activities Preparatory to Research.....	166
27.6	Research Using Decedent's Information	167
27.7	Storage and Use of PHI for Future Research.....	167
27.8	Corollary and Sub-studies.....	168
27.9	De-identification of PHI under the Privacy Rule.....	168
27.10	Limited Data Sets and Data Use Agreements	170
27.11	Research Subject Access to PHI	171
27.12	Revoking Authorization.....	171
27.13	Accounting of Disclosures.....	172

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.

27.14	Breach/Unauthorized Disclosure Notification and Reporting.....	172
28	Special Topics	173
28.1	Mandatory Reporting.....	173
28.2	Certificates of Confidentiality.....	173
28.2.1	Definitions	174
28.2.2	Protections and Requirements	174
28.2.3	NIH and CDC	175
28.2.4	IRB Review	176
28.3	Case Reports	177
28.4	Databases, Registries, & Repositories	177
28.4.1	Non-research Repositories	178
28.4.2	Research Repositories	178
28.5	Research Involving or Generating Genetic Information	180
28.5.1	Genetic Information Nondiscrimination Act (GINA).....	181
28.6	Genomic Data Sharing	182
28.6.1	Definitions	183
28.6.2	Procedures.....	183
28.7	Department of Defense	186
28.7.1	Key DoD Standards and Requirements.....	187
28.7.2	Additional Requirements for DoD Research	192
28.8	International Research	193
28.8.1	IRB Responsibilities	194
28.8.2	Investigator Responsibilities.....	194
28.8.3	Consent Documents.....	195
28.8.4	Monitoring of Approved International Research	195

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.

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 IRB members, 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 the NJH Institutional HRPP Policy. As stated in that policy, the operating procedures in this document "...serve as the governing procedures for the conduct and review of all human research conducted under the auspices of the NJH." These standard operating procedures 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 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

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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 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\(b\)](#)]

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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 27].
- **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 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.

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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."
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 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).

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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 28), 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](#).

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 pre-existing studies once the revised Common Rule ('2018 Rule') goes into effect

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.

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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) and IRB Registration

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.

Likewise, federal regulations require IRBs to register with DHHS if they will review human subjects research conducted or supported by DHHS or research subject to FDA regulations.

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

National Jewish Health's Federal Registration Numbers	
FWA	FWA00000778
IORG	IORG0000018
IRB Registration	IRB00000024

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 NJH 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.

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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 an NJH- designated IRB. 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 Staff prior to initiating any research activities at or involving NJH.

The Director of RRA, IRB Co-Chairs, with the assistance of the HRPP staff and the Compliance and Regulatory Affairs Office as needed, are authorized to determine whether NJH is engaged in a particular research study. 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

These SOPs for Human Research Protection detail the procedures, standards, and requirements for research with human subjects under the auspices of NJH and the requirements of the NJH IRB. This is not a static document. The SOPs are reviewed at a minimum of annually and revised by the Director of RRA 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 and within the IRB’s electronic system. Changes to the SOPs are communicated to investigators and research staff, and IRB members and HRPP Staff by way of emails, and other forums, as appropriate.

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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, the Director of Research Regulatory Affairs, the NJH IRB, Research Administration, legal counsel, the Institutional Biosafety Committee (IBC), Research Radiation Safety Committee (RSC), Corporate Compliance Officer (for individual and Institutional COI), HRPP Staff, 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, Executive Director of Compliance and Regulatory Affairs is the Institutional Official. The IO is responsible for ensuring that the NJH HRPP and NJH IRB have the resources and 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 the IRB, investigators, and staff receive training related to human research protections.

At a minimum of annually, the IO reviews the HRPP SOPs and IRB functions, 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;
- Ensuring that the NJH IRB functions independently by, among other mechanisms, being directly accessible to the IRB Chair(s) and members if they experience undue influence or if they have concerns about the function of the IRB;
- Oversight of the NJH Institutional Review Board (IRB);
- Oversight over the conduct of human subjects research under the auspices of National Jewish Health;

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- Providing training and educational opportunities for NJH IRB members and staff to support their ability to review 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 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 Staff will support the continuing education of the IO by providing information and updates on topics 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 Director of RRA and NJH IRB Chair have access to the IO for any concerns or issues related to the HRPP or NJH IRB.

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 Director of Research Regulatory Affairs (RRA)

The Director of Research Regulatory Affairs (RRA) is selected by, and reports to, the Institutional Official (IO) and 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 the NJH IRB;
- Advising the IO on key matters regarding human subjects research;
- Implementing the organization's HRPP SOPs;
- Overseeing the administration of the HRPP and NJH IRB, including the supervision of HRPP staff;
- 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);
- Managing the finances of the NJH RRA Office and NJH IRB;
- Assisting the NJH 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;

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- 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 RB members, 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
- Serving as an internal expert resource for questions and other matters regarding the protection of human subjects.

1.10.3 HRPP Staff

In addition to the leadership structure described above, the staffing for the HRPP and IRB includes NJH IRB Coordinator, External IRB Coordinator, and Quality Assurance and Education Manager. The HRPP staff for NJH must comply with all ethical standards and practices. The duties and responsibilities for all staff are found in their respective job descriptions, and their performance is evaluated on an annual basis. The NJH HRPP Staff report to the Director of RRA, who has day-to-day responsibilities for its operations.

1.10.4 Institutional Review Board (IRB)

NJH has one internal IRB, appointed by the Institutional Official (IO). The 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. 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.

As part of their responsibilities, the NJH IRB also confirms that resources are available for the study to be conducted safely and that the study has 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.

The NJH IRB functions independently of, but in coordination with, other organizational committees and officials. The NJH IRB, however, makes independent determinations whether to approve, require modification in, or disapprove research based upon whether human subjects are adequately protected.

Research that has been reviewed and approved by the NJH IRB may be subject to review and disapproval by officials of the organization. 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.

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1.10.5 Legal Counsel

The NJH relies on 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.

1.10.6 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 EVP and Chief Operating Officer (COO). The process outlined in the NJH Conflict of Interest and Commitment Policy is followed. Section 25 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.

1.10.7 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 approval of research that is proposed for funding by an external agency.

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

- The basis for the request

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- 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.

1.10.9 Other Related Units

1.10.9.1 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.

Grants and Contracts will confirm that the contract and the consent documents are consistent in terms of costs to subjects and who pays in case of injury. Sponsored Programs Administration and the IRB office coordinate efforts to ensure that all applicable individuals have filed appropriate COI disclosures to meet investigator COI policies.

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.

1.10.9.2 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, whether conducted inpatient or outpatient. The manufacture/compounding of drug products not commercially available is coordinated by NJH pharmacy. Waivers from use of the NJH pharmacy's policy of handling investigational drugs or biologics will be considered on a case by case basis by the Pharmacy director or designee, with review of required information from the PI

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regarding storage, accounting, dispensing etc. Documentation of waiver approval is forwarded to the IRB for placement in the study file.

The management of study drugs is guided by the Pharmacy Policy “Proper Control, Storage, Use and Handling of Investigational Drugs, Devices, and Biologics”.

1.10.10 Relationship Among Components

The RRA Office is the hub through which IRB (NJH or external) approval is requested and obtained by all NJH investigators. This centralized process also involves granting impacted components access to the IRB submission for review and allowance of the research activity in question to commence.

1.10.11 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
- Pharmacy
- Facilities where research activities will occur
- Records access permissions (e.g., Medical/Educational Records)
- Institutional Biosafety Committee
- Corporate Compliance Office (for COI)

Documentation of permission or approval may be required as a component of the IRB (NJH or external) application. The Director of RRA 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 (NJH or external).

2 Quality Assurance

The NJH HRPP staff 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 External Monitoring, Audit, and Inspection Reports

The RRA Office should be notified in advance, whenever possible, of upcoming audits or inspections of research whether the study is reviewed by the NJH IRB or an external IRB on NJH’s behalf. HRPP Office representatives

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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.

When research is under the oversight of the NJH IRB, all reports from external monitors, auditors, or inspectors must be submitted to the RRA Office for review. HRPP staff will forward reports with findings to the Director of RRA and IRB Co-Chair or designee, 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 convened NJH IRB to determine what additional actions are necessary, if any.

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

2.2 Investigator Compliance Reviews

HRPP Staff and, on occasion, other internal or external staff, conduct post-approval directed (for cause) and routine (not for cause) compliance reviews of human subjects research conducted under the auspices of NJH. Additionally, the NJH IRB may appoint a subcommittee for the purpose of conducting a for-cause or not for-cause compliance review of one or more research plans under its jurisdiction. The subcommittee may be composed of NJH IRB (when the NJH IRB is the IRB of record) members and HRPP staff from within, or individuals from and outside of the organization.

Compliance reviews are conducted to assess investigator compliance with federal, state, and local law, and NJH policies, and to identify areas for improvement, and to provide recommendations based on existing policies and procedures, and SOPs. The results of compliance reviews will be reported to the Director of RRA, the NJH IRB (when the IRB is the IRB of record), the investigator, and other NJH leadership, as appropriate. Any IRB (NJH or external) reporting and 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 Director of RRA.

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

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- 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.

2.3 IRB Compliance Reviews

HRPP Staff, or, on occasion, other internal or external staff, will periodically review the activities of the NJH IRB to assess compliance with regulatory requirements and to identify areas for improvement; this will include a review of NJH IRB records at least annually.

Review activities may include:

- Review of the NJH IRB minutes to evaluate whether adequate documentation of the meeting discussion and any required determinations has occurred and that quorum was met and maintained
- Reviewing NJH RB files to evaluate whether adequate documentation of exemptions, expedited review, and other outside of committee reviews has occurred
- Reviewing consent forms to evaluate whether all required elements are included
- Reviewing the NJH IRB databases to evaluate whether all required fields are completed accurately
- Verifying NJH RB approvals for external sites or investigators
- Reviewing metrics (for example, time from submission to first review) to evaluate the quality, efficiency, and effectiveness of the NJH IRB review process
- Reviewing the workload of the NJH IRB and HRPP Staff
- Other review activities as appropriate

The Director of RRA and IRB Co-Chair will review the results of IRB compliance reviews with the IRB and the Institutional Official. If substantive deficiencies are identified in the review, a corrective action plan will be developed by the Director of RRA, IRB Co-Chair and approved by the IO. The Director of RRA will have responsibility for implementing and reporting progress on the corrective action plan, the results of which will be evaluated by the IO.

2.4 HRPP Quality Assessment and Improvement

Annually, a meeting is held by the Director of RRA, IO, HRPP staff, and others as appropriate to establish a quality assessment/ improvement (QA/QI) plan to assess the compliance, and the quality, efficiency, and effectiveness, of the HRPP. The plan will include, at a minimum, the following:

- The goals of the plan with respect to achieving and maintaining compliance
 - At least one objective to achieve or maintain compliance
 - At least one measure of compliance

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- The methods to assess compliance and make improvements
- The goals of the plan with respect to achieving targeted levels of quality, efficiency, and effectiveness
 - At least one objective of quality, efficiency, or effectiveness
 - At least one measure of quality, efficiency, or effectiveness
 - The methods to assess quality, efficiency, or effectiveness and make improvements.

The Director of RRA will meet regularly throughout the year with the HRPP staff responsible for performing the assessments called for in the plan to review progress and to identify opportunities for improvement. At the end of each year, the Director of RRA, IO, and HRPP staff will evaluate whether the respective goals were achieved and determine if any additional actions or monitoring are necessary. If at any time substantive or concerning issues or trends are identified, the Director of RRA will report those issues or trends to the appropriate parties and, if appropriate, a proposed CAPA plan.

In addition to the above, HRPP staff is responsible for tracking internal data and metrics that are informative when considering HRPP and IRB efficiency, effectiveness, workload, and resources. Metrics reports will be provided to the Director of RRA and NJH IRB Co-Chair at least twice per year.

3 Education & Training

3.1 Training / Ongoing Education of NJH IRB Co-Chairs, Members, and Staff

Recognizing that a vital component of a comprehensive human research protection program is an education program, NJH is committed to providing training and on-going education for NJH IRB members and the RRA staff and study team members, related to ethical concerns and regulatory and organizational requirements for the protection of human subjects.

Orientation

New NJH IRB members, including alternate members, will meet with the IRB Chair, Director of RRA or designee for an orientation session. At the session, NJH IRB processes, regulations, and resources will be reviewed and the new member will be provided with a copy of the IRB Member Handbook. The handbook includes copies of the following and other relevant information:

- Belmont Report
- NJH Standard Operating Procedures for the Protection of Human Subjects
- Federal regulations relevant to the IRB
- Tools used by IRB reviewers (checklists etc.)
- NJH IRB Meeting Schedule
- Contact Information for Director of RRA and HRPP Staff

Initial Education

NJH IRB members and HRPP Staff must complete the required modules in the CITI Course in the Protection of Human Research Subjects, or other training determined to be equivalent by the Director of RRA. IRB members

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must complete the CITI IRB Member and Basic Biomedical coursework, and HRPP/HRPP Staff must complete the Basic biomedical course.

New NJH IRB members are required to complete orientation and the Initial Education requirement before they may serve as Primary Reviewer.

Continuing Education

To ensure that oversight of human research is ethically grounded and the decisions made by the IRB are consistent with current regulatory and policy requirements, training is continuous for IRB members throughout their service on the IRB.

In addition to CITI training, NJH also uses the following activities as a means for offering continuing education to IRB members and HRPP Staff:

- In-service training at IRB meetings
- Training workshops
- Webinars
- Email distribution of articles, announcements, presentations, and other materials relevant to human subject protections

NJH IRB members and HRPP Staff are also required to complete CITI basic or refresher training every 3 years or other training determined to be equivalent by the Director of RRA.

The activities for continuing education vary on a yearly basis depending on areas of need, as determined by the Director of RRA. Whenever possible, the HRPP provides support for staff and NJH IRB members to attend PRIM&R, OHRP, and other relevant conferences.

The Director RRA or designee determines minimum attendance requirements for continuing education and tracks participation. Fulfillment of training requirements is included as part of the evaluation of the performance of NJH IRB members, alternates, and HRPP staff. Continuing failure to complete training may result in a member's service being discontinued or not renewed.

3.2 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.

3.2.1 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 complete NJH's CITI Basic Biomedical Course and HIPS Course.

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Current training (date of completion within 3 years of application date) for each member of the research team is confirmed by the HRPP staff with every new or continuing study application, as well as requests to add personnel. IRB approval is withheld until all research team members are current in training.

Waiver of Initial Education

If individuals can provide documentation verifying that they have successfully completed human subject research training equivalent to that required by the NJH, they may request a waiver of NJH's specific training requirements. The Director of RRA or designee 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.

3.2.2 Continuing Education

Initial training is considered current for a period of three years by which time investigators and research staff must complete basic or 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 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 (NJH 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 individual with primary responsibility for the activity. This individual should make this determination based on the definitions of “[research](#)” and “[clinical investigation](#)” as provided by the Common Rule and FDA regulations, respectively, further assistance can be provided by completing the, Request for Human Subjects Research Determination Application available on the NJH IRB/HRPP Website. Consultation with the HRPP Office is strongly encouraged, the HRPP staff can assist the investigator in making the correct determination.

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.).

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Similarly, the responsibility for the initial determination of whether research involves “human subjects” rests with the investigator. 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 are urged to submit for a determination whenever they are uncertain if a research study involves “human subjects” as defined by the Common Rule or FDA. Such requests should be submitted via completion of the above referenced Submission Form 101.

Investigators **may not** self-determine that research involving the use of **coded** private information or specimens does not involve “human subjects”. Such determinations may only be made by the HRPP Office using the process described above. The only exception to this policy is when the research is not subject to FDA regulations and the coded private information or specimens are to be obtained from an NJH IRB-approved repository and the rules of that repository forbid the release of identifiable information, the key or code that would enable re-identification, or the release of sufficient information that investigators could readily ascertain the identity of subjects.

Human Subjects Research Determinations must be submitted, and determined, prospectively (i.e., before the proposed activity or research begins). Conducting an activity that constitutes human subjects research without IRB approval or exemption is noncompliance and will be managed as described in Section 19.

Determinations regarding whether an activity constitutes human subject research will be made by Director of RRA or designee, with input from others as deemed necessary, in accordance with the definitions in Section 1.3, applicable federal regulations, and federal guidance. A determination letter will be issued by HRPP Staff and sent via e-mail 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.

5 Exempt Determinations

All research using human subjects must be approved by NJH prospectively. Although certain categories of human subject research are exempt from IRB oversight, at NJH the determination of exempt status must be made by Director of RRA, or designee. NJH may also choose to accept an exempt determination made by an external IRB/Regulatory Office, on a case by case basis.

Individuals involved in making the determination of an IRB 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.).

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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).

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 observed. Exemption #2(iii), where identifiable information is obtained and the 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 students' 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.

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3. (i) 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 information collection and at least one of the following criteria is met:
 - A. 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;
 - B. 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
 - C. 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.
- (ii) 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.
- (iii) 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 "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

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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 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:

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1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article is subject to IRB review. [[21 CFR 56.104\(c\)](#)]

See Section 17.8 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 submit the following materials by email to the RRA office, with cc to the Privacy Officer:

1. A completed **Exemption Request** form;
2. The study protocol;
3. Any subject materials such as recruitment materials, information sheets, consents, scripts, and questionnaires, diaries, or surveys;
4. Letter(s) of permission from any non-NJH sites; or, when applicable, documentation of IRB approval or exemption from the external site;
5. The grant application (if the project is federally-funded and NJH is the IRB or serving as the IRB of record for the prime awardee);
6. Verification of current CITI training for all members of the research team; and

The Director of RRA or designee reviews all requests for exemptions and determines whether the request meets the criteria for exempt research. The reviewer's determination is documented on the **Exemption Determination Checklist** and is emailed to the PI. If the request does not appear to meet the definition of human subject research, the reviewer evaluates the 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 IRB Chair or an experienced Chair-designated member of the IRB. As with 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 the 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 to the IRB (i.e., within 7 business days). [45 CFR 46.108(a)(3)(iii)]

Continuing review is generally not required for research determined to be exempt, even when that research is subject to limited IRB review. However, the 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

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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)]

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 in the same manner and for the same length of time as other IRB review documentation.

Exempt determinations do not have a termination date. After a determination is made, the IRB (NJH or external), RRA office will archive the application and determination. Investigators must report any proposed modification to the research to the HRPP office for a determination of whether the research still qualifies for exemption, or any modification to study personnel, so that training and COI issues can be assessed. Investigators must notify the IRB office when an exempt research project is complete so that the organization can maintain an accurate database of research activities.

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 a 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**).

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 External IRB Coordinator in the RRA Office 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.

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Requests for NJH to either rely upon an external IRB or to 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 under most circumstances (<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html>). The reader is referred 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 8.2 (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).

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- Address whether the replying 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 NJH Serving as the Reviewing IRB

8.2.1 Factors Considered by the HRPP Office to have NJH provide IRB Services

The HRPP Office evaluates the following factors, and others as appropriate, when considering a request for an NJH IRB to serve as the IRB of record for a particular study or studies:

1. The terms of the external site(s) FWA;
2. The accreditation status of the external site(s)
3. Prior experience with the site(s) and investigators;
4. The compliance history of the site(s) and investigators (e.g., outcomes of prior audits or inspections, corrective actions);
5. The research activities to be conducted at the external site(s);
6. The willingness of the external site(s) to accept NJH's reliance terms and procedures; and/or
7. The ability the site(s) to collaboratively provide meaningful oversight of the proposed research, taking into account factors such as:
 - a. The risks and procedures of the research;
 - b. The resources available at each site and ability to accommodate or collaborate with each other in observing the consent process, performing compliance reviews, investigations of potential noncompliance, and similar matters;
 - c. The expertise and experience of the NJH IRB with the proposed research, subject population, and applicable regulations;
 - d. The ability of the NJH IRB to comply with the relevant local context considerations of the external site(s), as provided by that site(s); and/or
 - e. The willingness or ability of the external site(s) to provide information and respond to questions regarding investigator qualifications, conflicts of interest, organizational requirements, local context, and other matters that may inform the IRB review.

The HRPP Office staff will present relevant factors for consideration by the IO or Director of the HRPP Office, who will make the final decision regarding whether or not the NJH IRB will serve as the reviewing IRB. The PI will be notified of the decision.

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8.2.2 Responsibilities when NJH is the Reviewing IRB

8.2.2.1 Responsibilities of the NJH 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 NJH IRB responsibilities are to be applicable for all sites:
 - Have the final authority to decide whether NJH or external researcher or research staffs' 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 staff, researchers, and research staff, and ensure that changes to those policies are communicated as well.
 - Ensure that an NJH HRPP 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 NJH IRB.
- Adding sites to an already approved IRB study will be considered a modification, and will be conducted by the expedited or full board process. In order for the review to be conducted via the expedited process criteria, such a modification is usually considered a "minor change to previously approved research". Factors that will indicate that a full review is required may include, e.g., involvement of investigators with FCOI, FDA 483 issues that have not been resolved adequately, or any other site-specific issues that are deemed questionable. Additional site amendments (regardless of type of review) do not change the expiration date of the IRB approval for the 'main' protocol.

8.2.2.2 Responsibilities of the NJH Principal Investigator

- Submission of a plan for review to the IRB to ensure that the PI's 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 HRPP Office 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).

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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:

- WIRB
- COMIRB
- Schulman/Advarra
- NCI's Adult CIRB for NCI research involving adult subjects
- NCI's Pediatric CIRB for NCI research involving children
- HealthOne

NJH is a participating institution in the SMART IRB initiative as well, having signed an overarching agreement indicating willingness to cede to other institutions' IRBs, pending satisfactory evaluation of factors identified below.

Research that falls within the above parameters must be registered with NJH prior to submission to the external IRB following the procedures outlined below. Post-approval requirements for investigators are also summarized 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 Reliance 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 Reliance Administrator will present relevant factors for consideration by the IO or Director of the RRA, 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.

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

8.3.3.1 The External IRB has the same authority as the NJH 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 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. As with NJH IRB-reviewed research, officials of NJH may not approve research that is subject to a reliance 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 staff 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

- **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 providing investigators with a Reliance Arrangement Form that provides information relevant to their responsibilities.
- 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 HSR training, COI disclosure, local ICF content review and other required ancillary reviews and certifications have been satisfied.

8.3.4 Institutional Registration Requirement:

Studies that will be reviewed by external IRBs must be registered with NJH via the IRB electronic management system. Details for this registration requirement are available on the NJH website.

The RRA Office will review the information and verify that CITI training, COI review, and any other applicable approvals or requirements have been completed, and 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, and the external IRB will not be responsible for review (e.g., studies reviewed by the NCI CIRB), the Reliance Administrator will forward such requests to an NJH Privacy Officer or a designated expedited reviewer for review. There is current approval to use the CCRP HIPAA document for the NCI studies NJH performs through that group. The RRA Office will notify the investigators by e-mail or via the

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electronic management system once the proposed research has been cleared for submission to the external IRB. Once approved by the external IRB, investigators must submit in the electronic management system a copy of the approval letter and any approved consent document(s). For industry studies through commercial IRBs, current notification is through the SmartSheet project management software package that tracks all aspect of industry study start up. If the protocol was modified during the external IRB review process, the approved version of the protocol should be provided as well.

8.3.5 Post-IRB Approval Requirements:

- Investigators approved through external IRB review must report local unanticipated problems, complaints, and any serious and continuing noncompliance to the HRPP Office via the IRB electronic management system in addition to reporting to the external IRB. Copies of the report submitted to the external IRB are generally acceptable, but additional information may be requested on an as needed basis.
- Investigators must also submit copies of continuing review reports, updated protocols, updated consent forms, study closures and corresponding IRB approval or acknowledgment.
- Changes in PI must be submitted to the RRA Office prior to the new PI or research team member assuming any study responsibilities. CITI trainings, COI review, and any other applicable requirements will be verified.
- Notices about, and reports from, DSMB's, external monitors, auditors, or inspectors must be provided to the HRPP Office as well.
- In general, Investigators are reminded that all other Institutional reporting requirements remain applicable in addition to HRPP reporting requirements.

8.4 Exceptions to IRB vs. Local Site Responsibilities

Certain areas of responsibility can be handled by either the reviewing IRB or the NJH RRA, 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.

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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

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 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 that NJH 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.). The HRPP Office will consult with others within the organization as needed and make a recommendation to the IO for consideration. If NJH IRB can serve as the sIRB, the Reliance Administrator will assist the investigator in working with the Grants and Contracts Office to ensure accurate, direct cost, budgeting for the service.

9.2 Reliance Agreements for sIRB Studies

A Reliance Agreement (or "Authorization Agreement") between the sIRB and the participating sites is required. See Section 17.16.1 for details.

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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 an 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 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 University Hospital, IBC, RDRC 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 with NJH HRPP prior to submission to the external IRB following the procedures outlined in Section 8.3.4. Post-approval requirements for investigators are also detailed in Section 8.3.5. Research reviewed by external

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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 NJH Institutional Review Board

NJH has established an Institutional Review Board (IRB) to ensure the protection of human subjects in research conducted its auspices.

10.1 IRB Authority

The IRB derives its authority from NJH policy, as cited in Section 1.2. Under the federal regulations, IRBs have the authority:

1. To approve, require modifications to secure approval, or disapprove human subjects research activities, including exempt research activities under 45 CFR 46.104 for which limited IRB review is a condition of exemption (under 45 CFR 46.104(d)(2)(iii) and (d)(3)(i)(C));
2. To require that informed consent is obtained and documented in accordance with regulatory and policy requirements unless the criteria for the waiver or alteration of such requirements has been satisfied and approved by the IRB. The IRB may require that information, in addition to that specifically mentioned in the regulations, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects;
3. Regarding continuing review:
 - a. For research subject to the 2018 Rule: To conduct continuing review of research requiring review by the convened IRB at intervals appropriate to the degree of risk of the research, but not less than once per year;
 - b. When research is subject to other regulations (e.g., approved under the Pre-2018 Rule, FDA, DOJ) or requirements (e.g., grant or contract terms), the IRB will conduct continuing review of research at intervals appropriate to the degree of risk of the research, but not less than once per year
4. To suspend or terminate approval of research not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to participants;
5. To observe, or have a third party observe, the consent process; and
6. To observe, or have a third party observe, the conduct of the research.

The IRB functions independently. Attempts to coerce or otherwise unduly influence the actions of the IRB are forbidden by policy, and are to be reported as described in Section 10.6. Likewise, the IRB must remain free from the influence of financial and other organizational interests. No individual with responsibility for the business and financial interests of the organization may serve on the IRB.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of NJH. However, those officials may NOT approve research if it has not been approved or has been disapproved by the IRB. Reviewing officials may strengthen requirements and/or conditions, or add other modifications before approval, or may require approval by an additional committee, office, or person. Previously approved research

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proposals and/or consent forms must be re-approved by the IRB before initiating any changes or modifications that result from such additional organizational reviews.

10.2 Roles and Responsibilities

10.2.1 Co-Chairs of the IRB

The IO, in consultation with the Director of RRA, appoints Co-Chairs of the IRB to serve for renewable 3 year terms. Any change in appointment, including reappointment or removal, requires written notification.

The IRB Co-Chairs should be highly-respected individuals, fully capable of managing the IRB and the matters brought before it with fairness and impartiality. The task of making the IRB a respected part of the research community falls primarily on the shoulders of the Co-Chairs. The IRB must be perceived to be fair, impartial, and immune to pressure by administration, the investigators whose research plans are brought before it, and other committees and departments.

The IRB Co-Chairs are responsible for conducting IRB meetings. The IRB Co-Chairs are authorized to take immediate action to suspend a study or studies if subjects may be at risk of harm, when serious noncompliance may have occurred, or for any other reason where such action would be deemed appropriate. Such action requires subsequent notice to and review by the convened IRB.

The IRB Co-Chairs delegate responsibility to the IRB Coordinator to assign experienced IRB members to perform duties such as expedited reviews and other IRB functions.

The IRB Chairs advise the IO and the Director of RRA about IRB member performance.

The performance of IRB Co-Chairs will be reviewed on an tri-annual basis by the Director of RRA in consultation with the IO. Feedback from this evaluation will be provided to the Co-Chairs. If the Co-Chairs are not acting in accordance with the IRB's mission, following policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of the Co-Chair, s/he may be removed.

10.2.2 IRB Members

The role of an IRB member is to ensure that human research activities comply with federal regulations, state and local laws, and organizational policies and procedures, by:

- Completing member education and training, both initial and on-going (See Section 3.1)
- Maintaining the confidentiality of IRB deliberations and research reviewed by the IRB
- Conducting and documenting reviews in a timely fashion
- Attending IRB meetings as scheduled
- Recusing self from reviewing or voting on research when s/he has a conflict of interest (See Section 25.2)
- Participating in subcommittees of the IRB if requested and available
- Conducting themselves in a professional and collegial manner

Members should attend all meetings for which they are scheduled. If a member is unable to attend a scheduled meeting, they should inform the IRB Coordinator. If a member's availability changes and they are no longer able

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to regularly attend IRB meetings or will be absent for an extended period of time, they should inform the IRB Administrator. The Administrator will assess the situation, including the availability of the alternate when applicable, and make recommendations to the Director of RRA and IRB Co-Chair to ensure the IRB is able to meet quorum requirements and has the necessary expertise to review the research which regularly comes before it.

The performance of IRB members will be reviewed on a tri-annual basis by the Director of RRA and the IRB Co-Chair. Feedback from this evaluation will be provided to IRB members. Members who are not acting in accordance with the IRB's mission, not following NJH's position description they may be removed by the IO or his/her designee.

10.2.3 Alternate IRB members

The appointment and function of alternate members is the same as that for primary IRB members. An alternate's expertise and perspective should be comparable to those of the primary member. The role of the alternate member is to serve as a voting member of the IRB when the regular member is unavailable to attend a convened meeting, in part or in full, or when the regular member has a conflict of interest in regards to a protocol under review. When an alternate member substitutes for a primary member, the alternate member will receive and review the same materials prior to the IRB meeting that the primary member would have received.

The IRB roster identifies the primary member(s) or class of members (e.g., physician scientist) for whom each alternate member may substitute. When both the regular member and the alternate is in attendance at an IRB meeting, only one may be counted towards quorum and vote. The IRB minutes will document when an alternate member replaces a primary member.

Experienced alternate members may be designated by the Co-Chair to conduct expedited reviews.

10.2.4 Subcommittees of the IRB

The IRB Co-Chair, in consultation with the Director of RRA, may appoint one or more other IRB members to a subcommittee of the IRB to review issues and to make recommendations to the IRB (e.g., to supplement the IRB's review of research proposals or to review of reports of potential unanticipated problems or noncompliance). The size and composition of the subcommittee shall depend on the scope of duties delegated by the IRB Co-Chair. Any such subcommittee cannot approve research or issue determinations that require review by the convened IRB.

10.2.5 Composition of the IRB Membership

The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of the research that comes before it and possess the professional competence necessary to review specific research activities. The structure and composition of the NJH IRB is based upon regulatory requirements and the characteristics of the research it reviews. A member of the IRB may fill multiple membership position requirements (e.g., nonscientific and unaffiliated).

- The IRB will have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the organization. The IRB shall not consist entirely of members of one profession

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- The IRB will be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects
- In addition to possessing the professional competence necessary to review specific research activities, the IRB will be able to ascertain the acceptability of proposed research in terms of organizational commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB will therefore include persons knowledgeable in these areas
- The IRB will include members who are knowledgeable about and experienced working with subjects vulnerable to coercion or undue influence (e.g., children, prisoners, or adults with impaired decision-making capacity) that are regularly included in the research under its review
- Every nondiscriminatory effort will be made to ensure that the IRB does not consist entirely of men or entirely of women, including the organization's consideration of qualified persons of both sexes, so long as no selection is made to the IRB solely on the basis of gender
- The IRB includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas
- The IRB includes at least one member who is not otherwise affiliated with the organization and who is not part of the immediate family of a person who is affiliated with the organization
- The IRB includes at least one member who represents the general perspective of participants

Individuals from NJH Grants and Contracts Office or other business Offices may not serve as members of the IRB or carry out day-to-day operations of the IRB. Individuals from these offices may provide information to the IRB and attend IRB meetings when invited as guests.

On an annual basis, the IRB Co-Chair and the Director of RRA review the membership and composition of the IRB to determine if it continues to meet regulatory and organizational requirements.

10.3 Appointment of Members to the IRB

When the need for a new IRB member or alternate is identified, the Director of RRA informs the IO and seeks out qualified candidates. Department Chairs and others may forward recommendations to the Institutional Official, Director of RRA, or to the HRPP Office.

The final decision in selecting a new member is made by the Director of RRA, in consultation with the IO and IRB Co-Chair as required.

Initial appointments are made for a one-year probationary term. Subsequent appointments are made for a renewable three-year period of service. Any change in appointment, including reappointment or removal before the end of a member's term, requires written notification. Members may resign by written notification to the Director of RRA.

The Director of RRA will ensure that changes in IRB membership are reported via the federal IRB registration in accordance with the instructions provided on [OHRP's website](#).

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10.4 Liability Coverage for IRB Members

The NJH insurance coverage applies to employees and any other person authorized to act on behalf of NJH, including IRB members, for acts or omissions within the scope of their employment or authorized activity.

10.5 Use of Consultants

When necessary, the IRB Co-Chair, Director of RRA, or IRB Coordinator may solicit individuals from within or outside the organization with the expertise to assist in the review of research or issues which require expertise beyond or in addition to that available on the IRB. The RAA Office will ensure that all relevant materials are provided to the consulting reviewer prior to the convened meeting or expedited review.

The Director of RRA or designee reviews the COI policy for IRB members with consultants and consultants must confirm that they do not have a conflict of interest prior to review. Individuals who have a conflicting interest or whose spouse or immediate family members have a conflicting interest will not be invited to provide consultation.

The consultant's findings will be presented to the IRB for consideration either in person or in writing. If in attendance at an IRB meeting, consultants may provide information and assist in the IRB's deliberations, but may not participate in the vote.

Written statements from consultants will be kept in the IRB records. Information provided by consultants at IRB meetings will be documented in the minutes.

Ad hoc or informal consultations requested by individual members (rather than the convened board) will be managed in a manner that protects the investigator's confidentiality and that complies with the IRB COI policy.

10.6 Reporting and Investigation of Allegations of Undue Influence

If an IRB Co-Chair, member, or staff person feels that the IRB has been unduly influenced by any party, they shall make a confidential report to the Director of RRA or IO. The IO will ensure that a thorough investigation is conducted and, if the allegation is determined valid, that corrective action is taken to prevent additional occurrences. In the event that the allegation is regarding the IO, the matter will be referred to Chief Operating Officer for investigation and any necessary action.

Undue influence means attempting to interfere with the normal functioning and decision-making of the IRB, or to attempt to influence an IRB member or staff member or any other member of the research team, outside of the established processes or normal and accepted methods in order to obtain a particular result, decision, or action by the IRB or one of its members or staff.

11 IRB Actions, Failure to Respond, Appeals

11.1 IRB Actions

In conducting its review of research, the IRB may take any of the following actions. With the exception of disapproval, the actions listed below may be used for either expedited or convened board review, including limited IRB review. Disapproval can only be decided at a convened IRB meeting. An expedited reviewer cannot disapprove a study.

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Approval. The research, proposed modification to previously approved research, or another item is approved. The IRB has made all of the determinations required for approval (i.e., approval criteria and any applicable special determinations (e.g., waivers, alterations, vulnerable population determinations, etc.)). No further action is needed.

Conditional Approval: The research, proposed modification to the previously approved research, or other item is approved but conditions must be satisfied before the approval becomes effective.

The IRB may approve research with conditions if, given scope and nature of the conditions, the IRB is able, based on the assumption that the conditions are satisfied, to make all of the determinations required for approval (i.e., approval criteria and any applicable special determinations (e.g., waivers, alterations, vulnerable population determinations, etc.)). Any time the IRB cannot make one or more of the determinations required for approval, the IRB may not approve the study with conditions.

The IRB may require the following as conditions of approval of research:

1. Confirmation of specific assumptions or understanding on the part of the IRB regarding how the research will be conducted (e.g., confirmation that research excludes children);
2. Submission of additional documentation (e.g., certificate of training);
3. Precise language changes to the study, consent, or other study documents; or
4. Substantive changes to the study, consent, or other study documents along with clearly stated parameters that the changes must satisfy.

When the IRB approves research with conditions, the conditions will be documented in the IRB minutes for research reviewed at a convened meeting or in an applicable reviewer checklist for research reviewed under an expedited review procedure.

When the convened IRB approves research with conditions, final review may be conducted by the original reviewer, or any other qualified IRB member to review responsive materials from the investigator and determine that the conditions have been satisfied. If the conditions have not been satisfied, or are only partially satisfied, the responsive materials must be referred to the convened IRB for review. When an expedited reviewer approves research with conditions, the original expedited reviewer (and/or other qualified individual(s)) will receive the response materials.

After verification, the date that the IRB conditions were satisfied, i.e., the approval date, will be documented in IRB records and in written communication to the investigator:

The IRB will be informed of the outcome of the review of the investigator's response in the agenda of the next meeting.

Table: This action is taken by the IRB when modifications are required of the nature or amount that the full IRB cannot make or specify exact changes or parameters, or additional information or clarification is needed in order to determine that one or more criteria for approval are satisfied (e.g., the risks and benefits cannot be assessed until additional information is provided.).

The table action is documented in the IRB minutes for convened review and is communicated to the investigator in writing.

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When the convened IRB tables approval, the responsive materials from the investigator will be provided to the convened IRB for review at a subsequent meeting.

Defer: This action is taken by an expedited reviewer when modifications are required of the nature or amount that the reviewer cannot make or specify exact changes or parameters, or additional information or clarification is needed in order to determine that one or more criteria for approval are satisfied (e.g., the risks and benefits cannot be assessed until additional information is provided.). The defer action is documented in the reviewer checklist. When the original expedited reviewer is unavailable, the response will be reviewed by the IRB Chair or other qualified IRB member who has been designated to conduct expedited review.

Disapprove. This action is taken when the convened IRB determines that the proposed research activity does not satisfy the criteria for approval and that it cannot be modified to render it approvable (or the sponsor or investigator will not make necessary modifications that would render the research approvable).

In addition to the above actions, the IRB may **acknowledge** reports and other items that don't involve prospective changes to already approved research. For example, the IRB may acknowledge the report of a protocol deviation but approve, require modifications in, or disapprove any associated corrective action plan. Further, the IRB may approve an item but include **comments** noting certain requirements, restrictions, or understandings. For example, with collaborative research, the IRB may note that approval must also be obtained from another IRB with jurisdiction and that the letter documenting that approval must be submitted to the NJH IRB before human research activities involving the collaborating organization or personnel may commence.

11.2 Failure to Respond

Upon review of a research study, the IRB may require changes or request certain information from an investigator. Failure to respond to the IRB before the subsequent meeting prompts the HRPP staff to contact the PI to request a status update for the study, and to respond if the study will be proceeding. If the study is not being initiated (for new studies) or is not continuing (for continuing renewals), the HRPP staff assists the PI in either administratively withdrawing, or closing the study, respectively.

11.3 Reporting IRB Actions

All IRB actions are communicated to the investigator, and/or designated contact person for the research study, via an e-mail within ten (10) working days, whenever possible, of the review. When applicable, a stamped or watermarked copy of the approved consent form, parental permission form, and/or assent form will also be provided. For IRB actions of conditions required for approval or tabled, the notification will include a listing of the conditions or requirements that must be satisfied or responded to. For a disapproval, suspension, or termination, the notification will include the basis for the action and will offer the investigator an opportunity to respond in person or in writing.

The IRB reports its findings and actions to the organization in the form of its minutes, which are which are kept on file with the RRA Office for review by the IO.

11.4 Appeal of IRB Decisions

When the IRB suspends, terminates, or disapproves research, the IRB letter communicating the decision will include the basis for the action and will offer the investigator the opportunity to respond in person or in writing.

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Additionally, whenever an investigator disagrees with an IRB requirement or decision, or believes that providing the IRB with additional information may result in a different outcome, they may request that the IRB reconsider its decision by submitting a memo and other supportive materials via e-mail to the HRPP Office. The investigator may be invited to attend the IRB meeting to discuss the request and provide information, but will be asked to leave prior to the IRB's final deliberations and vote.

12 IRB Review Process

The NJH IRB will review and ensure that research under its oversight meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research. The IRB may conduct their review using the following review methods:

- Expedited Review
- Review by Convened IRB

12.1 Expedited Review

An IRB may use the expedited review procedure to review the following:

- Some or all of the research appearing on the list of categories of research eligible for expedited review unless the reviewer determines that the research involves more than minimal risk, and, for research that is FDA-regulated or DoJ funded, found by the reviewer(s) to involve no more than minimal risk.
- Minor changes in research previously approved by the convened IRB. Note: review of minor changes does not alter the end-date of study approval
- Research for which limited IRB review is a condition of exemption under 45 CFR 46.104(d)(2)(iii), or (d)(3)(i)(C).

The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--used by the IRB.

12.1.1 Definitions

Minimal Risk. Minimal risk means 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.

Minor Change. A minor change is one which, in the judgment of the IRB reviewer, makes no substantial alteration in:

1. The acceptability of the risk-to-benefit analysis (i.e., the change does not increase the level of risk);
2. The research design or methods (adding procedures that are not eligible for expedited review (See Section 12.1.2) would be considered more than a minor change);
3. The number of local subjects to be enrolled in the research (usually not greater than 10% of the total requested);

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4. The qualifications of the research team (i.e., the change does not negatively impact the expertise available to conduct the research);
5. The facilities available to support safe conduct of the research; or
6. Any other factor which would warrant review of the proposed changes by the convened IRB.

12.1.2 Categories of Research Eligible for Expedited Review

NJH applies the categories of research eligible for expedited review, which were published in the Federal Register notice 63 FR 60364-60367, November 9, 1998.

The categories in this list apply regardless of the age of subjects, except as noted in category 2.

The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

The expedited review procedure may not be used for classified research.

Expedited Categories one (1) through seven (7) may be used for both initial and continuing review:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
 - a. Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
 - b. Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
 - a. From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or
 - b. From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week. (Note: Children are defined as "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.)
3. Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated

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saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization; (k) vaginal swabs that do not go beyond the cervical os; rectal swabs that do not go beyond the rectum; and nasal swabs that do not go beyond the nares.

4. Collection of data through noninvasive procedures, not involving general anesthesia or sedation, routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Note: Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46 101(b)(2) and b(3). This listing refers only to research that is not exempt.)
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior); or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Categories 8 and 9 apply only to continuing review.

8. Continuing review of research previously approved by the convened IRB as follows:
 - a. Where (i) the research at NJH is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects (Note: "Long-term follow-up" includes research *interactions* that involve no more than minimal risk to subjects (e.g., quality of life surveys); and collection of *follow-up* data from procedures or interventions that would have been done as part of routine clinical practice to monitor a subject for disease progression or recurrence, regardless of whether the procedures or interventions are described in the research study, but not

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interventions that would not have been performed for clinical purposes, even if the research interventions involve no more than minimal risk.); **or**

- b. Where no subjects have ever been enrolled at NJH and no additional risks have been identified (Note: “no additional risks have been identified” means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB’s most recent prior review.); **or**
 - c. Where the remaining research activities at NJH are limited to data analysis. (Note: Simply maintaining individually identifiable private information without using, studying, or analyzing such information is not human subject research and thus does not require continuing review.
9. Continuing review of research previously approved by the IRB at a convened meeting that meets the following conditions:
- a. The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE); **and**
 - b. Expedited review categories (2) through (8) do not apply to the research; **and**
 - c. The IRB has determined and documented at a convened meeting that the research, or the remaining research activity involving human subjects, involves no greater than minimal risk to the subjects; **and**
 - d. No additional risks of the research have been identified. (Note: “no additional risks have been identified” means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB’s most recent prior review.)

12.1.3 Expedited Review Procedures

Under an expedited review procedure, IRB review is carried out by the IRB Chair or by one or more reviewers designated by the Chair from among members and alternate members of the IRB. Designated reviewers must be experienced (having served on the IRB for at least one year) and knowledgeable of the requirements to approve research under expedited review.

IRB members do not participate in the review of research in which they have with a conflict of interest (see Section 25.2) but may answer questions about the research if requested.

When reviewing research under an expedited review procedure, the IRB Chair, or designated reviewer, will receive and review the same materials that would be reviewed if the research were to be reviewed by the convened IRB, and for previously approved research, will have access to the study history. The reviewer evaluates and documents whether the research qualifies for expedited review using a checklist. When a reviewer determines that research subject to the 2018 Rule falls within the expedited categories but involves more than minimal risk, the reviewer will document the rationale for that determination in the checklist and refer the research for review by the convened IRB. If the research otherwise does not meet the criteria for expedited review, then the reviewer will indicate that the research requires review by the convened IRB and the submission is placed on the next available IRB meeting agenda.

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In reviewing the research, expedited reviewers will apply the same criteria for review and approval of research described throughout this manual and may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may only be disapproved by the convened IRB.

Reviewers will use the appropriate reviewer checklist (e.g., initial, modification, continuing) to assess the criteria for approval and to document their review. For initial and continuing reviews, the documentation will include the category(ies) under which the research qualifies for expedited review. The checklist is maintained by the HRPP Office in electronic HRPP folders. When expedited review is carried out by more than one IRB member and the reviewers disagree, the IRB Chair may make a final determination or refer the submission to the convened IRB for review.

A letter documenting the outcome of the review will be prepared by the HRPP Staff and provided to the investigator.

Approval of expedited studies is effective on the day that the study is approved without conditions, and expires one year from the effective approval date.

12.1.4 Informing the IRB

Members of the IRB will be apprised of expedited review approvals, including limited IRB reviews conducted using expedited review procedures, via a list in the agenda of the next scheduled meeting. Any IRB member can request to review the materials for any study by contacting the HRPP Office.

12.2 Convened IRB Meetings

Except when an expedited review procedure is used, the IRB will conduct initial and continuing reviews of all non-exempt research at convened meetings at which a quorum of the members is present.

12.2.1 IRB Meeting Schedule

The IRB meets on a regular basis throughout the year (a minimum of once per month). The schedule for the IRB may vary due to holidays, lack of quorum, or other reasons. The schedule for IRB meetings is posted on the IRB website:

<https://www.nationaljewish.org/research-science/support/compliance/irb/submissions> .

Special meetings may be called at as needed by the Co-Chair or Director of RRA.

12.2.2 Preliminary Review

The HRPP staff will perform a preliminary review of all submissions for determination of completeness and accuracy, including elements of consent checklist, when applicable. Only complete submissions will be placed on the IRB agenda for review. The investigator will be informed by e-mail of missing materials and any recommended changes. If an investigator is submitting for the first time or is not well-versed in submission procedures, consultations can be arranged with HRPP staff.

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12.2.3 Primary and Secondary Reviewers

After it has been determined that a submission is complete, the IRB Coordinator, with the assistance of the IRB Chair as needed, will assign submissions for review paying close attention to the subject matter of the research, the potential reviewer's area(s) of expertise, and representation for any vulnerable populations involved in the research. A "primary reviewer" will be assigned to each submission and will receive and review the full submission materials. When the IRB is presented with a research study which may be outside of the knowledge base or representative capacity of the IRB members, an outside consultant will be sought (See Section 10.5). For new studies, in addition to the primary reviewer NJH IRB has a community member also complete a review. Research studies for which appropriate expertise cannot be obtained for a given meeting will be deferred to another meeting when appropriate expertise is available.

Primary and secondary reviewers are responsible for:

- Performing an in-depth review of the submission materials and having a thorough understanding of the details
- Leading the discussion at the IRB meeting, by providing a summary and leading the IRB through the regulatory criteria for approval and any required determinations
- Completing all applicable IRB reviewer checklists

All IRB members receive and are expected to review all studies, not just those assigned as primary or secondary reviewer.

Absent reviewers can submit their written comments for presentation and consideration at the convened meeting. If an absent reviewer submits comments, those can indicate a recommendation regarding approval, but such recommendation will not be counted as a vote.

12.2.4 Materials received by the IRB

All required materials need to be submitted to the HRPP office either 3 weeks (for new studies) or 2 weeks (for continuing studies) prior to the convened meeting date for inclusion on the IRB agenda. On occasion, when a review is time-sensitive, the HRPP office may make an exception to this rule provided that there is still sufficient time for all members to review the submission materials. The meeting agenda will be prepared by the HRPP staff in consultation as needed with the IRB Chair or Director of RRA. All IRB members receive the IRB agenda, prior meeting minutes, applicable business items, and research submission materials approximately one week before the scheduled meeting to allow sufficient time for review.

All IRB members receive an e-mail that contains all materials submitted for all studies on the agenda, which include the following, as applicable:

- New Protocol Application
- Informed Consent/authorization form (with version/date)
- Protocol (Sponsor / Investigator; with version/date)
- Conflict of Interest and Scientific Misconduct forms for all members of the research team
- Current (within 3 years) Certification of Human Research Protections for all members of the research team (if not on file with the IRB)

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- Certification of HIPAA Privacy Training for all members of the research team (if not on file with the IRB)
- Current (within 3 years) CVs for all investigators (if not on file with the IRB)
- Proposed recruitment materials, including advertisements intended to be seen or heard by potential study participants
- Any other subject materials, such as questionnaires or diaries
- The grant application(s)
- The Investigator Brochure(s)

Additionally, for HHS-supported multicenter clinical trials, the IRB should receive and review a copy of the HHS-approved sample consent form(s) and the complete HHS-approved protocol, if they exist.

If an IRB member requires additional information to complete the review, they may contact the HRPP office or the investigator. Any additional information should be provided to the other members.

Primary and secondary reviewers will complete any applicable reviewer checklists, which serve as a guide for the review and a tool for summarizing recommendations prior to board discussion.

12.2.5 Quorum

A quorum of the IRB consists of a majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. When research involving an investigational new drug is on the agenda for review, a physician should be included in the quorum. At meetings of the IRB, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote.

The IRB Chair, with the assistance of the HRPP staff, will confirm that quorum is present before calling the meeting to order. The IRB Chair, with the assistance of the HRPP staff, will be responsible to ensure that the IRB meeting remains appropriately convened. If a quorum is not maintained, either by losing a majority of the members, or losing all non-scientific members or another required member, the IRB may not take votes until quorum is restored. When IRB members leave the meeting room, HRPP Staff will document the time of departure and notify the IRB Chair if a quorum is not present.

It is generally expected that at least one unaffiliated member and at least one member who represents the general perspective of participants (one individual can serve in both capacities) will be present at all IRB meetings. The IRB may, on occasion, meet without this representation; however, this should be the exception (i.e., no more than 20% of meetings).

When the IRB regularly reviews research that involves subjects vulnerable to coercion or undue influence, such as children, prisoners, or adults with impaired decision-making capacity, one or more individuals (e.g., IRB members, alternate members, or consultants) who are knowledgeable about and experienced with such subjects should be present during the review of the research.

IRB members are considered present and participating at a duly convened IRB meeting when either physically present or participating through electronic means (e.g., teleconferencing or video conferencing) that permits them to listen to and speak during IRB deliberations and voting. When not physically present, the IRB member must have received all pertinent materials prior to the meeting and must be able to participate actively and equally in all discussions.

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Opinions of absent members may be considered by the attending IRB members but may not be counted as votes or to satisfy quorum requirements for convened meetings.

12.2.6 Meeting Procedures

The IRB Chair will call the meeting to order, once it has been determined that a quorum is in place. The Chair will remind IRB members to recuse themselves from the discussion and votes by leaving the room when they have a conflict. The IRB will review and discuss the minutes from the prior meeting and determine if there are any revisions/corrections to be made. If there are no changes to be made, the minutes will be accepted as presented and considered final. If major revisions/corrections are necessary, the minutes will be amended and presented at the following IRB meeting. Minor revisions/corrections may be verified by the IRB Chair or Vice Chair outside of the meeting.

The IRB reviews submissions for initial and continuing review, requests for modifications to previously approved research, and other business items, as applicable (e.g., potentially serious noncompliance, unanticipated problems etc.). The Primary and Secondary Reviewer presents an overview of the submission and assists the Chair in leading the IRB through the evaluation of the regulatory criteria for approval or other required determinations using their checklist(s) as a guide. HRPP Staff project materials relevant to the board's review and discussion to facilitate the review process. For the research to be approved, or any motion on a business item of the agenda to pass, it must receive the approval of a majority of those voting members present at the meeting.

HRPP staff are responsible for taking minutes at each IRB meeting.

12.2.7 Guests

Investigators and research staff may be invited to the IRB meeting, at the discretion of the IRB, to make a brief presentation or to answer questions about proposed or ongoing research. The investigator/research staff may not be present for the deliberations or vote on the research.

The Director of RRA and HRPP Staff regularly attend IRB meetings and may participate in the IRB discussion and deliberations, but may not vote unless attending as a member or alternate.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and the Director of RRA. Such guests may be asked to sign a confidentiality agreement and do not participate in discussion unless requested by the IRB; under no circumstances may they vote.

12.3 Criteria for IRB Approval of Research

For the IRB to approve human subjects research, either through expedited review or by the convened IRB, it must determine that the following requirements are, or remain, satisfied.

1. Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB

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should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

3. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving subjects vulnerable to coercion or undue influence, such as children, prisoners, mentally disabled persons, or economically or educationally disadvantaged persons.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by the Federal Regulations [\[45 CFR 46.116/21 CFR 50\]](#).
5. Informed consent will be appropriately documented, in accordance with, and to the extent required by the Federal Regulations [\[45 CFR 46.117/21 CFR 50\]](#).
6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

12.4 Risk/Benefit Assessment

The goal of the assessment is to ensure that the risks to research subjects posed by participation in the research are justified by the anticipated benefits to the subjects or society. Toward that end, the IRB must:

- Judge whether the anticipated benefit, either of new knowledge or of improved health or other direct benefit for the research subjects, justifies asking any person to undertake the risks; and
- Disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

The assessment of the risks and benefits of proposed research involves a series of steps:

1. **Identify the risks** associated with the research, as distinguished from the risks of activities, diagnostic tests, treatments, or therapies the subjects would receive or undergo even if not participating in the research;
2. **Determine whether the risks will be minimized** to the extent possible by evaluating the necessity of procedures that impart risk and whether the data could be gained by procedures that are already being performed for other purposes or by alternative procedures that impart less risk;

Identify the anticipated benefits to be derived from the research, both direct benefits to subjects and possible benefits to society, science and others;

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3. **Determine whether the risks are reasonable in relation to the benefits**, if any, and assess the importance of the knowledge that can reasonably be expected to result from the research.

In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research - as distinguished from risks and benefits subjects would receive even if not participating in the research.

The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks and benefits that fall within the purview of its responsibility.

The IRB should not consider any compensation that subjects may receive to be a benefit of the research.

When research subjects are assigned to different arms or otherwise undergo differing interventions, procedures, or exposures, the evaluation of risk and benefit should be made for each subject group (i.e., a “component analysis”). This is especially important when a subset of subjects will have no possibility of direct benefit but will be exposed to greater than minimal risks.

12.5 Scientific or Scholarly Review

In order to assess the risks and benefits of proposed research, the IRB must determine that:

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

In making this determination, the IRB may draw on its own knowledge and expertise, or the IRB may draw on the knowledge and expertise of others, such as reviews by a funding agency, a scientific review committee, or departmental review. When scientific or scholarly review is conducted by an individual or entity external to the IRB, documentation of the outcome and details of that review must be provided to the IRB for review and consideration.

12.6 Equitable Selection of Subjects

The IRB evaluates whether the selection of subjects is equitable with respect to gender, age, class, etc. by reviewing the IRB application, protocol, and other materials and information. The IRB will not approve a study that does not provide adequately for the equitable selection of subjects or has not provided an appropriate scientific and ethical justification for excluding classes of persons who might benefit from the research. In making this determination, the IRB evaluates:

- The purposes of the research;
- The setting in which the research occurs;
- Scientific and ethical justification for including subjects vulnerable to coercion or undue influence such as children, prisoners, mentally disabled persons, or economically or educationally disadvantaged persons;
- The scientific and ethical justification for excluding classes of persons who might benefit from the research; and
- The inclusion/exclusion criteria, and the procedures/materials intended for use for the identification and recruitment of potential subjects.

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At the time of the continuing review the IRB evaluates whether subject selection has been equitable.

12.7 Recruitment of Subjects

The investigator will provide the IRB with a plan for recruitment of potential subjects. All recruiting materials will be submitted to the IRB, including advertisements, flyers, scripts, information sheets and brochures. The IRB should ensure that the recruitment plan and materials appropriately protect the rights and welfare of the prospective subjects (e.g., do not present undue influence). See Section 12.12.9 for a discussion of IRB review of advertisements and Section 12.12.10 for a discussion of IRB review of payments.

12.8 Informed Consent

The IRB will ensure that informed consent will be sought from each prospective subject or the subject's legally authorized representative (LAR), in accordance with, and to the extent required by [45 CFR 46.116](#) and [21 CFR 50.20](#). In addition, the IRB will ensure that informed consent will be appropriately documented, in accordance with, and to the extent required by [45 CFR 46.117](#) and [21 CFR 50.27](#). The IRB will ensure, as part of its review, that the information in the consent document and process is consistent with the research plan, and, when applicable, the HIPAA authorization. See Section 15 for a detailed discussion on informed consent.

12.9 Data and Safety Monitoring

For research that is more than minimal risk, the investigator should submit a data and safety monitoring (DSM) plan. The initial plan submitted to the IRB should describe the procedures for safety monitoring, reporting of unanticipated problems involving risks to subjects or others, descriptions of interim safety reviews and the procedures planned for providing DSM findings to the IRB. DSM may be performed by a researcher, medical monitor, safety monitoring committee, or other means.

The IRB reviews the safety monitoring plan and determines if it makes adequate provision for monitoring data to ensure the safety of subjects and for addressing problems that may arise over the course of the study. If a plan was not submitted, the IRB determines whether a plan is required, and, depending on the circumstances, what the plan should include. The overall elements of the monitoring plan depend on the potential risks, complexity, and nature of the research study.

The principles the IRB applies in evaluating the adequacy of a proposed DSM plan include:

- Monitoring should be commensurate with the nature, complexity, size, and risks of the research
- Monitoring should be timely. Frequency should be commensurate with risk. Conclusions are reported to the IRB
- For low risk studies, continuous, close monitoring by the study investigator or an independent party may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor, and regulatory bodies, as applicable
- For greater than minimal risk studies that do not include a plan for monitoring by a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), and that are blinded, multi-site, involve vulnerable populations, or involve high-risk interventions or procedures, the IRB will carefully evaluate the proposed

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DSM plan and may require establishment of a DSMB, DMC, or other methods to enhance the monitoring and management of safety

Data and Safety Monitoring plans should specify:

- The entity or person(s) who will perform the monitoring, and the independence or affiliation that the entity or person(s) has with the sponsor or investigator
- The safety information that will be collected and monitored, including serious adverse events and unanticipated problems
- The frequency or periodicity of review of safety data
- The procedures for analysis and interpretation of the data
- The procedures for review of scientific literature and data from other sources that may inform the safety or conduct of the study
- The conditions that trigger a suspension or termination of the research (i.e., stopping rules), when appropriate
- The procedures for reporting findings to the IRB, including a summary description of what information, or the types of information, that will be provided

For a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), the plan should also describe the composition of the board or committee. Generally, a DSMB or DMC should be composed of experts in all scientific disciplines needed to interpret the data and ensure subject safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease/condition and treatment under study should be part of the monitoring group or be available if warranted.

The National Institutes of Health (NIH) requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants.

When DSMBs or DMCs are used, IRBs conducting continuing review of research may rely on a current statement, or the most recent report, from the DSMB or DMC which indicates that it has and will continue to review study-wide adverse events, study wide interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB.

12.10 Privacy and Confidentiality

The IRB will determine whether adequate procedures are in place to **protect the privacy** of subjects and to **maintain the confidentiality of the data**.

12.10.1 Definitions

Privacy. Having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. It is the state or condition of being free from unauthorized intrusion, being observed or disturbed by other people.

Confidentiality. Methods used to ensure that information obtained by investigators about subjects is not improperly divulged.

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Private information. Information 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).

Sensitive Information. Data or information, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, unauthorized access, misuse, alteration, or loss or destruction of the information (e.g., could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation).

Identifiable information. Information where the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

12.10.2 Privacy

The IRB must determine whether the activities in the research appropriately protect the privacy of potential and enrolled subjects. In order to make that determination, the IRB must obtain information regarding how the investigators plan to access subjects or subjects' private, identifiable information, and the subjects' expectations of privacy in the situation. Investigators must have appropriate authorization to access the subjects or the subjects' information.

In developing strategies for the protection of privacy, consideration is given to the:

- Methods used to identify and contact potential participants
- Settings where recruitment and research activities will occur
- Appropriateness of personnel and others present for research activities
- Methods to verify the identity of subjects prior to disclosing information (e.g., with phone calls)
- Methods used to obtain information about participants, and the nature of the requested information, including whether the data is the minimum necessary to achieve the aims of the research
- Information that is obtained about individuals other than the "target subjects", (e.g., a subject provides information about a family member for a survey) and whether such individuals meet the regulatory definition of "human subject"

12.10.3 Confidentiality

The IRB must determine if appropriate protections are in place to minimize the likelihood that information about subjects or their participation in research will be inappropriately accessed or divulged. Safeguards designed to protect confidentiality should be commensurate with the potential of harm from unauthorized, inappropriate or unintentional disclosure.

The IRB assesses whether there are adequate provisions to protect data confidentiality by evaluating the methods used to obtain, record, share, and store information about individuals who may be recruited to participate in studies and about subjects. The investigator will provide the IRB with a plan regarding the procedures to be taken to protect the confidentiality of research data and sensitive information. The investigator will provide information regarding information security procedures and plans to address the protection of paper documents, other physical media (e.g., audio or videotapes), and electronic data, and information regarding the use, maintenance, storage,

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and transmission of information. The IRB will review the information received from the investigator and determine whether the confidentiality of research data is sufficiently protected. See Section 28.2 for details on use of Certificates of Confidentiality to protect sensitive data.

In reviewing confidentiality protections, the IRB shall consider whether or not the data or other information accessed or gathered for research purposes is sensitive, and the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. The IRB will evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, methods of transmission, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections. In reviewing confidentiality protections, the IRB will also consider regulations and organizational requirements and policies regarding the use of information and information security.

Research regulated by the FDA that involves the use of electronic data collection/storage systems must comply with the requirements of [21 CFR Part 11](#).

12.11 Vulnerable Populations

Certain individuals, by nature of their age or mental, physical, economic, educational, or other circumstances, may be more vulnerable to coercion or undue influence than others. At the time of initial review, and when a proposed modification includes the involvement of vulnerable subject populations, the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. When appropriate, the IRB may determine and require that additional safeguards be put into place for vulnerable subjects, such as those without decision-making capacity.

For an extensive discussion about the IRB's review process for specific populations of vulnerable subjects, please refer to Section 16.

12.12 Additional Considerations

12.12.1 Determination of Risk Level

At the time of initial review, the IRB will make a determination regarding the risks associated with the research. Risks associated with the research will generally be classified as either "minimal" or "greater than minimal" with additional classifications as required by the various subparts or FDA regulations. Risk determinations may vary over the life of a research study depending on the procedures and risks that subjects will be exposed to as the research progresses. Because of this, the IRB may reevaluate the risk determination with modifications to the research, at continuing review, and when new information becomes available. The level of risk associated with the research influences eligibility for expedited review. The meeting minutes will reflect the convened IRB's determination regarding risk levels; expedited reviewers will document the determination of risk level on the reviewer's checklist.

12.12.2 Period of Approval

At the time of initial review and at continuing review, the IRB will make a determination regarding the period of approval. All studies will be reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year. For research subject to the 2018 Rule, the IRB will conduct continuing review of research requiring

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review by the convened IRB at intervals appropriate to the degree of risk of the research, but not less than once per year.

In some circumstances, a shorter review interval (e.g., semi-annually, quarterly, or after accrual of a specific number of participants) may be required (see below). The meeting minutes will reflect the convened IRB's determination regarding review frequency; expedited reviewers will document the determination of risk level on the reviewer's checklist.

IRB approval is considered to have lapsed at the end of the day of the expiration date of the approval (i.e., the expiration date is the last day research can be conducted). For a new study reviewed by the convened IRB, the approval commences on the date that the IRB conducts its final review of the study; that is, the date that the convened IRB or expedited reviewer approves the research or the date (effective date) when it has been verified that the requirements of the IRB have been satisfied following an action of "Conditional Approval". The expiration date of the approval period, which is the date by which the first continuing review must occur, is one year from the date of the IRB meeting at which the study was last reviewed.

The approval date and approval expiration date are clearly noted on IRB determination letters and must be strictly adhered to. Investigators should allow sufficient time for development and review of continuing review submissions. As a courtesy, the HRPP Office sends reminders to the investigator prior to the study's expiration date, notifying him or her that the study is due for a continuing review or when approval has expired. Reminder notices are sent by the HRPP office approximately 5 weeks, and again 2 weeks before either study expiration (if an expedited study) or required meeting date (if a full review study)

IRB review of a proposed modification to research ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full research project, not simply a change to it.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur before midnight of the date when IRB approval expires. If the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur.

12.12.3 Review More Often Than Annually

The following factors will be considered when determining which studies require review more frequently than on an annual basis:

1. The probability and magnitude of anticipated risks to subjects;
2. The likely medical/psychological/social/legal/educational condition of the proposed subjects;
3. The overall qualifications of the investigator and other members of the research team;
4. The specific experience of the investigator and other members of the research team in conducting similar research;
5. The nature and frequency of adverse events observed in similar research at this and other institutions;
6. The novelty of the research making unanticipated adverse events/unanticipated problems more likely;
7. The involvement of especially vulnerable populations likely to be subject to undue influence or coercion (e.g., terminally ill);

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8. A history of serious or continuing noncompliance on the part of the investigator; and
9. Any other factors that the IRB deems relevant.

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of enrolled subjects. If a maximum number of subjects is used to define the approval period, it is understood that the approval period in no case can exceed one year unless the study does not require continuing review. If an approval period of less than one year is specified by the IRB for research subject to continuing review, the reason for more frequent review must be documented in the minutes or the reviewer's checklist.

12.12.4 Independent Verification That No Material Changes Have Occurred

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB use sources other than the investigator to independently verify that no material changes occurred since previous IRB review.

In support of this requirement, the National Jewish Health IRB requires the submission of Other Reportable Information (See Section 21) including reports from external monitors, auditors, or inspectors (See Section 2.1).

The IRB will also determine the need for verification from outside sources on a case-by-case basis. The following factors will be considered when determining which studies require independent verification:

1. The nature, probability, and magnitude of anticipated risks to subjects;
2. The degree of uncertainty regarding the risks involved;
3. Whether the research involves novel therapies or procedures;
4. The vulnerability(ies) of the subject population;
5. The projected rate of enrollment;
6. The experience and expertise of the investigators;
7. The IRB's previous experience with the investigators or the sponsor (e.g., compliance history, complaints from subjects, etc.);
8. The probable nature and frequency of changes that may ordinarily be expected in the type of research;
9. Whether the research undergoes routine independent monitoring;
10. Whether concerns about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources; and
11. Any other factors that suggest independent verification is warranted.

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may require such verification at the time of continuing review, review of modification requests, and/or unanticipated problems.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken (see Section 19 on Noncompliance).

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12.12.5 Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that monitoring of the consent process by an impartial observer (e.g., consent monitor) is required in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being followed, or ensure that subjects are truly giving informed consent.

Such monitoring may be particularly warranted for:

1. High risk studies;
2. Studies that involve particularly complicated procedures or interventions;
3. Studies where recruitment will occur in situations or circumstances that may negatively impact the consent process (e.g., the Emergency Room);
4. Studies involving highly vulnerable populations (e.g., ICU patients, children who are wards);
5. Studies involving study staff with minimal experience in administering consent to potential study participants; or
6. Other situations when the IRB has concerns that consent process may not be/is not being conducted appropriately (e.g., prior investigator noncompliance, etc.).

Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

If the IRB determines that consent monitoring is required, the IRB may consult with the Director of RRA, IRB Coordinator, and others to develop an appropriate plan. The consent monitoring may be conducted by HRPP Staff, IRB members, or another appropriate designee. The investigator will be notified of the IRB's determination and the reasons for the determination. Arrangements will be made with the investigator for the monitoring of the consent process, typically for a specified number of subjects. When warranted, the investigator may not be notified until after the observation has occurred. When observing the consent process, the monitor will evaluate whether:

1. The informed consent process was appropriately conducted and documented;
2. The participant had sufficient time to consider study participation, and to ask questions and have them answered;
3. The consent process involved coercion or undue influence;
4. The information was accurate and conveyed in understandable language; and
5. The subject appeared to understand the information and provided their voluntary consent.

Following the monitoring, a report of the findings will be submitted to the IRB, which will determine the appropriate action to be taken, if any.

For all studies in which NJH is the IRB of record, passive monitoring of consents are performed and it is requested at the time of CR that a redacted copy of a completed consent form be submitted for the HRPP staff and NJH IRB to review.

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12.12.6 Investigator Qualifications

The IRB relies upon other 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 research team are appropriately qualified to conduct the research.

12.12.7 Significant New Findings

During the course of research, significant new knowledge or findings about the research, the test article, and/or the condition under study may develop. The investigator must report any significant new findings to the IRB and the IRB will review them and evaluate the impact on the subjects' rights and welfare. When the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the IRB may require that the investigator contact subjects to inform them of the new information. The IRB will communicate this requirement to the investigator. If the study is still enrolling subjects, the consent document should be updated. The IRB may require that the currently enrolled subjects be re-consented or otherwise provided with the new information. When appropriate, the IRB may also require that former subjects be provided with the new information (e.g., late emerging safety information).

12.12.8 Conflicts of Interest (COI)

The IRB research application solicits information about investigator and research staff COI disclosure and whether any conflict management plans are in place. As part of its review process, the IRB will make a final determination as to whether any COI is adequately addressed and protects the human subjects in the research. Likewise, when there is an institutional COI, the IRB/HRPP Office has final authority to determine whether the conflict and the management plan, if any, allow the study to be approved. (See Section 25 for a more detailed discussion of COI).

12.12.9 Advertisements and Recruitment Materials

The IRB must review and approve all advertisements and recruitment materials prior to posting, use, or distribution. The IRB will review:

- The information contained in the advertisement/recruitment material
- The mode/method of its communication;
- The final copy of printed advertisement/recruitment material
- The proposed script and final version of any audio/video advertisements/recruitment materials

This information must be submitted to the IRB with the initial application, or, if proposed after study approval, as a modification request.

The IRB reviews the material to assure that the material is accurate and is not coercive or unduly optimistic, creating undue influence to the subject to participate. This includes, but is not limited to the following (as applicable):

1. Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent form and the research plan;

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2. Claims, either explicit or implicit, that the test article (drug, biologic or device) or intervention is safe or effective for the purposes under investigation;
3. Claims, either explicit or implicit, that the test article or intervention is known to be equivalent or superior to any other drug, biologic, device, or intervention;
4. Using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article or intervention is investigational;
5. Promising “free medical treatment” when the intent is only to say participants will not be charged for taking part in the investigation;
6. Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media;
7. Offers for a coupon good for a discount on the purchase price of an investigational product once it has been approved for marketing; and
8. The inclusion of exculpatory language.

Recruitment materials should be limited to the information prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included:

1. The name and address of the investigator and/or research facility;
2. The condition being studied and/or the purpose of the research;
3. In summary form, the criteria that will be used to determine eligibility for the study;
4. The time or other commitment required of the subjects;
5. The location of the research and the person or office to contact for further information;
6. A clear statement that the activity is research and not treatment;
7. A brief list of potential benefits (e.g., no-cost health exam).

Once approved by the IRB, advertisements and recruitment materials cannot be altered or manipulated in any way without prior IRB approval.

Directory listings of research such as [ClinicalTrials.Gov](https://www.clinicaltrials.gov) are not considered advertisements and therefore do not require IRB review and approval if the listing is limited to the following basic trial information: title, purpose of the study, summary description of the research, basic eligibility criteria, study site location(s), and how to contact the study site for further information.

The first contact prospective study subjects make is often with a person who follows a script to determine basic eligibility for the specific study. The IRB should review the script and procedures to ensure that the screening procedures adequately protect the rights and welfare of the prospective subjects.

12.12.10 Payments and Reimbursements

Payments to research subjects are commonly proposed as an incentive for participation in recognition of the time, effort, inconveniences, and discomforts that participation in the proposed research may entail. In contrast to payments, reimbursement is provided to cover actual costs incurred by subjects as a result of participation (e.g., travel, parking, lodging, etc.). Payment arrangements should be managed separately from reimbursement

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whenever possible because the ethical considerations differ (as well as the potential tax implications). Reimbursement offsets costs and may decrease financial risks associated with participation and in doing so may facilitate equitable selection of subjects. In contrast, the amount, timing, and nature of payments may unduly influence potential subjects' decision-making, influencing them to accept discomforts or risks that they otherwise would find unacceptable and interfering with truly voluntary informed consent. Payment arrangements may also create issues with equitable selection of subjects, including the societal distribution of research risks and benefits and the generalizability of the research results.

The IRB must consider the proposed amount of payment, the method and timing of disbursement, the subject population, the recruitment methods and materials, and the information provided within the proposed consent form in order to evaluate the acceptability of a proposed payment plan. The IRB does not consider payment as a benefit when weighing the risks and benefits of the research, payment is an incentive not a benefit of the research.

Investigators who wish to pay research subjects must include in their application to the IRB the amount and schedule of all payments and the justification or basis for payment. Such justification should substantiate that proposed payments are reasonable and commensurate with the time and inconveniences associated with study participation and do not constitute (or appear to constitute) undue pressure on the potential subject to volunteer for the research study.

When research involves multiple visits or interactions, payment should be prorated and not be contingent upon the participant completing the entire study. Further, any amount paid as a bonus for completion of the entire study should not be so great that it could unduly induce subjects to remain in the study when they otherwise would have withdrawn.

The consent form must describe the terms of payment including the amount and schedule of payments and any conditions under which subjects would receive partial payment (e.g., if they withdraw from the study before their participation is completed) or no payment.

Plans to reimburse subjects for incurred expenses must also be outlined in the application to the IRB and described within the consent.

NJH has policies in place to address how and what information is collected and reported for subjects who receive the amount of compensation required to be reported to the Internal Revenue Service (IRS). When applicable, the consent form must disclose the information that will be collected (e.g., Social Security Number), who will be provided or have access to the information, and the circumstances that necessitate IRS reporting.

12.12.11 Non-Monetary Gifts and Incentives

Similar to financial incentives, non-monetary gifts or incentives can also present problems of undue influence or coercion that impact a potential subject's ability to fully and freely consider participation in research.

If subjects will be provided with non-monetary gifts or tokens of appreciation, such as course credit, totes, books, toys, or other non-monetary gifts or incentives, the approximate retail value must be described to the IRB and the IRB will be provided with a description, photo, or sample product to review.

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The IRB will review all gifts and incentives being particularly sensitive to the influence of power or authority, whether perceived or actual, over free decision-making. Overt coercion (e.g., threatening loss of credit, or access to services or programs, to which the potential subjects are otherwise entitled) is never appropriate. Moreover, it must be clear that choosing to not participate will not adversely affect an individual's relationship with the organization or its staff or the provision of services in any way (e.g., loss of credits or access to programs).

Investigators should carefully structure incentives and methods of disbursement so that while the incentives may serve as a factor in a subject's decision to participate, that they have not served to unduly influence or coerce participation.

12.12.12 State and Local Laws

The IRB considers and adheres to all applicable state and local laws in the jurisdictions where the research is taking place. The HRPP and IRB rely on the Compliance Office and Outside Counsel for the interpretation and application of Colorado law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. The IRB, with these resources, will ensure that consent forms are consistent with applicable state and local laws.

12.13 Continuing Review

For research that is FDA-regulated, or subject to the Pre-2018 Rule (i.e., initial approval received before January 21, 2019), the IRB will conduct continuing review of ongoing research at intervals that are appropriate to the level of risk of the research, but not less than once per year.

For research subject to the 2018 Rule (i.e., initial approval received on or after January 21, 2019), the IRB will conduct continuing review of ongoing research requiring review by the convened IRB at intervals that are appropriate to the level of risk of the research, but not less than once per year, except as described below. The date by which continuing review must occur will be recorded in IRB Manager and on initial and continuing review approval letters.

Unless an IRB determines otherwise, continuing review of research subject to the 2018 Rule is not required in the following circumstances:

- Research eligible for expedited review in accordance with 45 CFR 46.110;
- Research reviewed by the IRB in accordance with the limited IRB review described in Section 5.4;
- Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
 - Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
 - Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

Studies that fall into these categories and are determined to not require continuing review are still subject to prompt reporting requirements (e.g., proposed amendments, personnel changes, unanticipated problems involving risk to subjects or others, protocol deviation/violations/non-compliance). **They will also require submission of an annual progress report** that will collect information regarding status of the research activity. Investigators will receive courtesy reminder e-mail notices for completion of the progress

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report. IRB/HRPP staff will review the report for compliance with institutional policies (verification of human subjects training, COI review, etc). Failure to submit an annual progress report as required will constitute non-compliance with NJH's HRPP policy and may result in suspension of the study until compliance with this policy is confirmed.

Studies that fall into these categories may still be determined to require continuing review. For example, the IRB may determine that continuing review is required when:

1. Required by other applicable regulations (e.g., FDA);
2. Required by the terms of a grant, contract, or other agreement
3. The research involves topics, procedures, or data that may be considered sensitive or controversial;
4. The research involves particularly vulnerable subjects or circumstances that increase subjects' vulnerability;
5. An investigator has minimal experience in research or the research type, topic, or procedures; and/or
6. An investigator has a history of noncompliance

When the NJH IRB determines that continuing review is required for such research, it will document the rationale in the IRB record and communicate the requirement to the investigator in the IRB determination letter.

12.13.1 Continuing Review Process

As a courtesy to investigators, the HRPP Staff will send out a reminder notice to investigators in advance of the expiration date, however, it is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

Investigators must submit the following for continuing review, as applicable to the research:

1. The Continuing Review Application (this serves as the progress report);
2. Current, stamped, version of approved protocol
3. Last stamped, approved informed consent form(s)
4. The most recent signed consent document(s) (redacted, i.e., with the subject name and any other identifiers blacked-out);
5. Redacted copy(ies) of the last, signed HIPAA Authorization (HIP-004)
6. The most recent report from the DSMB or DMC;
7. The most recent annual report or progress report to the FDA and/or funding agency;
8. Any proposed modifications to the research including any changes to materials;
9. Any previously un-submitted publications or presentations resulting from the research;
10. Any previously un-submitted reports identified while completing the Continuing Review Application

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HRPP office staff attend the convened meetings and bring the complete study files for each study on the agenda. IRB members can request the study file or any additional materials from the HRPP Staff prior to the meeting.

In the case of expedited review, the reviewer may request that the IRB office staff provide them with any additional materials required for their review.

12.13.2 IRB Considerations for Continuing Review

In order to re-approve research at the time of continuing review, the IRB must determine that the regulatory criteria for approval continue to be satisfied. Because the research was previously found to satisfy the criteria for approval, the IRB focuses its considerations at the time of continuing review on whether any new information is available that would affect the IRB's prior determination that the criteria for approval are satisfied. The IRB pays particular attention to four aspects of the research and then makes a determination of whether or not the approval criteria are still met:

1. Risk assessment and monitoring;
2. Adequacy of the informed consent process;
3. Local investigator and organizational issues; and
4. Research progress.

12.13.3 Convened Board Review

In conducting continuing review of research not eligible for expedited review, IRB members are provided all of the materials listed in Section 12.2.4 and are responsible for reviewing, at a minimum, the Continuing Review Application, the current IRB-approved consent form(s) (when applicable), and any proposed modifications to the research or consent form(s). The complete IRB file and relevant IRB meeting minutes are available to IRB members upon request. The Primary and Secondary Reviewers are responsible for reviewing the complete materials submitted for continuing review and completing the reviewer checklist to facilitate the review and discussion at the meeting. At the meeting, the Primary and Secondary reviewers provide a summary of the research, their evaluation of the research and continuing review materials, and recommendations.

12.13.4 Expedited Review

In conducting continuing review under expedited procedures, the IRB Chair or designated reviewer(s) receive all of the previously noted materials. The reviewer(s) complete the continuing review checklist to determine whether the research meets the criteria allowing continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval. If the research no longer requires continuing review under the 2018 Rule (See Section 12) and the IRB reviewer determines that continuing review is required, the reviewer shall document the rationale in the checklist.

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, unless it has progressed to the point that it involves only one or both of the following:

- Data analysis, including analysis of identifiable private information or identifiable biospecimens, or

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- Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care;

and in limited circumstances described by expedited review categories (8) and (9) (see Expedited Review Categories in Section 12.1.2). It is also possible that research activities that previously qualified for expedited review, have changed or will change, such that expedited continuing review would no longer be permitted.

12.13.5 Possible IRB Actions after Continuing Review

As with Initial Review, at the time of Continuing Review, the convened IRB or IRB Member(s) conducting expedited review may take any of the actions described in Section 11.

If an IRB member conducting expedited review believes that continuation of the research should be disapproved, they will refer the proposed modification to the convened board for review. If the proposed changes raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research (See Section 13 for a detailed discussion of suspensions and terminations).

If a research study receives Conditional Approval at the time of the continuing review, the IRB will specify whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions or requirements that must be adhered to until the conditions of approval have been satisfied. For example, if at the time of continuing review, the IRB requires the investigator to change the research protocol to include a specific new procedure for screening prospective subjects, the IRB could approve the research with the following condition: *“Research activities involving currently enrolled subjects may continue, but no new subjects may be enrolled until a designated IRB member reviews a revised protocol and verifies that the protocol includes the new screening procedure”*. Additionally, the IRB may specify a time period, such as 1, 2, or 3 months, for the condition(s) to be satisfied as long as the activity with conditions is not begun or restarted until final approval is granted.

12.13.6 Lapses in Continuing Review

The regulations permit no grace period or approval extension after expiration of approval. Research that continues after the approval period has expired is research conducted without IRB approval. If re-approval does not occur within the time set by the IRB, all research activities must stop, including recruitment (media advertisements must be withdrawn), enrollment, consent, interventions, interactions, and data collection. **This will occur even if the investigator has submitted the continuing review materials before the expiration date. Therefore, investigators must submit their continuing review materials enough in advance of expiration to allow sufficient time for IRB review before the expiration date.**

When the IRB approves research with conditions at the time of continuing review before the expiration date of the preceding IRB approval period, IRB approval does not lapse if the investigator needs additional time – beyond the date on which the preceding IRB approval would have expired – to satisfy some or all of the IRB’s conditions. However, the investigator and the IRB should make every effort to resolve any conditions and finalize approval in as timely a manner as possible.

In the event that study approval does expire, the HRPP staff contacts the investigator to assess project status, and relays instructions that all research activities must stop. If the study is completed, the investigator is advised to submit a completion report. If the study is to continue, the investigator is advised to submit a continuing review

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application. HRPP Staff will assess if the study has subjects currently enrolled, and if yes, will refer the matter to the IRB Chair to evaluate as possible noncompliance (See Section 19).

The lapse of IRB approval due to a failure to complete continuing review and obtain re-approval prior to expiration of the prior approval does not ordinarily constitute a suspension or termination of IRB approval, for federal reporting purposes; however, the failure to meet continuing review obligations may be grounds for suspension or termination of the research. If the IRB notes a pattern of noncompliance with the requirements for continuing review (e.g., an investigator repeatedly or deliberately neglects to submit materials for continuing review in a timely fashion or the IRB itself is not meeting the continuing review dates), the IRB should determine the reasons for the non-compliance and take appropriate corrective actions. When research is subject to federal reporting mandates, the IRB must report to FDA/OHRP any instance of serious or continuing noncompliance with FDA regulations or IRB requirements or determinations.

12.13.6.1 Management of Enrolled Subjects During Lapse

While enrollment of new subjects cannot occur after the expiration of IRB approval, the IRB recognizes that temporarily continuing participation of already enrolled subjects may be necessary or appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects, or when withholding those interventions or safety monitoring procedures would place subjects at increased risk. In these instances, the investigator must, at the earliest opportunity, contact the IRB office and submit a request to continue those research activities that are in the best interests of subjects. Such a request should specifically list the research activities that should continue, provide justification, and indicate whether the request applies to all or only certain subjects. The IRB Chair or designee will review the request and provide a determination regarding what activities, if any, may continue during the lapse. Such a determination may include a time limit or other conditions or restrictions. If the IRB decides that already enrolled subjects should continue to receive the interventions that were being administered to subjects under the research project, data collection (especially safety information) should also continue for such subjects.

When there is insufficient time to obtain an IRB determination (e.g., the study regimen includes daily administration of an investigational agent), the investigator may make an initial determination in consultation with the subjects' treating physician, if appropriate. In such cases, the investigator must, as soon as possible, contact the IRB office and submit a request for confirmation that the IRB agrees with the determination. The IRB Chair or designee will review the request and provide a determination. In the event that the IRB does not agree with the investigator's determination, or only agrees in part (e.g., agrees that some but not all of the activities are in the best interests of subjects), the IRB will notify the investigator who must then comply with the IRB's requirements or request a re-review of the determination by providing additional justification or information that the IRB may not have considered.

12.14 Modification of an Approved Protocol

Investigators may wish to modify or amend approved research. **Investigators must seek IRB approval before making any changes, no matter how minor, in approved research** unless the change is necessary to eliminate an immediate hazard to the subject (in which case the IRB must then be notified at once).

Investigators should consider whether the proposed changes to the research alter the original scope, purpose, or intent of the research. When the research itself is fundamentally changed, the IRB will typically require a new study application rather than allow such changes to be made through a modification to the existing research plan.

Page | 75

NOTE:

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12.14.1 Procedures

Investigators proposing to modify a study must submit to the RRA Office a Change to Protocol and/or Consent Form and all supporting documents identified in the form for review. The modifications may not be implemented until the IRB has reviewed and approved the proposed changes. When the modification involves the addition of investigators or study personnel, the investigators/personnel may not assume any study responsibilities involving human subjects or their identifiable data until the IRB has approved their participation.

RRA office staff will review the submission and make an initial determination whether the proposed changes may be approved through an expedited review process (i.e., changes to expedited research that do not alter the eligibility of the research for expedited review or minor changes to convened board studies) or whether the modification warrants convened board review. The IRB reviewer(s) using the expedited procedure has the ultimate responsibility to determine that the proposed changes may be approved through the expedited review procedure and, if not, must refer the research study for convened board review.

12.14.1.1 Convened Board Review of Modifications

When a proposed change in a convened board research study is not minor, or when a proposed change to an expedited study renders it no longer eligible for expedited review, the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is implementation of a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB must be promptly informed of the change following its implementation and will review the change to determine whether it was consistent with ensuring the subjects' continued welfare.

All IRB members are provided and review all documents provided by the investigator. The complete IRB file and relevant IRB meeting minutes are available to IRB members upon request. The Primary Reviewer completes the reviewer checklist to facilitate the review process and discussion at the meeting.

At the meeting, the Primary Reviewer presents an overview of the proposed modifications and assists the IRB Co-Chair in leading the NJH IRB through the criteria for approval and evaluating whether the modification alters any previous determinations (e.g., the risk determination), or necessitates any additional determinations (e.g., for vulnerable populations).

When the NJH IRB reviews modifications to previously approved research, the IRB considers whether information about those modifications might relate to subjects' welfare or willingness to continue to take part in the research, and, if so, whether to provide that information to future, current, or past subjects.

12.14.1.2 Expedited review of Modifications

An IRB may use expedited review procedures to review changes to expedited research (as long as the proposed changes would not make the research no longer eligible for expedited review) and for minor changes to studies normally subject to convened IRB review. An expedited review may be carried out by the IRB Chair or the experienced members that have been designated by the Chair to conduct expedited reviews.

Expedited reviewer(s) complete the reviewer checklist to determine whether the modifications meet the criteria allowing review using the expedited procedure, and, if so, whether the research with the proposed modifications continues to meet the regulatory criteria for approval. The reviewer(s) will also evaluate whether the modification

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alters any previous determinations (e.g., a Subpart determination), or necessitates any additional determinations (e.g., for vulnerable populations).

The reviewer will also consider whether information about the modifications might relate to future, current, or past subjects' welfare or willingness to continue to take part in the research, and, if so, whether to provide that information to subjects.

12.14.2 Possible IRB Actions after Modification Review

As with initial review, the convened IRB or IRB Member(s) conducting expedited review may take any of the actions described in Section 11. (see Section 11 for a detailed description of these actions):

If an IRB member conducting expedited review believes that the proposed modifications should be disapproved, they will refer the proposed modification to the convened board for review. If the proposed changes raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research (See Section 13 for a detailed discussion of suspensions and terminations).

12.15 Protocol Exceptions

Protocol exceptions are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a research plan. Unlike modifications that apply to all subsequent subjects in the research, a protocol/research plan exception only applies to a specific subject or group of subjects.

Exceptions are planned, and the investigator gets approval from the IRB ahead of time. For sponsored research, prior approval from the sponsor is generally required. Depending on the nature of the exception, an expedited review may be possible. For an exception to be approved under expedited review, the research as a whole must be eligible for expedited review, or, for convened board research, the proposed exceptions must not increase risk or decrease benefit, negatively impact the risk/benefit analysis, negatively affect the participant's rights, safety, or welfare, or negatively affect the integrity of the resultant data.

Procedures for exceptions are the same as for a Protocol Modification. The investigator must submit a "Change to Protocol and/or Consent Form" along with any new or revised materials, and documentation of sponsor approval, if applicable.

The only time a protocol/Research Plan exception would not require prior sponsor or IRB approval is when the exception is necessary to avoid an apparent immediate hazard to the subject(s). In such cases, the exception must be submitted to the IRB as soon as possible.

12.16 Closure of Research Studies

The completion or early termination of the study, is a change in research activity and should be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report to the IRB allows it to close its files as well as providing information that may be used by the IRB in the evaluation and approval of related studies.

Studies may be closed when the involvement of human subjects ceases (interventions, interactions, observations, and the gathering, use, study, and analysis of identifiable private information, including specimens, are all complete).

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For multi-center research, the study may be closed once all research activities (as above) are complete at NJH and any sites for which the IRB is serving as the “IRB of record”. If the investigator is serving as the lead investigator or the site is the coordinating center, the study must remain open as long as the lead investigator or coordinating center is still receiving, studying, using, or analyzing identifiable private information from other sites (even if local interventions, interactions, observations, and data gathering is complete).

Investigators may submit study closures to the IRB on a Study Closure Report. With closure submissions, the investigator must provide a summary of the research activity and any findings available at that time.

Investigators may maintain the data that they collected, including identifiable private data, if this is consistent with the IRB-approved research plan. However, investigators may not conduct any additional analysis of identified data without applying for IRB approval or exemption. Investigators must continue to protect the confidentiality of the data as described to the IRB and honor any other commitments that were agreed to as part of the approved research including, for example, future use of data or specimens, provision of research results to subjects, and provision of any outstanding payments or compensation.

The IRB will review study closure reports, typically by expedited review, and either approve the closure of the study or request additional information or confirmation of facts from the investigator.

13 Suspensions and Terminations

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 Section 18 for a discussion of unanticipated problems and Section 19 for a discussion of 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 IO and IRB Co-Chairs have the authority to suspend or terminate the organization’s approval of research. Such actions will be promptly reported to the IRB so that the IRB can review the circumstances and take any necessary actions relevant to IRB review and oversight.

13.1 Definitions

Suspension of IRB approval is a directive of the convened IRB or (or IO or IRB Co-Chairs as above) to temporarily stop some or all previously approved research activities. The IRB Chair may temporarily suspend IRB approval, in part or in full, when the available information suggests that actions must be taken to protect human subjects or the integrity of the research, prior to the next convened meeting of the IRB. Suspensions by the IO or Co-Chairs will be reported to the convened IRB at the next scheduled meeting at which time the convened IRB will determine if the suspension should continue, be lifted, or be modified. Suspended research studies remain open and require continuing review. Investigators must continue to provide reports to both the IRB and sponsors just as if there had never been a suspension (i.e., all events that need to be reported during a study need to continue to be reported during the suspension period).

When approval of some or all research activities is suspended by the IRB, the IRB will consider whether subjects should be notified and any actions necessary to ensure that the rights, safety, and welfare of subjects are appropriately protected.

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The IRB will notify the investigator of suspensions in writing; a call or email may precede the written notice when appropriate. Written notices of suspensions will include a statement of the reason(s) for the IRB's action and any requirements or conditions associated with the suspension (e.g., notification of subjects). The investigator will be provided with an opportunity to respond in person or in writing.

Suspensions of IRB approval must be reported promptly to the IO, sponsors including federal department or agency heads, and federal oversight agencies as applicable. See Section 22 for a detailed discussion of reporting requirements.

Termination of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously approved research study. Terminated research studies are closed and no longer require continuing review. Terminations of IRB approval of research studies must be made by the convened IRB.

When study approval is terminated by the IRB, in addition to stopping all research activities, the IRB will consider notification of subjects and any actions necessary to ensure that the rights, safety, and welfare of subjects are appropriately protected.

The IRB will notify the investigator of terminations in writing; a call or email may precede the written notice when appropriate. Written notices of terminations will include a statement of the reasons for the IRB's action and any requirements associated with the termination (e.g., notification of subjects). The investigator shall be provided with an opportunity to respond in person or in writing.

Terminations of IRB approval must be reported promptly to the IO, sponsors including federal department or agency heads, and federal oversight agencies as applicable. See Section 22 for a detailed discussion of reporting requirements.

13.2 Protection of Currently Enrolled Participants

Before a study termination or suspension, is put into effect the IRB Chair/Vice Chair or convened IRB considers whether any additional procedures need to be followed to protect the rights and welfare of current participants. Such procedures might include:

- Transferring subjects to another investigator/site
- Making arrangements for clinical care outside the research
- Allowing continuation of some research activities under the supervision of an independent monitor
- Requiring or permitting follow-up of subjects for safety reasons
- Requiring adverse events or outcomes to be reported to the IRB and the sponsor
- Notification of current subjects
- Notification of former subjects

14 Documentation and Records

NJH prepares and maintains adequate documentation of the IRB's activities. 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.

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14.1 IRB Records

IRB records include, but are not limited to:

1. Written operating procedures;
2. IRB membership rosters;
3. IRB member files including documentation of appointments, experience, education/training, and expertise;
4. IRB correspondence including reports to regulatory agencies;
5. IRB Protocol Files (See Section 14.2);
6. Documentation of exemptions including exemptions related to emergency uses and when limited IRB review is a condition of exemption;
7. Convened IRB meeting minutes;
8. Documentation of review by an external IRB, when appropriate;
9. Documentation of IRB reliance and cooperative review agreements;
 - a. For nonexempt research involving human subjects covered by the Common Rule (or exempt research for which limited IRB review takes place as described in Section 5.4) 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;
11. Federal Wide Assurances;
12. Federal IRB Registrations; and
13. Documentation of complaints and any related findings and/or resolution.

14.2 IRB Protocol Files

The IRB maintains a separate file for each protocol (including expanded access), HUD, emergency use, or report it receives for review electronically in a secure drive, or, if FDA regulated, in paper form in secure cabinets. Each study is assigned a unique identification number. As applicable, protocol files include, but are not limited to the following:

1. The initial application and all associated documents and materials;
2. Modification requests and all associated documents and materials;

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3. Continuing review/progress reports and all associated documents and materials, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in Section 12;
4. Closure reports and all associated documents and materials;
5. Reports submitted after study or HUD approval including reports of significant new findings, data and safety monitoring reports, protocol violation reports, complaints, noncompliance, and reports of injuries to subjects including reports of potential unanticipated adverse device events and unanticipated problems involving risks to subjects or others;
6. IRB-approved consent, parental permission, and assent forms;
7. DHHS-approved sample consent form and protocol;
8. DHHS grant application
9. IRB reviewer forms and checklists;
10. Documentation of scientific or scholarly review;
11. Documentation of the type of IRB review. For exempt determinations and expedited review, this will include the category under which the review is allowed;
12. For expedited review, documentation of any findings and determinations required by the regulations and study-specific findings supporting those determinations, including, but not limited to, waiver or alteration of consent, waiver of documentation of consent, research involving pregnant women, fetuses, and neonates, research involving prisoners, and research involving children. For research reviewed by the convened board these findings and determinations are recorded in the minutes;
13. For expedited review, documentation of the risk determination and period of approval (when continuing review is required). For research reviewed by the convened board these determinations are recorded in the minutes;
14. For expedited review, the rationale for an expedited reviewer's determination under 45 CFR 46.110(b)(1)(i) that research appearing on the expedited review list described in 45 CFR 46.110(a) is more than minimal risk.
15. Documentation of all IRB review actions;
16. Notification of expiration of IRB approval to the investigator;
17. Notification of suspension or termination of research;
18. Letters to investigator informing them of IRB review outcomes;
19. IRB correspondence to and from investigators related to the protocol;
20. All other IRB correspondence related to the research;
21. For studies evaluating the safety or effectiveness of medical devices, documentation of the device determination (exempt, non-significant risk, significant risk);
22. Reports of unanticipated problems involving risk to subjects or others; and
23. Any statements of significant new findings provided to subjects.

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14.3 The IRB Minutes

Draft minutes of IRB meeting proceedings are written and available for review by the next regularly scheduled IRB meeting. Once reviewed and accepted by the members, a copy is saved on the RRA drive and made available to the IO. Changes may not be made to finalized minutes without re-review by the IRB to verify accuracy.

Minutes of IRB meetings must contain sufficient detail to show the following, as applicable:

1. Attendance
 - a. Each member's (or alternate's) full name;
 - b. Each member's (or alternate's) representative capacity (e.g., scientist, non-scientist, unaffiliated, member who represents the general perspective of research subjects)
 - c. The names of members or alternate members who are participating through videoconference or teleconference and documentation that those attending remotely received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions;
 - d. Names of alternates attending in lieu of specified (named) absent members. (Alternates may substitute for specific absent members or categories of members only as designated on the official IRB membership roster);
 - e. Names of any consultants present, a brief explanation of their expertise, and documentation to support that the consultant(s) did not vote;
 - f. The names of non-members and guests in attendance, such as IRB staff, investigators, and study coordinators
2. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area;
3. Business Items discussed and any education provided;
4. Actions taken, including separate deliberations, actions, and votes for each submission undergoing review by the convened IRB;
5. Vote counts on these actions (Total Number Voting; Number voting for; Number voting against; Number abstaining; Number of those recused). When a member is recused due to conflict of interest, the name of the member and reason for the recusal will be noted;
6. Basis or justification for actions disapproving or requiring changes in research;
7. Summary of controverted issues and their resolution;
8. Approval period for initial and continuing reviews (when applicable), including identification of research that warrants review more often than annually and the basis for that determination;
9. Risk determination for initial and continuing reviews, and modifications when the modification alters the prior risk determination;

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10. The rationale for requiring continuing review of research that otherwise would not require continuing review as described in Section 12;
11. Justification for deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document;
12. Study-specific findings supporting that the research meets each of the required criteria when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain informed consent altogether;
13. Study-specific findings supporting that that the research meets each of the required criteria when the requirements for documentation of consent are waived;
14. Study-specific findings supporting that the research meets each of the criteria for approval for vulnerable populations under any applicable Subparts;
15. Exempt/significant risk/non-significant risk device determinations and the basis for those determinations;
16. Determinations related to conflicts of interest and acceptance or modification of conflict management plans;
17. Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research;
18. Review and determinations related to interim reports (e.g., unanticipated problems or safety reports, serious or continuing noncompliance, suspensions or terminations, etc.);
19. A list of research approved under expedited review procedures, including limited IRB reviews conducted using expedited procedures, since the time of the last such report;
20. An indication that, when an IRB member or alternate has a conflicting interest (see Section 25.2) with the research under review, the IRB member or alternate was not present during the final deliberations or voting; and
21. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.

14.4 IRB Membership Roster

A membership list of IRB members will be maintained; it will identify members sufficiently to describe each member's chief anticipated contributions to IRB deliberations. The list will contain the following information about members:

1. Name;
2. Earned degrees;
3. Employment or other relationship between each member and the organization (i.e., affiliated or non-affiliated). To be categorized as non-affiliated, neither the member nor an immediate family member of the member may be affiliated with NJH.

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4. Status as scientist or non-scientist. Members whose training, background, and occupation would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline are considered a scientist for the purposes of the roster. Members whose training, background, and occupation would incline them to view research activities from a standpoint outside of any biomedical or behavioral scientific discipline are considered a nonscientist. Physicians, nurses, and pharmacists are considered scientists;
5. Indications of experience, such as board certifications, licenses, and areas of practice sufficient to describe each member's chief anticipated contributions to IRB deliberations;
6. Representative capacities of each IRB member; including which IRB member(s) is a prisoner representative, and which IRB members are knowledgeable about or experienced in working with children adults with impaired decision-making capacity, and other subjects vulnerable to coercion or undue influence commonly involved in NJH research;
7. Role on the IRB (Chair, non-scientist, pediatric specialist, etc.);
8. Voting status; and
9. For alternate members, the primary member or class of members for whom the member could substitute.

The IRB office must keep the IRB membership list current. Changes in IRB membership are reported to OHRP and FDA on the federal IRB registration within 90 days of the change.

14.5 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 the IRB action taken on those aspects of the research subject to limited IRB review in accordance with the procedures described for the review procedures used (expedited or convened board) elsewhere in this SOP.

14.6 Documentation of Expedited Reviews

IRB records for initial and continuing review by the expedited procedure must include the reviewer's verification that the study qualifies for expedited review including the specific permissible category(ies) or status as exempt but requiring limited IRB review, documentation that the activity satisfies the criteria for approval, the period of approval (when applicable), and any determinations required by the regulations including study-specific findings justifying the following determinations:

1. Approving a procedure which waives or alters the informed consent process;
2. Approving a procedure which waives the requirement for documentation of consent;
3. Approving research involving pregnant women, human fetuses, or neonates;
4. Approving research involving prisoners;
5. Approving research involving children.

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14.7 Access to IRB Records

IRB protocol files are secured either electronically on a secure drive, or in secure cabinets (for FDA regulated research). Access to these files is controlled by the IRB office. All other IRB records (e.g., membership rosters) are kept secure in a limited access file on NJH servers, locked filing cabinets or locked storage rooms.

Ordinarily, access to IRB records is limited to the IO, Director of RRA and HRPP staff, IRB members, authorized organizational officials, and officials of federal and state regulatory agencies (e.g., OHRP and FDA). Research investigators are provided reasonable access to files related to their research. Appropriate accreditation bodies are provided access.

Records are accessible for inspection and copying by authorized representatives of federal regulatory agencies during regular business hours.

IRB member rosters are only provided to regulatory agencies, accreditation bodies, and persons or offices within NJH with a legitimate need (e.g., Corporate Compliance, Counsel, etc.).

All other access to IRB records is limited to those who have legitimate need for them, as determined by the IO or Director of RRA.

14.8 Record Retention

In order to comply with the requirements of OHRP, FDA, and HIPAA, IRB records are maintained for at least seven (7) years after completion of the research.

IRB records for research cancelled without participant enrollment will be retained for at least three (3) years after closure.

IRB minutes are retained until all of the studies that were reviewed at that meeting have been completed for at least three (3) years.

After the noted times, IRB records may be shredded or otherwise securely destroyed.

15 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 as provided in Sections 15.10, 15.11, and 15.12 of these procedures, 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 training and be knowledgeable about the study procedures,

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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 to be able to answer questions about the study including those regarding risks, procedures, and alternatives. The NJH IRB application solicits information regarding who will obtain consent; proposed changes to the personnel authorized to obtain consent must be submitted to the NJH 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 National Jewish Health 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).

15.1 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 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

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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.

15.2 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 IRB 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.

15.3 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 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.

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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 NJH 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 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 Section 16.7.

15.4 Basic Elements of Informed Consent

To be valid, the consent process must provide the following basic elements of information to potential subjects:

1. A statement that the **study involves research**, an explanation of the **purposes** of the research and the **expected duration** of the subject's participation, a description of the **procedures** to be followed, and identification of any **procedures which are experimental**;

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2. A description of any reasonably foreseeable **risks or discomforts** to the subject;
3. A description of any **benefits** to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which **confidentiality** of records identifying the subject must be maintained;
6. **For research involving more than minimal risk**, an explanation as to whether any compensation **and** an explanation as to whether any medical treatments are available if injury occurs **and**, if so, what they consist of, or where further information may be obtained;
7. An **explanation of whom to contact** for answers to pertinent questions about the research **and** research subjects' rights, **and** whom to contact in the event of a research-related injury to the subject;
8. A statement that participation is **voluntary**, refusal to participate will involve **no penalty or loss of benefits** to which the subject is otherwise entitled, and the subject **may discontinue participation** at any time without penalty or loss of benefits to which the subject is otherwise entitled;
9. One of the following statements about any research that involves the **collection of identifiable private information or identifiable biospecimens**:
 - a. A statement that **identifiers might be removed** from the identifiable private information or identifiable biospecimens **and that**, after such removal, the information or biospecimens **could be used** for future research studies or distributed to another investigator for future research studies **without additional informed consent** from the subject or the legally authorized representative, if this might be a possibility; or
 - b. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, **will not be used or distributed** for future research studies.
10. For **FDA-regulated studies**, a statement that notes the possibility that the Food and Drug Administration may inspect the records;
11. For [applicable](#) **FDA-regulated clinical trials**, the following statement must be included verbatim:

"A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

15.5 Additional elements of informed consent to be applied, as appropriate:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
3. Any additional costs to the subject that may result from participation in the research;

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4. When applicable, the amount and schedule of all payments;
5. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
6. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject;
7. The approximate number of subjects involved in the study.
8. A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
9. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions;
10. For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

15.6 NJH Requirements

In addition to the federal elements of consent described above, NJH has defined specific additional information that must be included in consent documents when applicable to the research (e.g., 1099 language). A list of these requirements is provided on the NJH IRB's website for investigator and reviewer reference.

15.7 Subject Withdrawal or Termination

A subject enrolled in a research study may decide to withdraw from the research, or an investigator may decide to terminate a subject's participation in research regardless of whether the subject wishes to continue participating. Investigators must plan for the possibility that subjects will withdraw from research and include a discussion of what withdrawal will mean and how it will be handled in their research plans and consent documents.

When seeking informed consent from subjects, the following information regarding data retention and use must be included:

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. This should be disclosed in the consent; 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

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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.

15.8 Documentation of Informed Consent

Except as provided in Sections 15.10, 15.11 and 15.12 of this document, informed consent must be documented by the use of a written consent form approved by the IRB.

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**

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

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- 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 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.

15.9 Special Consent Circumstances

15.9.1 Enrollment of persons with Limited English Proficiency

1. **Expected enrollment:** In some studies, the investigator may be able to anticipate enrollment of persons who do not speak or read, or have limited proficiency in, oral or written English. When the target subject population includes such persons or the investigator or the IRB otherwise anticipates that consent will be conducted in a language other than English, the IRB requires a translated consent document and other subject materials, as applicable. Generally, translated consent forms should not be prepared until the final approved version of the English-language version is available. To ensure that translated documents are accurate, the IRB may choose to require a certified translation, to have an independent back-translation, or to have a review of the translated documents by an IRB member or other person who is fluent in the language.
2. **Unexpected enrollment:** If a person who does not speak or read, or has limited proficiency in, English unexpectedly presents for possible enrollment, an IRB-approved translated version of the written consent may not be available for use. Investigators should carefully consider the ethical and legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented during the consent process or in subsequent discussions, his/her consent may not be informed or legally effective.

If an investigator decides to enroll a subject into a study for which there is not an extant IRB-approved consent document in the prospective subject's language, the investigator must receive IRB approval to follow the procedures for a "short form" written consent in as described in Section 15.8.

3. **Use of interpreters in the consent process:** Unless the person obtaining consent is fluent in the prospective subject's language, an interpreter will be necessary to facilitate the consent discussion. Preferably someone who is independent of the subject (i.e., not a family member) should assist in presenting information and obtaining consent. Whenever possible, interpreters should be provided copies of the translated consent, or short form and the IRB-approved consent script (typically the English-

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language version of the consent document), well before (24 to 48 hours if possible) the consent discussion with the subject. If the interpreter also serves as the witness, s/he may sign the translated consent, or short form consent document and script, as the witness and should note “Interpreter” under the signature line. The person obtaining consent must document that the “short form” process was used in the subject’s research record, including the name of the interpreter.

15.9.2 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 15.9.4).

15.9.3 Consenting in American Sign Language (ASL)

For deaf subjects who are fluent in ASL, the IRB may approve a consent process using ASL and the IRB-approved written consent form. When this process is approved, the individual authorized to consent prospective subjects must use a certified interpreter fluent in ASL to conduct the consent process and the documentation of the consent process must conform to the requirements set forth in Section 15.8.

15.9.4 Oral Consent

When subjects are unable to read a written consent form (such as blind or illiterate subjects), the 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 according to the criteria in Section 15.11.

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.

15.9.5 Physically-Challenged Subjects

A person who is physically challenged (e.g., physically unable to talk or write) can enroll in research if competent and able to indicate voluntary consent to participate. Whenever possible, the subjects should sign the consent form or make their mark by initialing or making an X. As with oral consent, a witness to the consent process is recommended and the circumstances and consent process should be carefully documented in the research records.

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15.10 Waiver or Alteration of Informed Consent

General Waiver or Alteration:

An IRB may waive the requirement to obtain informed consent, provided the IRB finds and documents that the below criteria are satisfied.

Likewise, an IRB may approve a consent procedure that omits some, or alters some or all, of the basic and additional elements of informed consent (an “alteration”), provided that the IRB finds and documents that the below criteria are satisfied.

1. The research or clinical investigation involves no more than minimal risk to the subjects;
2. The research or clinical investigation could not practicably be carried out without requested waiver or alteration;
3. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
4. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
5. Whenever appropriate, the subjects or LARs will be provided with additional pertinent information after participation.

This option applies to both FDA-regulated and DHHS-conducted or supported research.

Public Benefit or Service Programs Waiver or Alterations

An IRB may waive the requirement to obtain informed consent, provided the IRB finds and documents that the below criteria are satisfied.

Likewise, an IRB may approve a consent procedure that omits some, or alters some or all, of the basic and additional elements of informed consent (an “alteration”), provided that the IRB finds and documents that the below criteria are satisfied.

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
 - a. Public benefit or service programs;
 - b. Procedures for obtaining benefits or services under those programs;
 - c. Possible changes in or alternatives to those programs or procedures; or
 - d. Possible changes in methods or levels of payment for benefits or services under those programs; and
2. The research could not practicably be carried out without the waiver or alteration.

This option **does not** apply to FDA-regulated research.

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15.10.1 Screening, recruiting, or determining eligibility

An IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if either of the following conditions are met:

1. The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, or
2. The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

15.11 Waiver of Documentation of Informed Consent

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds any of the following:

1. The only record linking the subject and the research would be the consent document and the principle risk would be potential harm from a breach of confidentiality (e.g., domestic violence research where the primary risk is discovery by the abuser). Each subject (or LAR) must be asked whether they want documentation linking them with the research, and their wishes must govern.

This option **does not** apply to FDA-regulated research.

OR

2. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-investigators (e.g., marketing surveys, telemarketing).

This option **does** apply to FDA-regulated research (most commonly in the context of [minimal risk screening activities](#) that are necessary to determine eligibility for enrollment in a clinical trial.)

OR

3. If the subjects or LARs are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

This option **does not** apply to FDA-regulated research.

Unless the IRB has granted a full waiver of the requirement to obtain informed consent, investigators who seek and receive approval for a waiver of documentation of consent still must perform an appropriate consent process.

In cases in which the documentation requirement is waived, the IRB requires the investigator to provide in the application materials a written summary of the information to be communicated to the subject, and the IRB will consider whether to require the investigator to provide subjects with a written statement regarding the research.

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15.12 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 provisions equivalent to those of the FDA with the exception of the requirements specified in Sections 15.12.2.1 and 15.12.2.2 below. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

15.12.1 Definitions

Planned Emergency Research. It is research that involves subjects who, are in a life-threatening situation for which available therapies or diagnostics are unproven or unsatisfactory, and because of the subjects' medical condition and the unavailability of legally authorized representatives of the subjects, it is generally not possible to obtain legally effective informed consent.

Family Member. For this Section means any one of the following adult and legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

15.12.2 Procedures

The IRB may approve the planned emergency research without requiring informed consent of all research subjects prior to initiating the research intervention if the IRB finds and documents that the following conditions have been met:

1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
2. Obtaining informed consent is not feasible because:
 - a. The subjects will not be able to give their informed consent as a result of their medical condition;
 - b. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
 - c. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
3. Participation in the research holds out the prospect of direct benefit to the subjects because:

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- a. Subjects are facing a life-threatening situation that necessitates intervention;
 - b. Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
 - c. Risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
4. The research could not practicably be carried out without the waiver.
 5. The proposed research plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
 6. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sections 46.116 and 46.117 of [45 CFR 46](#) and Sections 50.20, 50.25 and 50.27 of [21 CFR 50](#). These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research consistent.
 7. Additional protections of the rights and welfare of the subjects will be provided, including, at least:
 - a. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;
 - b. Public disclosure to the communities in which the research will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
 - c. Public disclosure of sufficient information following completion of the research to apprise the community and investigators of the study, including the demographic characteristics of the research population, and its results;
 - d. Establishment of an independent data monitoring committee to exercise oversight of the research; and
 - e. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

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In addition, the IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the research, the details of the research and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the research and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into research with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the research is to be provided to the subject's legally authorized representative or family member, if feasible.

15.12.3 FDA-regulated Planned Emergency Research

A licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation must concur that the conditions described in Section 15.12.2 are satisfied.

Studies involving an exception to the informed consent requirement under this Section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies that such studies may include subjects who are unable to consent. The submission of those studies in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for such investigations may not be submitted as amendments under [312.30](#) or [812.35](#).

If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided in the regulations or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

The IRB determinations and documentation required in Section 15.12.2 and the above paragraph are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with [56.115\(b\)](#).

15.12.4 Documentation and Reporting of Planned Emergency Research Not Subject to FDA Regulations

The IRB responsible for the review, approval, and continuing review of the research must approve both the research and a waiver of informed consent and have (i) found and documented that the research **is not** subject to regulations codified by the FDA at [21 CFR Part 50](#), and (ii) found and documented **and** reported to the OHRP that the conditions required Section 15.12.2 have been met relative to the research.

15.13 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**

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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, as required by the protocol.

16 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. The 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.

16.1 Definitions

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 IRB 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 IRB 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:

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.

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).

Fetus. A fetus means the product of conception from implantation until delivery [\[45 CFR 46.202\(c\)\]](#).

Dead fetus. A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord [\[45 CFR 46.202\(a\)\]](#).

Delivery. Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means [\[45 CFR 46.202\(b\)\]](#).

Neonate. A neonate is a newborn [\[45 CFR 46.202\(d\)\]](#).

Viable. As it pertains to the neonate, viable means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration [\[45 CFR 46.202\(h\)\]](#). If a neonate is viable, then, for the purposes of participation in research, the neonate is considered a child and the rules regarding participation of children in research apply.

Nonviable neonate. A nonviable neonate means a neonate after delivery that, although living, is not viable [\[45 CFR 46.202\(e\)\]](#).

Pregnancy. Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery [\[45 CFR 46.202\(f\)\]](#).

Prisoner. Prisoner means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing [\[45 CFR 303\(c\)\]](#).

16.2 Involvement of Vulnerable Populations in Research

When the NJH 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.

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

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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.

16.3 Procedures

The following policies and procedures apply to all research involving subjects vulnerable to coercion or undue influence under the oversight of the National Jewish Health IRB regardless of funding. Subsequent sections address additional procedures and requirements that apply to specific populations.

16.3.1 Initial Review of Research Proposal:

1. The investigator identifies the potential to enroll vulnerable subjects in the proposed research at initial review and provides the justification for their inclusion in the study;
2. The investigator describes safeguards to protect the subject's rights and welfare in the research proposal;
3. HRPP Staff, in collaboration with the IRB Chair as needed, ensure that the IRB has the relevant expertise with the vulnerable population, and, if necessary, arrange for consultation. When the research involves no more than minimal risk and is eligible for expedited review, the designated reviewer may determine the need for additional expertise to ensure the protection of the vulnerable population(s);
4. The IRB evaluates the proposed safeguards, including, if applicable, the proposed plans for identifying, recruiting, and obtaining consent from subjects or their legally authorized representatives and the plans for assent of children and adults unable to provide consent;
5. When applicable, the IRB considers any costs associated with participation in the proposed research and any plans for reimbursement of expenses or provision of compensation, and the potential impact of such on the vulnerable population(s);
6. The IRB evaluates the research to determine whether the proposed plan is adequate or if additional protections are needed such as interim monitoring, review more than annually, or the use of a data and safety monitoring board, consent monitor, or research subject advocate.

16.3.2 Modifications to Research

1. When an investigator proposes to add inclusion of a vulnerable population after research has already been approved by the IRB, the investigator must submit a modification request to the IRB identifying the population they would like to add, justification for inclusion of the population, and any modifications to the research plan to ensure protection of the subjects' rights and welfare;
2. The HRPP Staff and IRB will follow the procedures outlined for initial review above.

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16.3.3 Continuing Review

1. At continuing review, the investigator should identify the number and categories of vulnerable subjects enrolled and any problems that arose relevant to their rights and welfare. When research does not include any interaction or intervention with subjects, and such information is not gathered, this should be noted on the continuing review report;
2. HRPP Staff, in collaboration with the IRB Chair as needed, ensure that the IRB has the relevant expertise with the vulnerable population, and, if necessary, arrange for consultation. When the research involves no more than minimal risk and is eligible for expedited review, the designated reviewer may determine the need for additional expertise to ensure the protection of the vulnerable population(s);
3. The IRB reviews the continuing review information, and any relevant information reported to the IRB during the period of approval, and determines whether the inclusion of vulnerable populations and the plans to protect the rights and welfare of vulnerable subjects remains appropriate.

16.4 Research Involving Pregnant Women, Human Fetuses and Neonates

The following applies to all research involving pregnant women, human fetuses, and neonates reviewed by the National Jewish Health IRB, with exceptions noted.

If a woman becomes pregnant while participating in a study that has not been approved for inclusion of pregnant women, the IRB must be notified immediately so that the IRB can determine whether the subject may continue in the research, whether additional safeguards are needed, and to make the determinations required by the regulations and these policies.

16.4.1 Research Involving Pregnant Women or Fetuses

16.4.1.1 Research Not Conducted or Supported by DHHS

For research not conducted or supported by DHHS, where the risk to the pregnant women and fetus is no more than minimal, no additional safeguards are required by policy and there are no restrictions on the involvement of pregnant women in research. However, the IRB may determine that additional safeguards or restrictions are warranted for a specific study.

Pregnant women or fetuses may be involved in research not funded by DHHS **involving more than minimal risk** to pregnant women and/or fetuses if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent;

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.

5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 16.1) who are pregnant, assent and permission are obtained in accord with the requirements of state law and the IRB;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. The IRB may allow individuals whose normal responsibilities include determining the viability of fetuses to be engaged in the research, if their involvement in the determination of viability for an individual fetus cannot be avoided. Confirmation of the determination regarding viability will be sought from a qualified individual who is not otherwise engaged in the research whenever possible prior to involving the subject(s) in the research. The opinion of the independent qualified individual will be documented and made available upon request to the IRB or HRPP representative. When advance confirmation is not possible, the investigator will obtain it as soon as s/he can after enrollment, but in all cases within 5 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within 10 business days.

16.4.1.2 Research Conducted or Supported by DHHS

For DHHS-conducted or supported research, 45 CFR Subpart B applies to all non-exempt human subject research involving pregnant women, fetuses, and neonates.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.

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.

5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 16.1) who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 16.6.2;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

16.4.2 Research involving Neonates of Uncertain Viability or Nonviable Neonates

16.4.2.1 Research Not Conducted or Supported by DHHS

Neonates of uncertain viability and nonviable neonates may be involved in research **involving more than minimal risk** if all of the conditions listed below are met. The IRB will determine on a case-by-case basis whether safeguards or restrictions should be required for minimal risk research.

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
3. The IRB may allow individuals whose normal responsibilities include determining the viability of neonates to be engaged in the research, if their involvement in the determination of viability for an individual neonate cannot be avoided. In such cases, confirmation of the determination regarding viability must be made by a qualified individual who is not otherwise engaged in the research whenever possible prior to involving the subject(s) in the research. The opinion of the independent qualified individual will be documented and made available upon request to the IRB or HRPP representative. When advance confirmation is not possible, the investigator will obtain it as soon as s/he can after enrollment, but in all cases within 5 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within 10 business days.
4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below) have been met as applicable.

Neonates of Uncertain Viability. Until it has been ascertained whether a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:

The IRB determines that:

NOTE:

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1. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
2. The purpose of the research is the development of important knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
3. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's LAR is obtained in accord with the provisions of permission and assent, except that the consent of the father or his LAR need not be obtained if the pregnancy resulted from rape or incest.

Nonviable Neonates. After delivery, nonviable neonates may not be involved in research unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;
3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important knowledge that cannot be obtained by other means; and
5. The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.

However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a LAR of either or both of the parents of a nonviable neonate will not suffice.

16.4.2.2 Research Conducted or Supported by DHHS

Neonates of uncertain viability and nonviable neonates may be involved in research conducted or supported by DHHS if all of the following conditions are met:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
3. Individuals engaged in the research will have no part in determining the viability of a neonate.
4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below) have been met as applicable.

Neonates of Uncertain Viability. Until it has been ascertained whether a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:

NOTE:

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The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

1. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
2. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's LAR is obtained in accord with the provisions of permission and assent, except that the consent of the father or his LAR need not be obtained if the pregnancy resulted from rape or incest.

Nonviable Neonates. After delivery, nonviable neonates may not be involved in research unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;
3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
5. The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.

However, if either parent is unable to consent because of unavailability or incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a LAR of either or both of the parents of a nonviable neonate will not suffice.

16.4.3 Viable Neonates

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements for research involving children (i.e., a viable neonate is a child for purposes of applying federal research regulations and NJH policies).

16.4.4 Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material

Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, must be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

If information associated with material described above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent sections of these policies and procedures are applicable.

NOTE:

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16.4.5 Research Not Otherwise Approvable

16.4.5.1 Research Not Conducted or Supported by DHHS

If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the research is not approvable under the provisions described previously in this section, the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:

1. That the research in fact satisfies the conditions detailed above, as applicable; or
2. The following:
 - a. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
 - b. The research will be conducted in accord with sound ethical principles; and
 - c. Informed consent will be obtained in accord with the requirements for informed consent described in this manual.

16.4.5.2 Research Conducted or Supported by DHHS

DHHS-conducted or supported research that falls in this category must be approved by the Secretary of Health and Human Services. If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the research will be sent to OHRP for DHHS review.

16.5 Research Involving Prisoners

16.5.1 Applicability

For research not conducted or supported by DHHS, where the risk to prisoners is no more than minimal (as defined in Section 16.5.2), only the restrictions outlined in the Colorado Department of Corrections Regulation 1400-03 are required under these policies and procedures. However, the NJH IRB may determine that additional safeguards or restrictions are warranted for a specific study.

For research involving more than minimal risk, and for research conducted or supported by DHHS (unless the research qualifies for exemption and only incidentally includes prisoners (See Section 5)), the requirements outlined in this section apply.

As applicable, investigators must obtain permission from and abide by the requirements of correctional authorities and state or local law.

NOTE:

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16.5.2 Minimal Risk

Minimal risk, in studies involving prisoners, means the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

16.5.3 Composition of the IRB

In addition to satisfying the general membership requirements detailed in other Sections of these policies and procedures, when reviewing research involving prisoners, the IRB must also meet the following requirements:

1. A majority of the IRB (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership on the IRB;
2. At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement; and
3. The prisoner representative must be a voting member of the IRB. A comment may be added to the roster indicating that the prisoner representative will only count towards quorum when s/he is in attendance and reviewing studies involving prisoners.

16.5.4 Review of Research Involving Prisoners

16.5.4.1 Initial Review of Research Proposal

1. The prisoner representative must review research involving prisoners, focusing on the requirements outlined in Subpart C and these policies;
2. The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer); and
3. The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved. The prisoner representative may attend the meeting by phone, video-conference, or webinar, so long as the representative is able to participate in the meeting as if they were present in person at the meeting.
4. The IRB must be familiar with the specific conditions in the local prison(s) or jail site(s) that are pertinent to subject protections, before approving the proposal for the local site ([45 CFR 46.107\(a\)](#)).

16.5.4.2 Modifications to Research

1. Minor modifications to research involving prisoners may be reviewed using the expedited procedure described below;
2. Modifications reviewed by the convened IRB must use the same procedures for initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting (as described above).

NOTE:

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16.5.4.3 Continuing Review

1. Continuing review will follow the same procedures as initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting (as described above).

16.5.4.4 Expedited Review

NJH does not permit expedited review of any research involving prisoners.

16.5.4.5 Incarceration of Enrolled Subjects

1. If a subject becomes a prisoner while enrolled in a research study that was not reviewed according to these procedures, the investigator must promptly notify the IRB and the IRB shall:
 - a. Confirm that the subject meets the definition of a prisoner;
 - b. Consult with the investigator to determine if it is in the best interests of the subject to continue participation in the study, in part or in full, and if so, if there are specific study activities which are in the best interests of the subject that should continue until the IRB is able to review the research applying the standards and requirements for research involving prisoners.
2. If the subject should continue, one of two options are available:
 - a. Keep the subject enrolled in the study and review the research applying the standards and requirements for research involving prisoners. If some of the requirements cannot be met or are not applicable (e.g., procedures for the selection of subjects within the prison), but it is in the best interests of the subject to remain in the study, keep the subject enrolled and, if the research is DHHS-conducted or supported, inform OHRP of the decision along with the justification; or
 - b. Remove the subject from the study and keep the subject on the study intervention under an alternate mechanism such as compassionate use or off-label use.
3. If a subject is incarcerated temporarily while enrolled in a study:
 - a. If the temporary incarceration has no effect on the study (i.e., there is no need for study activities involving the prisoner subject to take place during the temporary incarceration), keep the subject enrolled.
 - b. If the temporary incarceration has an effect on the study, follow the guidance outlined above.

16.5.5 Additional Duties of the IRB

In addition to the responsibilities of the NJH IRB described in other sections of this manual, the NJH IRB will review research involving prisoners and approve such research only if it finds that:

1. The research falls into one of the following **permitted categories** [\[45 CFR 46.306\(a\)\(2\)\]](#):
 - a. Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

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- b. Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
 - c. Research on conditions particularly affecting prisoners as a class (for example, research on diseases or social and psychological problems much more prevalent in prisons) provided that the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research;
 - d. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols/research plans approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research; or
 - e. The research qualifies under the HHS Secretarial waiver that applies to certain epidemiological research ([68 FR 36929, June 20, 2003](#)). The criteria for this category are that the research must have as its sole purpose (i) to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease.
2. Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
 3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
 4. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research proposal;
 5. The information is presented in language which is understandable to the subject population;
 6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
 7. Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

16.5.6 Certification to DHHS

Under [45 CFR 46.305\(c\)](#), the institution responsible for conducting research involving prisoners that is conducted or supported by DHHS shall certify to the Secretary (through OHRP) that the IRB has made the seven findings

Page | 110

NOTE:

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required under [45 CFR 46.305\(a\)](#) and receive OHRP authorization prior to initiating any research involving prisoners. Certifications, and requests for DHHS Secretarial consultation, do not need to be submitted to OHRP for research not conducted or supported by DHHS.

For all DHHS-conducted or supported research, National Jewish Health will send to OHRP a certification letter to this effect, which will also include the name and address of the institution and specifically identify the research study in question and any relevant DHHS grant application or protocol/research plan. DHHS-conducted or supported research involving prisoners as subjects may not proceed until OHRP issues its authorization in writing to National Jewish Health on behalf of the Secretary.

Under its authority at [45 CFR 46.115\(b\)](#), OHRP requires that the institution responsible for the conduct of the proposed research also submit to OHRP a copy of the research proposal so that OHRP can determine whether the proposed research involves one of the categories of research permissible under [45 CFR 46.306\(a\)\(2\)](#), and if so, which one.

The term “research proposal” includes:

1. The NJH IRB-approved protocol; any relevant DHHS grant application or proposal;
2. Any IRB application forms required by the IRB; and
3. And any other information requested or required by the IRB to be considered during initial IRB review.

OHRP also encourages the organization to include the following information in its prisoner research certification letter to facilitate processing:

1. The OHRP Federalwide Assurance (FWA) number;
2. The IRB registration number for the designated IRB; and
3. The date(s) of IRB meeting(s) in which the study was considered, including a brief chronology that encompasses:
 - a. The date of initial IRB review; and
 - b. The date of subpart C review, if not done at the time of initial IRB review.

16.6 Research Involving Children

The following applies to all research involving children, regardless of funding source. The requirements in this section are consistent with [Subpart D](#) of 45 CFR 46, which applies to DHHS-funded research and [Subpart D](#) of 21 CFR 50, which applies to FDA-regulated research involving children.

16.6.1 Allowable Categories

In addition to the IRB’s normal duties, research involving children must be reviewed by the IRB to determine if it fits within and is permissible under one or more federally-defined categories (OHRP/FDA). Each procedure or intervention that the child will undergo for the research must be taken into consideration, and, if the research includes more than one study group assignment (e.g., placebo vs. active, investigational agent vs. comparator) the category determination must be made for each group assignment. In other words, a component analysis must be conducted by the IRB. The categories are as follows:

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1. **Research/Clinical Investigations not involving greater than minimal risk** [\[45 CFR 46.404/21 CFR 50.51\]](#). Research determined to not involve greater than minimal risk to child subjects may be approved by the IRB only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in Section 16.6.2.
2. Research/Clinical Investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects [\[45 CFR 46.405/21 CFR 50.52\]](#). Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may be approved by the IRB only if the IRB finds and documents that:
 - a. The risk is justified by the anticipated benefit to the subjects;
 - b. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative options; and
 - c. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 16.6.2.
3. Research/Clinical Investigations involving greater than minimal risk and no prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition [\[45 CFR 46.406/21 CFR 50.53\]](#). Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, may be approved by the IRB only if the IRB finds and documents that:
 - a. The risk represents a minor increase over minimal risk;
 - b. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
 - c. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
 - d. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 16.6.2.
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children [\[45 CFR 46.407/21 CFR 50.54\]](#). When the IRB does not believe that the research meets the requirements of any of the above categories, and the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB shall refer the research for further review as follows:
 - a. DHHS-conducted or supported research in this category will be referred for review by the Secretary of Health and Human Services. However, before doing so the IRB must determine that the proposed research also meets all of the requirements of the Common Rule.

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- b. FDA-regulated research in this category will be referred for review by the Commissioner of Food and Drugs.
- c. For research that is not DHHS conducted or supported and not FDA-regulated, the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:
 - i. That the research in fact satisfies the conditions of the previous categories, as applicable; or
 - ii. The following:
 - 1. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
 - 2. The research will be conducted in accord with sound ethical principles; and
 - 3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 16.6.2.

16.6.2 Parental Permission and Assent

16.6.2.1 Parental Permission

The IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian.

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in Section 15.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Categories 1 [45 CFR 46.404/21 CFR 50.51] & 2 [45 CFR 46.405/21 CFR 50.52] above. The IRB's determination of whether permission must be obtained from one or both parents will be documented in the reviewer's notes when a study receives expedited review, and in meeting minutes when reviewed by the convened committee.

Permission from both parents is required for research to be conducted under Categories 3 [45 CFR 46.406/21 CFR 50.53] & 4 [45 CFR 46.407/21 CFR 50.54] above unless:

- 1. One parent is deceased, unknown, incompetent, or not reasonably available; or
- 2. When only one parent has legal responsibility for the care and custody of the child.

The IRB may waive the requirement for obtaining permission from a parent or legal guardian if:

- 1. The research meets the provisions for waiver in Section 15.10; or
- 2. For research that is not FDA-regulated, if the IRB determines that the research is designed to study conditions in children or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children) provided that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal, State, or local law. The choice of an

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appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol/research plan, the risk and anticipated benefit to the research subjects, and the child's age, maturity, status, and condition.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by Section 15.8.

16.6.2.2 Assent from Children

The IRB is responsible for determining that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. This judgment may be made for all children to be involved in the study, or for each child, as the IRB deems appropriate.

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accordance with the applicable regulations. It is important to note that the FDA regulations do permit the IRB to waive the assent requirement if it finds and documents that:

1. The clinical investigation involves no more than minimal risk to the subjects;
2. The waiver will not adversely affect the rights and welfare of the subjects;
3. The clinical investigation could not practicably be carried out without the waiver; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Because "assent" means a child's affirmative agreement to participate in research, the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way.

The IRB should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity, but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.

Parents and children will not always agree on whether the child should participate in research. Where the IRB has indicated that the assent of the child is required in order for him or her to be enrolled in the study, dissent from the child overrides permission from a parent. Similarly, a child typically cannot decide to be in research over the

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objections of a parent. There are individual exceptions to these guidelines but in general, children should not be forced to be research subjects, even when permission has been given by their parents.

16.6.3 Documentation of Assent

When the IRB determines that assent is required, it also is also responsible for determining whether and how assent must be documented. When the research targets the very young child or children unable or with limited capacity to read or write, an oral presentation accompanied perhaps by some pictures with documentation of assent by the person obtaining assent in a research note is likely more appropriate than providing the child a form to sign. In this case, the investigator should provide the IRB with a proposed script and any materials that they intend to use in explaining the research.

When the research targets children who are likely able to read and write, investigators should propose a process and form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form should:

1. Tell why the research is being conducted;
2. Describe what will happen and for how long or how often;
3. Say it's up to the child to participate and that it's okay to say no;
4. Explain if it will hurt and if so for how long and how often;
5. Say what the child's other choices are;
6. Describe any good things that might happen;
7. Say whether there is any compensation for participating; and
8. Ask for questions.

Whenever possible, the document should be limited to one page. Illustrations might be helpful, and larger type and other age appropriate improvements are encouraged when they have the potential to enhance comprehension. Studies involving older children or adolescents should include more information and may use more complex language.

16.6.4 Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406/21 CFR 50.53 or 45 CFR 46.407/21 CFR 50.54 (Categories 3 & 4 in Section 16.6.1), **only if such research** is:

1. Related to their status as wards; or
2. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in *loco parentis*.

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The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

Wards shall not be subjected to experimental research or hazardous treatment procedures, if the ward if the ward implicitly or expressly objects to the procedures.

16.7 Adults with Impaired Decision Making Capacity

When vulnerable populations are included in research, regulations require that additional safeguards are put in place to protect the rights and welfare of these subjects. [\[45 CFR 46.111\(b\)/21 CFR 56.111\(b\)\]](#) Adults who lack or who have impaired, fluctuating, or diminishing decision-making capacity (collectively referred to as “adults with impaired decision-making capacity” in this section) are particularly vulnerable. Investigators and IRBs must carefully consider whether inclusion of such subjects in a research study is appropriate; and when it is, must consider how best to ensure that these subjects are adequately protected. The principles and procedures outlined in this section are intended to assist National Jewish Health investigators and the IRB with the development and review of research involving adults with impaired decision-making capacity.

16.7.1 Informed Consent

Obtaining legally effective informed consent before involving human subjects in research is one of the central ethical principles described in the Belmont Report and provided for by federal regulations governing research.

As discussed previously, the informed consent process involves three key features: (1) providing the prospective subject the information needed to make an informed decision (in language understandable to him or her); (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether to participate in the research.

Among other requirements, for consent to be legally effective, the potential subject or their LAR must have the necessary decision-making capacity to make a rational and meaningful choice about whether to participate (or continue participating) in a study.

16.7.2 Decision-Making Capacity

“Decision-making capacity” refers to a potential subject’s ability to make a rational and meaningful decision about whether or not to participate in a research study. This ability is generally thought to include at least the following four elements:

1. Understanding, i.e., the ability to comprehend the disclosed information about the nature and purpose of the study, the procedures involved, the risks and benefits of participating versus not participating, and the voluntary nature of participating;
2. Appreciation, i.e., the ability to appreciate the significance of the disclosed information and the potential risks and benefits for one’s own situation and condition;
3. Reasoning, i.e., the ability to engage in a reasoning process about the risks and benefits of participating versus alternatives, and;

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4. Choice, i.e., the ability to express a choice about whether or not to participate.

“Decision-making capacity” should not be confused with the legal concept of “competence.” While the court may consider information about a person’s decision-making capacity in making a competency determination, the terms are not synonymous. Incompetence is a legal determination made by a court of law. For example, someone who is judged legally incompetent to manage their financial affairs may retain sufficient decision-making capacity to make meaningful decisions about participating in a research protocol. Likewise, people who have normal cognitive functioning and are considered legally competent may be put into circumstances where their decision-making capacity is temporarily impaired by a physical or mental condition or by alcohol or drugs.

Decision-making capacity is protocol and situation-specific. Thus, a person may have capacity to consent to participate in low risk research in usual circumstances, but not have the capacity to consent to a higher risk protocol when s/he is under significant stress or faced with unfamiliar circumstances.

16.7.3 Inclusion of Adults with Impaired Decision-Making Capacity in Research

Research involving adult subjects without the ability to provide consent or with impaired decision-making capacity should only be conducted when the aims of the research cannot reasonably be achieved without their participation.

Investigators must disclose to the IRB both plans and justification for including adults with impaired decision-making capacity in a given research proposal. If adults with questionable or fluctuating capacity will be included, investigators must specify procedures for assessing capacity prior to providing informed consent and, if appropriate, for re-evaluating capacity during study participation. If a prospective subject’s capacity to consent is expected to diminish, the investigator should consider requesting that the subject designate a future LAR prior to enrollment in the research, including the future LAR in the initial consent process, and obtaining written documentation of the subject’s wishes regarding participation in the research. When the study includes subjects likely to regain capacity to consent while the research is ongoing, the investigator should include provisions to inform them of their participation and seek consent for ongoing participation.

Plans for evaluation of capacity should be tailored to the subject population and the risks and nature of the research. In some instances, assessment by a qualified investigator may be appropriate. However, an independent, qualified assessor should evaluate subjects’ capacity when the risks of the research are more than a minor increase over minimal or the investigator is in a position of authority over a prospective subject. In all cases, the person(s) evaluating capacity must be qualified to do so and use appropriate, validated tools and methods (e.g., University of California, San Diego Brief Assessment of Capacity to Consent [UBACC], MacArthur Competence Assessment Tool for Clinical Research [MacCAT-CR]). Assessments of capacity should be documented in the research record, and when appropriate, in the medical record.

Under some circumstances, it may be possible for investigators to enable adults with a degree of decisional impairment to make voluntary and informed decisions to consent, assent, or refuse participation in research. Potential measures include repetitive teaching, audiovisual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess subject understanding, videotaping or audio-taping of consent discussions, use of waiting periods to allow more time for the potential subject to consider the information that has been presented, or involvement of a trusted family member or friend in the disclosure and decision making process. Audio or videotapes, electronic presentations, or written materials used to promote understanding must be provided to the IRB for review and approval prior to use.

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When a prospective subject is deemed to lack capacity to consent to participate in research, investigators may obtain informed consent from the individuals' surrogate or LAR (See Section 15.3). Under these circumstances, the prospective subject should still be informed about the research in a manner compatible with the subjects' likely understanding and, if possible, be asked to assent to participate. Potential subjects who express resistance or dissent (by word, gesture, or action) to either participation or use of surrogate consent, should be excluded from the study. Some subjects may initially assent but later resist participation. Under no circumstances may an investigator or caregiver override a subject's dissent or resistance. When assent is possible for some or all subjects, the investigator should provide the IRB with an assent plan that describes when and how assent will be obtained, provisions that will be taken to promote understanding and voluntariness, how assent will be documented, and a copy of the assent form. If the investigator intends to use audio or video recordings to document assent, provisions to ensure the security of the recordings should be described to the IRB.

When inclusion of adults with impaired decision-making capacity is **not anticipated** and a plan for inclusion of such subjects **has not been** reviewed and approved by the IRB, and an enrolled subject becomes unable to provide consent or impaired in decision-making capacity, the investigator is responsible for promptly notifying the IRB (as soon as possible but within 5 business days). The investigator should consider whether continuing participation is appropriate and, if so, present a plan for surrogate consent from a LAR and, if appropriate, a plan to periodically evaluate capacity and re-obtain consent if possible.

16.7.4 IRB Review

The IRB review process will include at least one member, or a consultant, who is experienced with or otherwise knowledgeable about the population when the research involves greater than minimal risk, or the research is minimal risk but includes interactions with subjects, and the proposed subject population includes adults with impaired decision-making capacity.

In evaluating research, the IRB must be able to determine that the risks to subjects are reasonable not only in relation to any benefits, but also in relation to the importance of the knowledge that may reasonably be expected to result. In considering the risks of research involving adults with impaired decision-making capacity, the IRB should consider whether any components of the research involve risks that are greater for participants with diminished capacity. For example, whether subjects might experience increased sensitivity or discomfort to certain stimuli or may not be able to verbalize or otherwise demonstrate when they are experiencing discomfort or pain.

As appropriate to the research, the IRB will consider the following in evaluating research involving adults with impaired decision-making capacity:

1. Whether the aims of the research cannot reasonably be achieved without inclusion of the population;
2. Whether the research is likely to improve the understanding of the condition, disease, or issue affecting the subject population;
3. Whether any experimental procedure or interventions have undergone pre-clinical testing or human testing on other populations and whether the data from that testing supports its use in the proposed research;
4. Whether the procedures or interventions that the subject will undergo in the research place them at increased risk and whether appropriate mechanisms are in place to minimize risks, when possible;

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5. Whether the data and safety monitoring plan, including any stopping rules, is appropriate given the risks of the research and the vulnerability of the population;
6. Whether the procedures for withdrawing individual subjects from the research are appropriate;
7. Whether the recruitment procedures, consent process, and any plans for financial compensation support voluntariness and minimize the likelihood of undue influence or coercion;
8. Whether the subjects will be exposed to financial or other risks that they might not consider acceptable if they had the capacity to provide consent, and whether appropriate mechanisms have been put into place to minimize these risks;
9. Whether the procedures for determining capacity to provide consent, and for evaluating capacity on an ongoing basis, if applicable, are appropriate;
10. Whether the procedures for informing subjects who regain capacity about their involvement in the research, and for obtaining consent for on-going participation, if applicable, are appropriate;
11. Whether assent should be required when possible, and, if so, if the proposed procedures to obtain and document assent are appropriate;
12. Whether periodic re-evaluation of capacity and/or periodic re-consent should be required; and
13. Whether a research subject advocate or consent monitor should be required, for some or all subjects.

In general, the IRB will only approve research involving subjects unable to provide consent or with impaired decision-making capacity when the aims of the research cannot reasonably be achieved without inclusion of the population, and there are appropriate provisions to: (1) evaluate capacity, (2) obtain consent (and assent if possible), and (3) otherwise protect subjects.

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

The following procedures describe the review of FDA-regulated research by the NJH IRB.

17.1 Definitions

Biologic. Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic 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

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microorganism — and may be produced by biotechnology methods and other technologies. In general, the term "drugs" includes therapeutic biological products.

Clinical Investigation. Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. [[21 CFR 50.3\(c\)](#)]

Dietary Supplement. A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. [[21 U.S.C. 321\(ff\)](#)]

Emergency Use. Emergency use is defined as the use of a test article on a human subject 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\(d\)](#)]

Humanitarian Use Device (HUD). A Humanitarian Use Device is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.

Investigational Drug. Investigational *or* experimental drugs are new drugs that have not yet been approved by the FDA or approved drugs that are being studied in a clinical investigation.

Investigational Device. Investigational device means a device (including a transitional device) that is the object of an investigation. Investigation, as it pertains to devices, means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

IND. IND means an investigational new drug application in accordance with [21 CFR Part 312](#).

IDE. IDE means an investigational device exemption in accordance with [21 CFR 812](#).

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\(a\)](#)]

Non-Significant Risk (NSR) Device. A non-significant risk device is an investigational device that does not meet the definition of a significant risk device.

Significant Risk (SR) Device. Significant risk device means an investigational device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or

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3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. [[21 CFR 812.3\(m\)](#)]

17.2 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of FDA regulations for IRB review:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [[21 CFR §56.104\(c\)](#)]
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\(d\)](#)]

17.3 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.
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:

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- 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 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 NJH 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 is responsible for investigational drug accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability. Such details will be provided in the IRB submission and reviewed by the IRB for acceptability.
 - b. The investigator may delegate in writing, as part of the IRB submission, the responsibility detailed in 'a' above to the Research Pharmacy.
 - c. Investigational drugs and devices must be labeled in accordance with federal and state standards.

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- 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.

17.4 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 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. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required under part 312.

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.

17.5 Clinical Investigations of Articles Regulated as Drugs or Devices

17.5.1 IND/IDE Requirements

For studies evaluating the safety or effectiveness of medical devices or experiments using drugs, biologics, dietary supplements, and other compounds that may be considered a drug or device under FDA regulations, the

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investigator must indicate on the IRB application whether an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed. Documentation must be provided by the sponsor or the sponsor-investigator. Documentation of the IND/IDE could be a:

1. Industry sponsored study with IND/IDE number indicated on the protocol;
2. Letter/communication from FDA;
3. Letter/communication from industry sponsor; or
4. Other document and/or communication verifying the IND/IDE.

For investigational devices, the study may be exempt from IDE requirements (IDE-exempt) or, in the case of Non-Significant Risk (NSR) device studies, follow abbreviated IDE requirements which do not require formal approval by the FDA. If a sponsor has identified a device study as IDE-exempt or NSR, then the investigator should include documentation with the submission providing the basis for IDE-exempt or NSR categorization for the IRB's consideration. If the FDA has determined that the study is IDE-exempt or NSR, documentation of that determination must be provided.

The IRB will review the application and, based upon the documentation provided, determine:

1. That there is an approved IND/IDE in place;
2. That the FDA has determined that an IND is not required or that a device study is IDE-exempt or NSR; or,
3. If neither of the above, whether an IND is necessary, or that a device study is exempt or NSR, or must be submitted to the FDA for an IDE or for a determination, using the criteria below.

The IRB cannot grant approval to the research until the IND/IDE status is determined, and, if necessary, an approved IND or IDE is in place.

17.5.2 IND Exemptions

For drugs, an IND is not necessary if the research falls in one of the following seven (7) categories:

1. The drug being used in the research is lawfully marketed in the United States and all of the following requirements are met:
 - a. The research is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug;
 - b. In the case of a prescription drug, the research is not intended to support a significant change in the advertising for the product;
 - c. The research does not involve a route of administration, dose, subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
 - d. The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts [56](#) and [50](#), respectively];
 - e. The research is conducted in compliance with the requirements of [21 CFR 312.7](#) (i.e., the research is not intended to promote or commercialize the drug product); and

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- f. The research does not intend to invoke FDA regulations for planned emergency research [[21 CFR 50.24](#)].

Please Note: FDA has provided specific guidance for evaluating whether this exemption applies to studies of marketed drugs/biologics for the treatment of cancer.

1. 21 CFR 312.2(b)(2): For clinical investigations involving defined (blood grouping serum, reagent red blood cells, and anti-human globulin) in vitro diagnostic biological products, an IND is not necessary if a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and b) it is shipped in compliance with 312.160
2. 21 CFR 312.2(b)(5): A clinical investigation involving use of a placebo is exempt from the requirements of part 312 if the investigation does not otherwise require submission of an IND.
3. 21 CFR 320.31(b) and (d): Bioavailability or Bioequivalence (BA/BE) studies if all of the following conditions are met:
 - a. The drug product does not contain a new chemical entity [21 CFR 314.108], is not radioactively labeled, and is not cytotoxic;
 - b. The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product;
 - c. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and
 - d. The sponsor meets the requirements for retention of test article samples [21 CFR 320.31(d)(1)] and safety reporting [21 CFR 320.31(d)(3)].
4. 21 CFR 361.1: Research using a radioactive drug or biological product if all of the following conditions are met:
 - a. It involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product;
 - b. The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA;
 - c. The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans, and
 - d. The total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.
5. FDA practices enforcement discretion for research using cold isotopes of unapproved drugs if all of the following conditions are met:
 - a. The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry;

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- b. The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject;
- c. The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies;
- d. The quality of the cold isotope meets relevant quality standards; and
- e. The investigation is conducted in compliance with the requirements for IRB review and informed consent. [21 CFR parts 56 and 50, respectively]

17.5.3 IDE Exemptions

For clinical investigations of medical devices, an IDE is not necessary if:

1. The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time;
2. The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of [21 CFR 807](#) in determining substantial equivalence (a “501k” device);
3. The research involves a diagnostic device, if the sponsor complies with applicable requirements in [21 CFR 809.10\(c\)](#) and if the testing:
 - a. Is noninvasive,
 - b. Does not require an invasive sampling procedure that presents significant risk,
 - c. Does not by design or intention introduce energy into a subject, and
 - d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
4. The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
5. The research involves a device intended solely for veterinary use;
6. The research involves a device shipped solely for research on or with laboratory animals and labeled in accordance with [21 CFR 812.5\(c\)](#);
7. The research involves a custom device as defined in [21 CFR 812.3\(b\)](#), unless the device is being used to determine safety or effectiveness for commercial distribution.

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17.5.4 Significant and Non-Significant Risk Device Studies

A device study is a Non-Significant Risk (NSR) Device study if it is not IDE exempt and does not meet the definition of a Significant Risk (SR) Device study.

Under [21 CFR 812.3\(m\)](#), an SR device means an investigational device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

If the FDA has already determined a study to be SR or NSR, documentation evidencing such should be provided to the IRB as described in Section 17.5.1. The FDA's determination is final and the IRB does not have to make the device risk determination.

Unless the FDA has already made a device risk determination for the study, the IRB will review studies that the sponsor or investigator have put forth as NSR at a convened meeting to determine if the device represents SR or NSR.

The sponsor or sponsor-investigator is responsible for providing the IRB with an explanation describing the basis for their initial determination of NSR and any other information that may help the IRB in evaluating the risk of the study (e.g., reports of prior investigations of the device).

The IRB will review the information provided by the sponsor and investigator including, but not limited to: the sponsor or investigator's NSR assessment, the description of the device, reports of prior investigations of the device (if applicable), the proposed investigational plan, and subject selection criteria.

The NSR/SR determination made by the IRB will be based on the proposed use of the device in the investigation, not on the device alone. The IRB will consider the nature of any harms that may result from use of the device, including potential harms from additional procedures subjects would need to undergo as part of the investigation (e.g., procedures for inserting, implanting, or deploying the device). The IRB may consult with the FDA or require the sponsor or investigator to obtain a determination from the FDA. The IRB will document the SR or NSR determination and the basis for it in the meeting minutes and provide the investigator, and sponsor when applicable, with the determination in writing.

Non-significant risk device studies do not require submission of an IDE application to the FDA but must be conducted in accordance with the abbreviated requirements of IDE regulations ([21 CFR 812.2\(b\)](#)). Under the abbreviated requirements, the following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under [812.20\(a\)](#) that approval of an application is required:

1. An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor (or sponsor-investigator):

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- a. Labels the device in accordance with [812.5](#);
- b. Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a significant risk device, and maintains such approval;
- c. Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless the requirement is waived by the IRB;
- d. Complies with the requirements of [812.46](#) with respect to monitoring investigations;
- e. Maintains the records required under [812.140\(b\) \(4\) and \(5\)](#) and makes the reports required under [812.150\(b\) \(1\) through \(3\) and \(5\) through \(10\)](#);
- f. Ensures that participating investigators maintain the records required by [812.140\(a\)\(3\)\(i\)](#) and make the reports required under [812.150\(a\) \(1\), \(2\), \(5\), and \(7\)](#); and
- g. Complies with the prohibitions in [812.7](#) against promotion and other practices.

When the FDA or IRB determines that a study is SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained.

17.6 Diagnostic or Treatment Use of Humanitarian Use Devices

A Humanitarian Use Device (HUD) is an approved (marketed) medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 8,000 individuals in the United States per year [[21 CFR 814.3\(n\)](#)]. Federal law requires that an IRB approve the use of an HUD at a facility. Once approved, the clinical use of the HUD may be considered as any other approved device, with the caution that effectiveness has not been shown in clinical trials.

17.6.1 Definitions

Humanitarian Device Exemption. A Humanitarian Device Exemption (HDE) is a “premarket approval application” submitted to FDA pursuant to Subpart A, [21 CFR Part 814](#) “seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the [FD&C Act] as authorized by section 520(m)(2) of the [FD&C Act].” HDE approval is based upon, among other criteria, a determination by FDA that the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

HDE Holder. An HDE Holder is a person or entity that obtains approval of an HDE from the FDA.

17.6.2 IRB Review Requirements

A Humanitarian Use Device (HUD) may only be used in a facility after an IRB has approved its use, except in certain emergencies. The HDE holder is responsible for ensuring that a HUD is provided only to facilities having an IRB constituted and acting in accordance with the FDA's regulations governing IRBs ([21 CFR Part 56](#)), including continuing review of use of the device.

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When a HUD is used in a clinical investigation (i.e., research involving one or more subjects to determine the safety or effectiveness of the HUD), the full requirements for IRB review and informed consent apply (21 CFR [50](#) and [56](#)) as well as other applicable regulations. It is essential to differentiate whether the HUD is being studied for the indication(s) in its approved labeling or for different indication(s). When the HUD is being studied for the indication(s) in its approved labeling, the IDE regulations at [21 CFR 812](#) do not apply. However, when the HUD is being studied for a different indication(s), [21 CFR 812](#) does apply, including the requirement for a FDA-approved IDE before starting the clinical investigation of a Significant Risk device.

17.6.3 Procedures

The relevant requirements and procedures for research described elsewhere in this manual apply to clinical investigations of HUDs. The material within this section applies to diagnostic or treatment uses of HUDs.

The health care provider seeking approval for diagnostic or treatment use of a HUD at NJH facilities is responsible for obtaining IRB approval prior to use of the HUD at the facility and for complying with the applicable regulations, including those for medical device reporting, organizational policies, and the requirements of the IRB.

Health care providers seeking initial IRB approval for diagnostic or treatment use of a HUD for the indication(s) in the HUDs approved labeling should submit the following materials to the IRB:

1. IRB Application form;
2. A copy of the HDE approval letter from the FDA;
3. A description of the device, such as a device brochure;
4. The patient information packet for the HUD;
5. The proposed clinical consent process or HUD-specific consent process and documentation, if requested by the IRB
6. Other relevant materials available to support the use of the HUD in the identified subject population.

The IRB will review the proposal at a convened meeting ensuring that appropriate expertise is available either within the membership in attendance or via the use of consultants. The IRB will review the risks to patients that are described in the product labeling and other materials, the proposed procedures to ensure that risks are minimized, and will evaluate whether the risks are reasonable in relation to the potential benefits to patients at the facility. The IRB will evaluate the patient information packet and proposed consent process and will determine if the materials are adequate and appropriate for the patient population.

The IRB may specify limitations on the use of the device, require additional screening and follow up procedures, require interim reports to the IRB, require continuing review more often than annually, or set other conditions or requirements as appropriate to minimize risks to patients and ensure the safe use of the device in the facility.

Once use of the HUD is approved, the health care provider is responsible for submitting any proposed changes to the IRB-approved plan or patient materials and obtaining approval for those changes prior to implementation, unless the change is necessary to avoid or mediate an apparent immediate risk to a patient. Proposed changes may be submitted using the Change to Protocol and/or Consent Form and should be accompanied by any revised materials or supporting documentation. The IRB may review these changes using expedited review procedures or refer the changes for review by the convened IRB.

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The health care provider is responsible for submitting reports to the FDA, the IRB, and the manufacturer/HDE Holder whenever a HUD may have caused or contributed to a death, and must submit reports to the manufacturer (or to FDA and the IRB if the manufacturer is unknown) whenever a HUD may have caused or contributed to a serious injury ([21 CFR 803.30](#) and [814.126\(a\)](#)). Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a bodily function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure ([21 CFR 803.3](#)). The specific requirements for this reporting are in the Medical Device Reporting (MDR) Regulation, at [21 CFR Part 803](#). The IRB will review these reports via either expedited or convened review, as appropriate, and will consider whether any changes are needed to the IRB-approved plan or patient materials.

The health care provider is responsible for submitting continuing review materials to the IRB sufficiently in advance of the expiration date to ensure IRB review and re-approval prior to expiration. Materials to be submitted include:

1. Continuing Review Application
2. The most recent periodic report to the FDA by the HDE holder;
3. The current patient information packet, if applicable;
4. The current consent, if applicable; and
5. Any other new relevant information or materials

The IRB may conduct continuing review using expedited review procedures or review by the convened IRB.

17.6.4 Emergency Uses of HUDs

If an appropriately trained and licensed health care provider in an emergency situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior IRB approval. The health care provider must, within 5 days after the emergency use of the device, provide written notification of the use to the NJH IRB Chair including the identification of the patient involved, the date of the use, and the reason for the use. [[21 CFR 812.124](#)]

If a HUD is approved for use in a facility, but an appropriately trained and licensed health care provider wants to use the HUD outside its approved indication(s) in an emergency or determines that there is no alternative device for a patient's condition, the physician should consult with the HDE holder and IRB in advance if possible, obtain informed consent if possible, and ensure that reasonable measures are taken to protect the well-being of the patient such as a schedule and plan for follow up examinations and procedures to monitor the patient, taking into consideration the patient's specific needs and what is known about the risks and benefits of the device. The provider should submit a follow up report to the HDE holder and the IRB and must comply with medical device reporting requirements.

The IRB may require additional reports, patient protection measures, or other requirement, as appropriate given the specifics of the situation.

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17.7 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 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 17.9.

17.7.1 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 consult with the HRPP office. Convened IRB review is generally required for intermediate or widespread expanded access unless the FDA has issued a waiver.

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

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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](#).

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 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 17.8.

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:

Page | 132

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Unless the conditions that permit an emergency use exemption (see Section 17.8.1) 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 the IRB office 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 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.

NOTE:

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17.7.2 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.

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

17.7.2.1 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 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);

NOTE:

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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 “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 17.8.2), 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 the HRPP office 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.

NOTE:

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Reference to ‘2018 Rule’ refers to research initially approved ***on or after*** January 21, 2019.

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 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.

17.7.3 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.

NOTE:

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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. 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.

17.8 Emergency Uses

17.8.1 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 17.8.1.1 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.

17.8.1.1 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 17.8.3), informed consent must be obtained in accordance with [21 CFR 50](#) and documented in writing in accordance with [21 CFR 50.27](#).

The 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.

17.8.2 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:

- 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:

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- 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 must contact the HRPP/IRB office as early in the process as possible and submit the Emergency Use Report – Devices and the supporting documentation called for in the form for review by the IRB Chair or designee. The IRB Chair or designee will review the information provided and determine whether the use conforms with FDA's requirements and expectations and whether the provisions for the protection of the patient appear adequate using the applicable criteria at 21 CFR 50 and 56 as guidelines (e.g., minimization of risks, risk/benefit, safety monitoring, informed consent, etc.).

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 the IRB office.

Reports of emergency uses will be brought to the convened IRB for their information.

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

17.8.3 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 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.

Page | 139

NOTE:

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17.9 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.

17.9.1 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\(b\)\(8\)\]](#).

17.9.2 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\(b\)\]](#)
- 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](#).

18 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 of UPIRTSOs to the NJH HRPP Staff. 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.

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

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18.1 Definitions

Unanticipated problems involving risks to subjects or others (UPIRTSOs) refer to any incident, experience, outcome, or new information that:

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 also encompass Unanticipated Adverse Device Effects, as defined below.

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 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 investigators 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.

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)].

18.2 Procedures

18.2.1 Reporting

Adverse events in clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. Unless specifically required by the IRB for a given protocol, the NJH HRPP does not accept reports of adverse events that are not UPIRTSOs, except in summary form at the time of continuing review.

Investigators must report the following events or issues to the HRPP as soon as possible but within 7 working days after the investigator first learns of the event using the "Event Report" form. If the study is not subject FDA regulation, the report can be emailed to the HRPP office. Otherwise, hardcopy must be provided.

If investigators are uncertain but believe that the event might represent an UPIRTSO, a report should be submitted.

Page | 141

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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)
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 an UPIRTSO. Such reports must be accompanied by an analysis from the sponsor explaining why the report represents an UPIRTSO and whether it has been reported to the FDA as such
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 to potential risk but that does not involve direct harm to subjects
13. A breach of confidentiality or loss of research data (e.g., a laptop or thumb drive is lost or stolen, nonphysical harm)

Page | 142

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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.

18.2.2 Review Procedures

1. Upon receipt of the Event Report, the HRPP Staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information.
2. The IRB Co-Chair/HRPP staff receives and reviews the report and makes an initial determination as to whether the event represents an UPIRTSO. If needed, the Co-Chair/HRPP staff may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, data safety monitoring boards, or steering committees).
3. If the reviewer determines that the problem does not meet the definition of an UPIRTSO, determination will be made regarding whether any additional actions are necessary to ensure the protection of human subjects. As warranted, the reviewer may refer the matter to the convened IRB for review. The results of the review will be recorded in study record (and meeting minutes, if the convened IRB reviews the matter) and communicated to the investigator.
4. If the reviewer determines that the event may be an UPIRTSO, the report will be referred for review by the IRB of record. The IRB will determine whether the event is a UPIRTSO and whether any additional actions, such as those outlined below, are necessary to ensure the protection of human subjects. If needed, the IRB may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, data safety monitoring boards, or steering committees). The results of the review will be recorded in the IRB minutes and communicated to the investigator.
5. Based upon the circumstances, the IRB may take any of the following actions, or others, to ensure the protection of human subjects:
 - a. Requiring modifications to the protocol or plan or procedures for implantation of the research (Research Plan) as described in the application and other materials submitted to the IRB;
 - b. Revising the continuing review timetable;
 - c. Modifying the consent process;
 - d. Modifying the consent document;
 - e. Providing additional information to current participants (e.g., whenever the information may relate to the subject's rights, welfare, or willingness to continue participation);
 - f. Providing additional information to past participants;

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- g. Requiring additional training of the investigator and/or study staff;
- h. Requiring that current subjects re-consent to participation;
- i. Monitoring the research;
- j. Monitoring consent;
- k. Reporting or referral to appropriate parties (e.g., the IO, Corporate Compliance, Privacy Officer etc.);
- l. Suspending IRB approval;
- m. Terminating IRB approval;
- n. Other actions as appropriate given the specific circumstances.

When the IRB determines that an event is an UPIRTSO, the HRPP Staff will follow the procedures for reporting to regulatory agencies, sponsors, and organizational officials in Section 22. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.

19 Noncompliance

This section provides definitions and procedures for the reporting and review of known or suspected noncompliance for research under the oversight of the National Jewish Health IRB. 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.

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

19.1 Definitions

Noncompliance is defined as the failure to follow federal, state, or local regulations governing human subject research, institutional policies related to human subject research, or the requirements or determinations of the IRB. Noncompliance may be minor or sporadic or it may be serious or continuing. Protocol deviations and violations are a form of noncompliance.

Serious Noncompliance is defined as noncompliance that, in the judgment of the convened IRB, creates an increase in risks to subjects, adversely affects the rights, welfare, or safety of subjects, or adversely affects the scientific integrity of the study. Willful violation of policies and/or federal regulations may also constitute serious noncompliance.

Continuing Noncompliance is defined as a pattern of noncompliance that, in the judgment of the convened IRB, suggests a likelihood that instances of noncompliance will continue unless the IRB or institution intervenes.

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

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19.2 Reporting

Investigators and their study staff are required to report instances of possible noncompliance to the HRPP staff within 7 working days of discovery using the “Event Report” form. Reports that are for studies not under FDA regulation may e-mail the report. Reports for FDA regulated studies must be provided in hardcopy. Additionally, anyone may report concerns of possible noncompliance to the HRPP Staff 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 Director of RRA, HRPP staff or an IRB Co-Chair directly to discuss the situation informally.

19.3 Review Procedures

1. Upon receipt of the Event Report, the HRPP Staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information. If the report came from someone other than the investigator verbally, by email, or by other means, the Director of RRA or assigned HRPP staff will develop a written report summarizing the available 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 Director of RRA, IRB Co-Chair, and, when appropriate, 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. The IRB Co-Chair/HRPP Staff receives and reviews the report and makes an initial determination as to whether the event represents noncompliance, and, if so, if the noncompliance may be serious or continuing. If needed, the IRB Chair may request additional information from the investigator or others. When circumstances warrant, the Director of RRA may bypass this step and assign the report for convened board review.
3. If the IRB Co-Chair/HRPP Staff determines that the event or issue is not noncompliance, or is noncompliance but not serious or continuing, s/he will review any proposed corrective and preventative action plans and determine if the plan is acceptable as proposed or if modifications to the plan or additional actions are required. As warranted, the Co-Chair/HRPP Staff may refer the matter to the convened IRB for review. The results of the review will be recorded in the study file (and minutes if the convened IRB reviews the matter) and communicated to the investigator.
4. If the IRB Co-Chair/HRPP Staff determines that the event or issue may be serious or continuing noncompliance, the report will be referred for review by the IRB of record. The IRB will determine whether the event is serious or continuing noncompliance. The IRB will review any proposed corrective and preventative action plans and determine if the plan is acceptable as proposed or if modifications to the plan or additional actions, such as those outline below, are necessary to ensure the protection of human subjects. If needed, the IRB may request additional information from the investigator or others. The results of the review will be recorded in the IRB minutes and communicated to the investigator.
5. When the IRB determines that an event is serious or continuing noncompliance, the IRB may take any of the following actions, or others, to ensure the protection of human subjects:

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- a. Requiring modifications to the protocol or research plan
 - b. Revising the continuing review timetable
 - c. Modifying the consent process
 - d. Modifying the consent document
 - e. Providing additional information to current participants (e.g., whenever the information may relate to the subject's willingness to continue participation)
 - f. Providing additional information to past participants
 - g. Requiring additional training of the investigator and/or study staff
 - h. Requiring that current subjects re-consent to participation
 - i. Monitoring the research
 - j. Monitoring consent
 - k. Reporting or referral to appropriate parties (e.g., the IO, Compliance, Risk Management, Privacy)
 - l. Suspending IRB approval
 - m. Terminating IRB approval
 - n. Other actions as appropriate given the specific circumstances
6. When the IRB determines that an event is serious or continuing noncompliance, the HRPP Staff will follow the procedures for reporting to regulatory agencies, sponsors, and organizational officials in Section 22. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.
 7. Investigators may request that the IRB reconsider its determination by following the procedures in Section 11.4.

20 Complaints

The HRPP staff & NJH IRB will be responsive and sensitive to the complaints or concerns expressed by 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 Staff 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 conducting research under the oversight of the NJH IRB report complaints using the Event Report Form. Investigators are encouraged to contact the Director of RRA 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 Staff is the direct recipient of complaints or concerns, the staff will do the following:

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1. Document the complaint or allegation. When appropriate, the staff may request that the subject submit the complaint in writing.
2. Reassure the subject that the HRPP/IRB 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.

For research under the oversight of the internal IRB, the IRB Co-Chair/HRPP Staff will consider the complaint or concern and take any reasonable steps necessary to investigate and/or resolve the issue, if appropriate, prior to review and consideration by the IRB. A report will be provided to the IRB at the next available meeting if the research is subject to convened IRB review, or provided to the designated expedited reviewer if the research is eligible for expedited review. When reviewing complaints, the IRB will consider whether the complaint was the result of, or related to, an UPIRTSO or noncompliance, and, if so, will follow the relevant procedures. The IRB Co-Chair may refer any complaint for review by the convened IRB. The IRB minutes, or reviewer comments for expedited reviews, will reflect the action(s) taken and, if necessary, notice to the appropriate officials and/or agencies.

The HRPP 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 Staff or IRB 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.

21 Other Reportable Information

When research is under the oversight of the NJH IRB, in addition to UPIRTSOs, noncompliance, and complaints, any change to the research implemented without IRB approval and any information that may impact the rights, safety, or welfare of subjects or inform the IRB's oversight of the research must be reported to the IRB within 7 working days of discovery using the Event Report Form. 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.

Other reportable information 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 in accordance with Section 2.1 of this SOP
3. Sponsor or coordinating center reports
4. Data Safety Monitoring reports, including reports from DSMBs, DMCs, and others

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5. When an existing subject becomes a member of a vulnerable population not previously approved by the IRB for inclusion in the study (e.g., incarceration, pregnancy, or change in decision-making capacity of an already enrolled subject)
6. Suspensions, or terminations of a study, in part or in full, by an investigator, sponsor, or others
7. Changes that impact the ability of the PI to conduct or supervise the study, temporarily or permanently
8. Changes that impact the qualifications of investigators or research staff members such as actions taken by regulatory authorities, licensing boards, or credentialing committees
9. Any other new information that may impact the rights, welfare, or willingness of subjects to continue in the research.

21.1 Review Procedures

1. Upon receipt of the report, the HRPP Staff pre-reviews the submission and, if needed, contacts 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 Director of RRA, IRB Chair, and, when appropriate, the IO and/or Research Integrity Officer, will be notified so that they can take any necessary steps to ensure the safety of subjects or investigate the matter.
2. The IRB Co-Chair/HRPP Staff receives and reviews the report and if the report may represent an UPIRTSO or noncompliance, reviews the report as described in Section 18 or 19. When circumstances warrant, the Director of RRA may bypass this step and assign the report for convened board review.
3. If the Co-Chair/HRPP Staff determines that the event or issue is not noncompliance or an UPIRTSO, they will review the event or issue, any proposed corrective and preventative action plans, and determine if any additional actions are needed to ensure the protection of human subjects. As warranted, the reviewer may refer the matter to the convened IRB for review. The results of the review will be recorded in the study record, and in the minutes of the convened IRB meeting in which the matter was addressed, and communicated to the investigator.

22 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 (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with the applicable federal regulations or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. NJH IRB complies with this requirement as follows. When research is under the oversight of an external IRB, the terms of the agreement with that IRB will guide reporting.

22.1 Procedures

HRPP Staff will initiate these procedures as soon as the IRB takes any of the following actions:

1. Determines that an event may be considered an unanticipated problem involving risks to participants or others

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2. Determines that noncompliance was serious or continuing
3. Suspends or terminates approval of research

The Director of RRA or designee is responsible for preparing reports or letters which includes the following information:

1. Reason for the report (Unanticipated problem involving risks to subjects or others, serious or continuing noncompliance, suspension or termination of IRB approval)
2. Name of the involved institution(s)
3. Title of the research project and/or grant proposal in which the problem occurred
4. Name of the investigator on the project
5. Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
6. A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision
7. Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring, etc.)
8. Plans, if any, to send a follow-up or final report by the earlier of:
 - a. A specific date
 - b. When an investigation has been completed or a corrective action plan has been implemented.

The IRB Chair and the IO review the letter and recommend modifications as needed. The IO is the signatory on all such letters, and the Director of RRA or designee sends a copy of the report to:

2. The IRB Chair
3. The IO
4. Federal agencies, as follows:
 - a. OHRP, if the study is subject to DHHS regulations or subject to a DHHS FWA.
 - b. If the study is conducted or supported by a Common Rule agency other than DHHS, the report is sent to OHRP or the head of the federal agency, as required by the agency.
 - c. If the study is conducted or supported by a federal agency that has not adopted the Common Rule, and reporting is required, the report is sent to the party identified by the agency.
 - d. FDA, if the study is subject to FDA regulations.

Note: Reporting to a regulatory agency is not required if the event occurred at a site that was not subject to the direct oversight of the organization, and the agency has been notified of the event by another party (e.g., sponsor).

5. Sponsor, if the study is sponsored
6. Investigator (if not previously advised of the reporting requirement)
7. Others as deemed appropriate by the IO

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The Director of RRA ensures that all steps of this policy are completed within 30 working days of the determination. For more serious actions, the Director will expedite reporting. If additional time is needed to gather facts, or determine corrective actions, a preliminary report will be submitted within 30 days, to be followed by a final report as described above.

23 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.

23.1 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;
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;

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- 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 to the IRB for evaluation and approval (note that investigators and staff may not begin work on the research until IRB-approved);
 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;
 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;

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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 manual.

23.2 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:

1. **OHRP** – research records must be retained for at least 3 years after the completion of the research
2. **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
3. **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
4. **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.

23.3 Investigator Concerns

Investigators who have concerns or regarding the conduct of research at National Jewish Health, NJH's HRPP or IRB(s), or the external IRBs upon which NJH relies should convey them to the Director of RRA, 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

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make necessary procedural or policy modifications, as warranted. In addition, the IRB Chair and Director of RRA are 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.

24 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.

The following describe the procedures required to ensure that all sponsored research meets this requirement.

24.1 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.

24.2 Responsibility

Sponsor grants, contracts, and other written agreements will be reviewed for the following by the Grants and Contracts office, with consultation with the IRB, 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.

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25 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.

25.1 Researcher Conflicts of Interest

NJH relies upon a COI Institutional Official, who will collaborate with the HRPP Office and IRB 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.

25.1.1 Procedures

25.1.1.1 Disclosure of Researcher COI

The COI Institutional Official ("COI IO") maintains a list of individuals who have declared financial interests following the NJH annual disclosure process, along with the COI Institutional Official's determination of whether or not they constitute significant financial interests (i.e., related to their institutional responsibilities). This list is provided to the HRPP Office, with review of investigator conflict performed at the time of new study submission, continuing review, with the addition of a new investigator, and whenever an investigator updates their NJH COI disclosure indicating a new or changed interest. HRPP Staff notify the COI IO whenever a submission is received with an identified study team member declares a COI. The COI IO reviews the investigators' disclosures against the study sponsor and other details and either notifies the HRPP Staff that no investigator COI was identified or that one or more investigators has an SFI that constitutes a financial conflict of interest. In the latter case, the COI IO provides a conflict management plan (CMP) to the HRPP Administrator who brings it to the convened IRB for review and final approval. If the COI IO has not completed his/her review at the time of IRB review, the IRB will defer the research study review or prohibit participation by the researcher with a potential COI until the COI IO process is completed and the results are made available to the IRB. When the research is under an external IRB, any conflicts identified as the result of COI review and any CMP are provided to the external IRB in accordance with the IRB reliance agreement.

25.1.1.2 Evaluation of COI

The IRB will review COIs and CMPs to determine:

1. Whether the COI affects the rights or welfare of research subjects;
2. Whether the COI might adversely affect the integrity or credibility of the research or the research program;
and

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3. Whether the CMP effectively protects research subjects and the integrity and credibility of the research and the research program.

In evaluating COIs and CMPs, among other factors the IRB will consider:

1. How the research is supported or financed;
2. The nature and extent of the conflict;
3. The role and responsibilities of the conflicted individual in the design, conduct, and reporting of the research; and
4. The ability of the conflicted individual to influence the outcome of the research.

25.1.1.3 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 COI IO, 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 COI IO.

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;
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.

25.2 IRB Member Conflict of Interest

No IRB member or alternate may participate in the review of any research project in which the member has a COI, except to provide information as requested. It is the responsibility of each IRB member to disclose any COI related to a study submitted for review and recuse himself or herself from the deliberations and vote by leaving the room.

All members and alternate members of the IRB complete a conflict disclosure when first appointed and annually thereafter or sooner when their circumstances change. These forms are submitted to the COI IO who reviews the disclosure and determines if a COI exists. To protect the privacy of members, the specific details of the conflict will not be given to staff or other members; however, the type of research where a COI exists will be provided (e.g., studies from X sponsor; studies using X device/drug; studies involving X investigator). The HRPP Staff, in turn, ensures that IRB members and alternates are not assigned to conduct reviews of studies for which the member

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has a conflict and reminds members of conflicts at convened meetings as needed to ensure recusal. HRPP Staff may consult with the COI IO to clarify whether a specific study involves a member COI.

IRB members, alternates, or consultants may be considered to have a conflicting interest requiring recusal when they, or an immediate member of their family, have any of the following:

1. Involvement in the design, conduct, and reporting of the research;
2. Significant financial interests related to the research being reviewed; or
3. Any other situation where an IRB member believes that another interest conflicts with his or her ability to deliberate objectively on a study.

The IRB Chair will ask IRB members at the beginning of each convened meeting if any members have a COI regarding any of the items to be reviewed and reminds members that they must recuse themselves by leaving the room during the discussion and vote of the specific research study. If a conflicted member is participating by conference call, videoconference or web meeting, the member's participation (connection) is terminated for discussion and voting.

IRB members with a conflicting interest are excluded from being counted towards quorum. Recusals of members with COIs are recorded in the minutes.

25.3 Institutional Conflict of Interest

As an organization that conducts and reviews research involving human subjects, the NJH recognizes its obligation to protect the rights and welfare of those subjects, and ensure the integrity of the research and the human research protection program. Toward this end, the financial interests of the 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.

25.3.1 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;

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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 25.3.2 below:
 1. Hold positions such as an officer, trustee, director, employee or consultant in commercial research sponsors, or any company that owns or controls products being studied or tested in human subjects
 2. 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);
 3. 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
 4. 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

25.3.2 Reporting

The following offices report at least semi-annually to the HRPP Office on interests described above:

1. Technology Transfer and Intellectual Property Office: to report licensing arrangements, patents, invention disclosures;
2. Development Office to report gifts

The following institutional officials are considered senior administrative officials.

- CEO
- CFO
- COO
- Executive Vice Presidents
- Chairs (of departments identified by the HRPP Office as conducting human research activities)

The HRPP Office, in consultation with the Compliance Office, will be advised of any annual disclosures from these individuals in which significant financial interests (SFI) relating to human research are identified. The HRPP Office will, in turn, contact the affected officials to receive confirmation that they will not be involved in the scientific merit, resource review, or any other review relating to research with which they have a SFI. Such confirmation will constitute the management plan that mitigates the potential COI (see also 'Conflict Management Plan' section below).

When a senior administrative official with an SFI is involved as an investigator in a human research project, the interest will be disclosed and managed as described in SOP Section 25.1 above.

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25.3.3 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.

25.3.4 Conflict Management Plan

If NJH's participation in a project is permitted notwithstanding the IFCOI, the NJH's participation will be subject to a conflict management plan developed by the Compliance Office, and reviewed by the IRB 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, 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

25.3.5 Timing

The review, evaluation, and where applicable, management of an IFCOI 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. IRB proposals will remain unapproved, pending acceptance by IRB of the IFCOI and the conflict management plan.

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25.4 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.

26 Participant Outreach

NJH is committed to ensuring that educational opportunities are offered to research participants, prospective research participants, and community members which will enhance their understanding of human subjects research at NJH and provide them the opportunity to provide input, seek information, and express concerns.

The following procedures describe how NJH fulfills that responsibility.

26.1 Outreach Resources and Educational Materials

1. The HRPP office dedicates a section of its website to research participants entitled "For Participants." This website includes resources, such as relevant links available at OHRP, FDA and a listing of relevant research-related links.
2. The website includes information regarding how to contact NJH with any questions or concerns about specific research projects or research in general.
3. The website includes a "Contact Us" link that allows members of the community to ask questions, express concerns, or provide feedback. Provision of contact information by the person is optional.

26.2 Evaluation

On an annual basis, NJH evaluates its outreach activities and makes changes when appropriate. In order to formally evaluate its outreach activities, the Director of RRA will review:

1. The specific community outreach activities being used
2. Whether or not these community outreach activities have an evaluative component (e.g., evaluation instrument distributed to participants), and if so whether the feedback was positive, negative, or neutral and if any suggestions were made that could be used to enhance future activities.
3. The number of times the participants' website is visited
4. Feedback provided via the "Contact Us" mechanism on the "Participant Outreach Corner"
5. Feedback provided from other sources (unaffiliated IRB members, investigators, research staff, students, etc.)

The results of the review will be used to establish both the adequacy of current outreach activities and any additional resources that may be needed to meet the needs of the research community regarding participant outreach.

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27 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.

27.1 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 limited data set that establishes the ways in which the information in the limited 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

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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:

(i) The individual's genetic tests; (ii) The genetic tests of family members of the individual; (iii) The manifestation of a 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: (i) A fetus carried by the individual or family member who is a pregnant woman; and (ii) 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.

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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 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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27.2 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.

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

The Privacy Rule does not change the composition of an IRB. When acting upon a request to waive or alter the Authorization requirement, an IRB must follow the procedural requirements of the Common Rule and FDA regulations, if applicable, including using either the normal review procedures (review by the convened IRB) or, as appropriate, the expedited review procedures.

When a request for a waiver or an alteration of the Authorization requirement is submitted to the HRPP Office, it is first shared with the Privacy Officer for his/her information and comment before being sent for IRB review.

- If the request will be considered by the convened IRB (e.g., as part of an initial submission, etc.), a majority of the IRB members must be present at the meeting, including at least one member whose primary concerns are in nonscientific areas. In order for an approval of a waiver or an alteration of the Privacy Rule's Authorization requirement to be effective, it must be approved by a majority of the IRB members present at the convened meeting. If a member of the IRB has a conflicting interest with respect to the PHI use and disclosure for which a waiver or an alteration approval is being sought, that member may not participate in the review.
- Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted if the research qualifies for expedited review under Common Rule requirements. For example, a modification to a previously approved research protocol, which only involves the addition of an Authorization for the use or disclosure of PHI to the IRB-approved informed consent, may be reviewed by the IRB through an expedited review procedure when it is considered to be no more than a minor change to research. If expedited review procedures are appropriate for acting on the request, the review may be carried out by the IRB Chair or by one or more experienced reviewers designated by the Chair from among the IRB members. A member with a conflicting interest may not participate in an expedited review. If an IRB uses expedited review procedures, it must adopt methods for keeping all its members advised of all requests for waivers or alterations of the Authorization requirement as well as those requests that have been granted under an expedited review procedure.

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;

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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
6. The signature of the IRB Chair or other member, as designated by the Chair, of the IRB, as applicable.

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

27.3 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 the 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 Section 27.12 for more information regarding an individual’s right to revoke, procedures, and exceptions.

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

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“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.

27.4 Waiver or Alteration of the Authorization Requirement

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

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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.

The Privacy Rule allows institutions to rely on a waiver or an alteration of Authorization obtained from a single IRB or Privacy Board to be used to obtain or release PHI in connection with a multi-site project. At NJH, the Privacy Officer will conduct an initial evaluation of the waiver's HIPAA compliance implications prior to action by the IRB.

27.5 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 Privacy Officer 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 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.

A 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."

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27.6 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.

27.7 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. See Section 27.4 of this policy manual for a discussion of waivers of authorization.

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.

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27.8 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 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.

27.9 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:

Page | 168

NOTE:

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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 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

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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.

The NJH HIPAA de-identification Form should be completed and submitted to the Director of Research Informatics or designee (if the proposal involves the investigator receiving the data set de-identified via the NJH-approved honest broker process available through the NJH research Database), or to the HRPP Office (if the proposal contains a process whereby the investigator him or herself is accessing PHI (via medical records etc.) but documenting the required health information without any of the 18 identifiers above.

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.

27.10 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;
13. URLs;
14. IP addresses;

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15. Biometric identifiers; and
16. Full-face photographs and any comparable images.

Before disclosing a limited 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 LDS 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 Officer.

27.11 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.

27.12 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 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.

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27.13 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.

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”.

27.14 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.

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28 Special Topics

28.1 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.

28.2 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.
- Research that is not funded by NIH or CDC may still have the protections afforded by CoCs through successful application to the NIH, FDA, HRSA, SAMHSA, or other authorized Federal agencies or departments.

Page | 173

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

28.2.1 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.

28.2.2 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
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.

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 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.

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.

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

28.2.3 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, 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.

28.2.3.1 NIH and CDC 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 requirements applies to research with NIH or CDC involvement or support. The questions outlined in the NIH policy and CDC requirements will be used to guide the analysis. When it has been determined that the NIH policy or CDC requirements do not apply, investigators are responsible for consulting with GCO whenever they are proposing changes to the NIH or CDC-funded activity that may impact or change the analysis.

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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.

28.2.3.2 Application Procedures for non-NIH, non-CDC Research

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 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](#).

28.2.4 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 NJH 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.

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28.3 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 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.

When information on more than three patients is included, the case series is considered to be a systematic investigation designed to contribute to generalizable knowledge (i.e., research), and therefore submission to the IRB is required.

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](#)). For all case reports and case series, a signed HIPAA authorization must be obtained from the patients or their legally authorized representatives for the use and disclosure of their Protected Health Information. The only exception to the requirement for obtaining authorization is if the author of a case report or case series believes that the information is not identifiable; in this case, the author must consult with the NJH Privacy Officer to seek an expert opinion about the magnitude of the risk of identifying an individual.

For case reports or case series containing more than three patients, the HIPAA authorization must be part of the consent form that is reviewed by the IRB.

For case reports or case series containing three or fewer patients, authors should prepare an authorization form using the templates provided by the Compliance Office or HRRP Office and arrange for review as indicated. Please note that for deceased patients, authorization must be obtained from the personal representative, who is the administrator or executor of the patient's estate.

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

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

28.4 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.

Page | 177

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28.4.1 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.

28.4.2 Research Repositories

Research repositories involve three distinct activities:

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

28.4.2.1 Collection

Informed consent and HIPAA authorization (when applicable) must be obtained unless the IRB determines that the criteria for a waiver are satisfied.

Informed Consent information should include:

- A clear description of
 - What data/specimens will be collected;
 - Where the data/specimens will be stored, who will have access, and how the data/specimens will be secured;
 - Whether the data/specimens will be identifiable, coded, or deidentified;
 - The types of research to be conducted and any limitations or restrictions on such; and
 - The conditions under which data/specimens will be released to recipient-investigators
- A statement regarding future withdrawal of the data from the study (i.e., state whether subjects may, in the future, request that their data be destroyed or that all personal identifiers be removed from data and how to make such a request)
- When appropriate, the plan for management of incidental findings and sharing of results

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28.4.2.2 Storage and Management

Repositories should have written policies describing:

- The conditions under which data/specimens will be accepted (e.g., inclusion criteria)
- Informed consent
- IRB review
- The sources of data/specimens
- Whether data/specimens will be identifiable, coded, or de-identified, and, if coded, management of the linkage key; and
- Physical and procedural mechanisms for the secure receipt, storage, and distribution of data/specimens

28.4.2.3 Distribution

Repositories should have written policies describing:

- How data/specimens may be requested and by whom
- Any requirements associated with a request for data/specimens (e.g., verification of IRB approval or that approval is not required)
- Any limitations or restrictions on how data/specimens may be used
- Whether released data/specimens will be identifiable, coded, or de-identified, and, if coded, any circumstances under which recipient investigators will access to or be provided with the key or other means to re-identify; and
- Agreements with recipient investigators specifying the terms of use.

28.4.2.4 IRB Oversight

IRB approval is required for the establishment and operation of a research repository when the data/specimens that are accessed, received, stored, or distributed are identifiable. In general, private information or specimens are considered individually identifiable when the identities of the subjects are known to investigators/repository operators or when the data/specimens can be linked to specific individuals either directly or indirectly through coding systems.

Separate IRB approval is required for the use of data/specimens from a repository when the recipient investigator(s) know or may readily ascertain the identity of individual subjects, 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). The only exception to this policy is when the coded private information or specimens are to be obtained from an IRB-approved repository and the rules of that repository forbid the release of identifiable information, the release of the key to the code or other means that would allow re-identification, or the release of sufficient information that investigators could readily ascertain the identity of subjects.

Page | 179

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28.5 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 to 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. Does the subject or family member be provided the option to receive or not receive results? How will this decision be recorded?
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 28.2)
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

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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](#)

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).

28.5.1 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](#).

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The NJH 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.

28.6 Genomic Data Sharing

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

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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).

For more information on CoCs, see Section 28.2.

28.6.1 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.

28.6.2 Procedures

IRB Submissions and GDS

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

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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 HRPP 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 the NJH IRB should include information about the proposed generation or use of genomic data including, as applicable:

- 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;
- Supplement J – Storing Data or Specimens for Future Use; 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.

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

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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 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.

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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/>.

28.7 Department of Defense

Research conducted or supported by the Department of Defense (DoD Research) is reviewed and conducted in compliance with part 219 of title 32 CFR, part 980 of title 10 USC, 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). Support of a study generally means the provision of funding, personnel (both military and civilian DoD employees), facilities, and any other resources.

DoD components (e.g., Army, Navy) may have additional requirements. The PI and a representative of the HRPP or IRB should contact the Human Research Protection Official (HRPO) for the DoD Component conducting or supporting the research. In most cases, protocols will also require review, approval and oversight by the DoD component HRPP. DoD review must be conducted 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.

NJH assures that DoD supported research complies with all relevant DoD human subjects protection requirements, including but not limited to:

- The Belmont Report
- Title 32 Code of Federal Regulations Part 219 ([32 CFR 219](#)), Department of Defense Regulations, “Protection of Human Subjects” (DoD adoption of the “Common Rule”)
- Title 45 Code of Federal Regulations Part 46, ([45 CFR 46](#)) Department of Health and Human Services Regulations, “Protection of Human Subjects,” Subparts B, C, and D as made applicable by [DoD Instruction \(DoDI\) 3216.02](#)
- Title [21 Code of Federal Regulations 50, 56, 312, and 812](#), Food and Drug Administration (FDA) Regulations
- [DoDI 3216.02](#), “Protection of Human Subjects and Adherence to Ethical Standards in DoD-supported Research”
- Title 10 United States Code Section 980 ([10 USC 980](#)), “Limitation on Use of Humans as Experimental Subjects”
- [DoDI 3210.7](#), “Research Integrity and Misconduct”
- [DoDD 6200.2](#), “Use of Investigational New Drugs in Force Health Protection”

It is the responsibility of the PI to ensure compliance with DoD requirements for human subject protection. IRB staff, chairs and members will use these SOPs, DoDI 3216.02, the DoD Reviewer Checklist, and any relevant DoD component-specific instructions or materials to guide the IRB review and oversight of DoD research.

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28.7.1 Key DoD Standards and Requirements

28.7.1.1 Minimal Risk

The definition of minimal risk based on the phrase “*ordinarily encountered in daily life or during the performance of routine physical or physiological examination or tests*” may not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

28.7.1.2 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. 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. The DoD component may evaluate the training policies of NJH to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.

28.7.1.3 Appointment of a Research Monitor

When DoD research involves **more than minimal risk**, the IRB **will** require and approve an independent research monitor by name. When research involves no more than minimal risk, an investigator may identify a research monitor or the IRB or IO may appoint a monitor. There may be more than one research monitor (e.g. if different skills or experience are needed). The monitor may be an ombudsman or a member of the data safety monitoring board.

The IRB must approve a written summary of the monitors’ duties, authorities, and responsibilities and the IRB or a HRPP official shall communicate with research monitors to confirm their duties, authorities, and responsibilities.

The duties of the research monitor are determined on the basis of specific risks or concerns about the research. The monitor:

- May perform oversight functions (e.g. observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and reports of unanticipated problems involving risks to participants or others, oversee data matching, data collection and analysis).
- May discuss the research protocol with researchers, interview human subjects, and consult with others outside of the study.
- The research monitor has the authority to stop a research study in progress, remove individual subjects from the study, and to take whatever steps are necessary to protect the safety and well-being of participants until the IRB can assess the monitor’s report.
- Research monitors are obligated to promptly report their observations and findings to the IRB or other designated official.

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28.7.1.4 Additional protections for vulnerable subjects

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

- The applicability of Subpart B is limited to non-exempt research involving:
 - Pregnant women as human subjects involved in research that is more than minimal risk and that includes interventions or invasive procedures to the woman or the fetus; or
 - Involving fetuses or neonates as subjects.
- For purposes of applying Subpart B, the phrase “biomedical knowledge” will be replaced with “generalizable knowledge.”
- Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.

Research involving **prisoners** as subjects must meet the requirements of Subpart C of the Common Rule, with the following modifications:

- Research involving prisoners cannot be reviewed by the expedited procedure.
- When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum. The prisoner representative may be a prisoner, an employee of the prison, or an individual not affiliated with the prison.
- In addition to the four allowable categories of research involving prisoners in Subpart C, two additional categories are allowable:
 - Epidemiological research that meets the following criteria:
 - The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
 - The research presents no more than minimal risk
 - The research presents no more than an inconvenience to the participant.
 - Prisoners are not a particular focus of the research
 - Research that would meet the criteria for exemption described at 32 CFR 219.101(b), can be conducted but must be approved by a convened IRB and meet the requirements of subpart C, DoDI 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:
 - The PI must promptly notify the IRB.
 - If the PI asserts to the IRB that it is in the best interest of the prisoner to continue to participate in the research while a prisoner, the IRB Chair may determine that the prisoner may continue to participate until the convened IRB can review the request to approve a change in the research protocol and until the IO and DoD Component office review the IRB’s approval to change the research protocol. Otherwise, the IRB Chair will require that all research interactions and

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interventions with the prisoner (including obtaining identifiable private information) cease until the convened IRB can review the request to approve a change in the research protocol.

- The convened IRB, upon receipt of notification that a previously enrolled human subject has become a prisoner, will promptly re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research from continuing as approved, the convened IRB may approve a change in the study to allow the prisoner to continue to participate in the research. This approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as participants.
- This type of request for change in the research protocol cannot be reviewed and approved by expedited review. The research does not have to meet one of the six allowable DoD categories for research involving prisoners.
- NJH will promptly report all decisions in this matter to the component HRPO. The HRPO must concur with the IRB decisions before the human subject can continue to participate while a prisoner.

Research involving **Children** as subjects must meet the requirements of Subpart D of the Common Rule, including that:

- The exemption for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Research involving **Military Personnel** as subjects must meet the following requirements:

- Service members must follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty and for approving off-duty employment or activities.
- Superiors (e.g., military and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) are prohibited from influencing the decisions of their subordinates (e.g., junior enlisted personnel and equivalent civilians) regarding participation as subjects in research.
- Superiors of Service members (e.g., unit officers, senior NCOs, and equivalent civilians) in the chain of command must not be present at any human subject recruitment sessions or during the consent process in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, the superiors so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session.
- When research involving Service members is greater than minimal risk and recruitment occurs in a group setting, the IRB will appoint an ombudsman. The ombudsman must not be associated in any way to the research and must be present during the recruitment to monitor that the voluntary involvement or recruitment of the Service members is clearly and adequately stressed and that the information provided

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about the research is clear, adequate, and accurate. The ombudsman may also be the research monitor.

Research involving **DoD Civilians** as subjects must meet the following requirements:

- DoD Civilians must follow their organization's policies regarding the requirement to obtain permission to participate in research
- Supervisors (e.g., military and civilian supervisors or anyone in the supervisory structure) are prohibited from influencing the decisions of their subordinates regarding participation as subjects in research
- Supervisors (e.g., military and civilian supervisors or anyone in the supervisory structure) must not be present at any human subject recruitment sessions or during the consent process in which DoD civilians under their supervision are afforded the opportunity to participate as human subjects. When applicable, supervisors so excluded shall be afforded the opportunity to participate as human subjects in a separate recruitment session
- For research involving civilians as human subjects when recruitment occurs in a group setting, the IRB will discuss appointing an ombudsman. The decision to require the appointment of an ombudsman should be based in part on the human subject population, the consent process, and the recruitment strategy.

Research involving **other vulnerable populations** must meet the following requirements:

- Investigators, IRBs, and IOs will consider the need for appropriate similar safeguards for other vulnerable populations, such as: research involving human subjects and investigators in supervisor-subordinate relationships, human subjects with decisional or mental impairments, human subjects with a physical disability, or any other kind of human subjects in circumstances that may warrant provision of additional protections. As appropriate, qualified individuals (e.g., research monitors, ombudsmen, advocates) may be appointed to perform oversight functions or assist the human subjects.

28.7.1.5 Limitation of Waivers and Exceptions from Informed Consent

For DoD-funded research, if the research meets the definition of "*research involving a human being as an experimental subject*," 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 IRB must determine that the research intends to benefit the individual subject.

The Assistant Secretary of Defense for Research and Engineering may waive the requirements for consent when all of the following are met:

1. The research is necessarily to advance the development of a medical product for the Military Services;
2. The research may directly benefit the individual experimental subject; and
3. The research is conducted in compliance with all other applicable laws and regulations.

Research involving a human being as an experimental subject is 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. If the research participant does not meet the definition of "experimental subject," policies and procedure allow the IRB to waive the consent process.

For classified research, waivers of consent are prohibited.

Page | 190

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An exception from consent in emergency medicine research is prohibited unless a waiver is obtained from the Secretary of Defense.

28.7.1.6 Limitations on Compensation for Human Subjects in Research

DoDI 3216.02 describes allowable and prohibited compensation for human subjects participating in DoD research and for Federal personnel such as civil servants and Service members. These provisions are intended to ensure compliance with the Dual Compensation Act and 24 U.S.C. 30. Summarized:

- Federal personnel while on duty and non-Federal personnel may be compensated for blood collections for research up to \$50 for each blood collection
- Federal personnel are prohibited from receiving pay or compensation for research during duty hours (except for blood collection as noted above)
- Non-Federal personnel may be compensated for research participation other than blood collections in a reasonable amount, as approved by the IRB according to local prevailing rates and the nature of the research
- Federal personnel may be compensated for research if the participant is involved in the research when not on duty in the same way as human subjects who are not Federal personnel (i.e., compensated for participation in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research). However, payment to off-duty Federal personnel for research participation other than blood draws must not be directly from a Federal source (payment from a Federal contractor or other non-Federal source is permissible)

Additional detail is available in DoDI 3216.02 or by consulting the component HRPO.

28.7.1.7 Reporting Requirements

The Institution must promptly (no longer than within 30 days) notify the HRPO of the following: when significant changes to the research protocol are approved by the IRB, the results of the IRB continuing review, if the IRB used to review and approve the research changes to a different IRB, when the institution is notified by any Federal department or agency or national organization that any part of its HRPP is under investigation for cause involving a DoD-supported research protocol, and all unanticipated problems involving risks to subjects or others, suspensions, terminations, and serious or continuing noncompliance regarding DoD-supported research involving human subjects.

28.7.1.8 Recordkeeping Requirements

Recordkeeping requirements for DOD-supported research with human subjects are longer than the Common Rule's requirement. DOD may require submitting records to DOD for archiving. Investigators should consult with the HRPO regarding record-keeping requirements for their research.

Records must be made accessible for inspection and copying by representatives of the DoD at reasonable times and in a reasonable manner as determined by the supporting DoD component. The fact that DoD may inspect records should be disclosed in the consent process.

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28.7.1.9 Addressing and Reporting Allegations of Non-Compliance with Human Research Protections

NJH must report the initiation of all investigations of allegations of non-compliance and report the results of all such investigations (regardless of the findings) to the HRPO.

28.7.1.10 Addressing and Reporting Allegations of Research Misconduct

NJH will adhere to the requirements of DODI 3210.7 and the terms of any DoD award when allegations or findings of research misconduct arise.

28.7.1.11 Prohibition of Research with Detainees

Involvement of detainees (e.g. civilian internees, retained persons, lawful and unlawful enemy combatants) as human subjects of research is prohibited. Research involving any person captured, detained, held or otherwise under the control of DoD personnel (military and civilian, or contractor employee) is prohibited. There is an exception for treatment of detainees with an investigational drug or device (described below).

A detainee is defined as any individual captured by, or transferred to the custody or control of, DoD personnel pursuant to the law of war. This does not include persons being held solely for law enforcement purposes, except where the United States is the occupying power.

The prohibition of research involving a detainee does not apply to the use of FDA-regulated investigational new drugs or investigational devices for the purpose of diagnosis or treatment of a medical condition in a patient. Such treatment (e.g., an investigational new drug) may be offered to detainees with the detainees' informed consent when the medical products are subject to FDA regulations as investigational new drugs or investigational medical devices, and only when the same product would be offered to members of the U.S. Military Services in the same location for the same medical condition and only when consistent with established medical practice involving investigational drugs and devices. Such permitted treatment involving detainees as subjects must comply with all sections of DoDI 3216.02.

28.7.2 Additional Requirements for DoD Research

IRB review must consider the scientific merit of the research. The IRB may rely on outside experts to provide an evaluation of scientific merit.

When conducting research with international populations, additional safeguards for research conducted with international populations the organization or researcher must have permission to conduct research in that country by certification or local ethics review. Researchers must follow all local laws, regulations, customs, and practices.

Disclosure regarding the provisions for research-related injury must follow the requirements of the DoD component.

Surveys performed on DoD personnel must be submitted, reviewed, and approved by the DoD component HRPO after the research protocol is reviewed by the IRB. When a survey crosses DoD components, additional review may be required by DoD.

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 DoDI 3216.02.

Page | 192

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When conducting multi-site or collaborative research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

Civilian researchers attempting to access military subjects should seek collaboration with a military researcher familiar with service-specific requirements.

28.8 International Research

The NJH IRB reviews transnational research involving human subjects to ensure that adequate provisions are in place to protect the rights and welfare of the subjects. All policies and procedures that are applied to research conducted domestically are applied to research in international settings, as appropriate. Approval of research is permitted if *“the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in 45 CFR 46.”*

For federally conducted or supported research, approval of research for foreign institutions or sites “engaged” in research is only permitted if the foreign institution or site holds a FWA with OHRP and local IRB review and approval is obtained.

Approval of research for foreign institutions or sites “not engaged” in research is only permitted if one or more of the following circumstances exist:

- When the foreign institution or site has an established IRB/EC, the investigator must obtain approval to conduct the research at the “not engaged” site from the site’s IRB/IEC or provide documentation that the site’s IRB/EC has determined that approval is not necessary for the investigator to conduct the proposed research at the site.
- When the foreign institution or site does not have an established IRB/IEC, a letter of cooperation must be obtained demonstrating that the appropriate institutional or oversight officials permit the research to be conducted at the performance site.
- IRB approval to conduct research at the foreign institution or site is contingent upon receiving documentation of the performance site’s IRB/EC determination, or letter of cooperation, as applicable.

The NJH IRB seeks sufficient knowledge of the local research context by requesting approval for the project from local IRBs or ethics committees (which may or may not be OHRP-registered) and/or local letters of support. The source of this information will depend on the nature of the study, on the country, and on the resources available to the investigator. Where there is a local IRB/EC, NJH IRB must receive and review the foreign institution or site’s IRB/EC review and approval of each study prior to beginning the research at the foreign institution or site.

In settings where there are no IRBs/ECs, NJH IRB may require additional verification and information from people outside the particular research project who are familiar with the customs, practices, or standards of care where the research will be taking place, including other IRBs or committees with experience reviewing research in the region, other NJH investigators with knowledge of the region, or a consultant who is an expert on the region, prior to approval. These individuals may either provide a written review of the research protocol or attend an IRB meeting to provide the NJH IRB with recommendations based on his or her expertise.

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28.8.1 IRB Responsibilities

In addition to the IRB review considerations discussed elsewhere in this manual, the IRB will consider the following when reviewing transnational research:

1. The qualifications of the investigator and research staff to conduct research in that country including knowledge of relevant laws, regulations, guidance and custom;
2. Whether the consent process and consent documents are appropriate for the language(s) of the subjects and the subject population, and that arrangements are made to be able to communicate with subjects throughout the study (e.g., to ask and answer questions);
3. How modifications to the research will be handled;
4. How complaints, noncompliance, protocol deviations and unanticipated problems involving risks to subjects or others are handled;
5. How post-approval monitoring will be managed;
6. Whether the investigator has obtained the appropriate host country permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local, or tribal). When appropriate, the IRB communicates and coordinates with the local institutions or ethics committees; and
7. Mechanisms for communicating with the investigators and research staff when they are conducting the research in other countries.

28.8.2 Investigator Responsibilities

The investigator conducting transnational research is responsible for:

1. Ensuring that the resources and facilities are appropriate for the nature of the research;
2. Verifying the qualifications of the investigators and research staff for conducting research in the country(ies);
3. Obtaining all appropriate host country permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local, or tribal);
4. Ensuring that the consent process and consent document are appropriate for the language(s) of the subjects and the subject population, and that arrangements are made to be able to communicate with subjects throughout the study (e.g., to ask and answer questions);
5. Ensuring that the following activities will occur:
6. Initial review, continuing review, and review of modifications;
7. Post-approval monitoring of the conduct of the research in accordance with the plan approved by the IRB; and
8. Handling of complaints, noncompliance and unanticipated problems involving risk to subjects or others;
9. Not relying upon an IRB or EC that does not have policies and procedures for the activities listed above;

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10. Ensuring that reportable information such as complaints, noncompliance, protocol deviations and unanticipated problems involving risks to participants or other are communicated to the IRB;
11. Notifying the IRB promptly if a change in research activities alters the performance site's engagement in the research (e.g., performance site "not engaged" begins to obtain consent of research participants, etc.); and
12. Ensuring that there are mechanisms for communicating with the IRB when they are conducting the research in other countries.

28.8.3 Consent Documents

The informed consent documents must be appropriate for and in a language understandable to the proposed subjects.

28.8.4 Monitoring of Approved International Research

The IRB is responsible for the ongoing review of international research conducted under its jurisdiction through the continuing review process in accordance with all applicable federal regulations. When the IRB and a local ethics committee are both involved in the review of research, there is a plan for coordination and communication with the local IRB/ECs.

The IRB requires documentation of regular correspondence between the NJH investigator and the foreign institution or site and may require verification from sources other than the NJH investigator that there have been no changes made to the research since its last review.

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