

This document serves as a reference and guide for all components of the Human Research Protection Program, including the Institutional Review Board, Investigators and their Research Teams, and other members of the Research Community.



Yale University
Human Research Protection Program
(HRPP)

Policy and Standard Operating Procedure Manual

Version Date: July 24, 2023

PART I

Yale HRPP Policies and Procedures

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1 Human Research Protection Program

Yale University (Yale) fosters a research environment that promotes respect for the rights and welfare of human subjects in research. In support of this, Yale has established a Human Research Protection Program (HRPP). The Yale HRPP, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under Yale'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.
- Provide timely and high-quality education, review, and oversight of human research projects.
- Facilitate best practices 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 and others.

1.2 Organizational Authority

The Yale HRPP operates under the authority of University Policy 1360 "Human Research Protection". As stated in that policy, the policies and procedures in this document serve as the governing procedures for the conduct and review of human research conducted under the auspices of the Yale University." The HRPP Policy and these operating procedures are made available to investigators and research staff and are posted on the [HRPP website](#).

1.3 Ethical Principles

Yale is committed to conducting research with the highest regard for the welfare of human subjects. Yale 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

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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

In addition to Belmont, Yale also adheres to other relevant human research standards (e.g., Council for International Organizations of Medical Sciences (CIOMS), etc.) and considers additional or alternative ethical principles that may apply when research is conducted transnationally.

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

1.4 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 Yale is conducted in accordance with applicable regulations and requirements including, but not limited to, the following:

Human Subjects 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 manual, references to the Common Rule will cite the DHHS regulations (45 CFR 46).

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 conducted or supported by the **Department of Justice (DOJ)** is subject to the **pre-2018 Common Rule** with regulations published at [28 CFR 46](#). The DOJ has established additional requirements for research conducted with the federal Bureau of Prisons ([28 CFR 512](#)) and research involving the National Institute of Justice ([28 CFR 22](#)). Investigators should consult these regulations and [resources provided by NIJ](#) when developing their research protocol. The IRB evaluates the research in accordance with these regulations when applicable. See section 44 of this manual for more information.

When human subjects research is not subject to the Common Rule, FDA, or DOJ regulations, Yale 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.

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](#). See Section 27 of this manual for more information.

Several other U.S. federal departments and agencies have additional rules that apply to human subjects research that is supported by, conducted for or with, or involving the personnel or facilities of the department or agency. The IRB will evaluate such research in accordance with the applicable rules and requirements. Additional information regarding department/agency specific rules is available in sections 42-47 of this manual.

1.4.1 Management of pre-existing studies subject to the Common Rule

For research subject to the Common Rule the following outlines when the pre-2018 rule or the revised rule will apply to research under auspices of Yale's HRPP. Yale did not adopt the burden-reducing provisions between July 19, 2018 and January 20, 2019.

- A. Research subject to the pre-2018 Common Rule requirements.** The pre-2018 requirements will apply to the following studies, unless a study is transitioned to comply with the revised rule as described in Section B below.
- All studies initially approved, waived under .101(i), or determined exempt before January 21, 2019 will be subject to the pre-2018 requirements through the close of study.
 - Studies subject to Department of Justice (DOJ) regulations at [28 CFR 46](#).
- B. Research subject to the revised Common Rule (2018 requirements). The 2018 requirements will apply to the following studies.**
- All studies initially approved, waived under .101(i), or determined exempt on or after January 21, 2019 will be subject to the 2018 requirements.
 - Studies not subject to DOJ regulations that were initially approved before January 21, 2019, may at the time of continuing review be transitioned to the revised Common Rule. The determination whether the study will be transitioned is made by the Yale IRB during the review. In its decision, the IRB will consider the benefits of the revised regulations against the possible increased administrative burden associated with the transition of ongoing research. Deciding factors will include remaining research activities (active recruitment with consent vs. analysis of data only) and engagement of multiple domestic sites in research. In addition, the IRB will consider requests from Principal Investigators to transition their studies in situations where the IRB would not typically consider the transition. All transitions will be documented in the study record in the IRB electronic system and communicated to the investigators.

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

Yale applies the International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines (sometimes referred to as ICH-GCP or E6) to clinical trials of drugs when required by a sponsor or funding agency. Yale applies the ICH-GCP guidelines only to the extent that they are compatible with FDA, DHHS, and other applicable regulations unless otherwise required by the sponsor. See the Section 46 of this manual for more information.

1.6 Federalwide Assurance (FWA) and IRB Registration

DHHS regulations require that institutions engaged in non-exempt human subjects research that is conducted or supported by any HHS agency file and maintain a Federalwide Assurance with the Office for Human Research Protections (OHRP). An FWA is an organization's assurance to the U.S. government that that non-exempt human subject research is conducted in compliance with federal regulations pertaining to the protection of human subjects. Yale maintains a FWA on file with OHRP and ensures that it remains current.

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. Yale's HRPP office maintains its FWA and IRB registration(s) in accordance with applicable regulations and guidance provided by [OHRP](#) and [FDA](#).

The [HHS registration system database](#) can be used to verify the status of Yale's FWA, IORG, and IRB registration. Yale's FWA # is 00002571 and the IORG# is 0000431. The individual IRB registrations are too numerous to list in these policies and procedures but are available on the [HRPP IRB Information webpage](#) under "IRB Panel Overview."

1.7 Research Under the Auspices of Yale's HRPP

Research under the auspices of Yale HRPP includes all human subjects research conducted at or using any property or facility of Yale or Yale New Haven Hospital (YNHH), conducted by or under the direction of any employee or agent of Yale (including students) or YNHH in connection with their Yale or YNHH position or responsibilities, or involving the use of Yale's and YNHH'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.

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

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

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1.8 Engagement in Research

Yale is responsible for ensuring appropriate oversight of the human subjects research it engages in, including IRB approval of non-exempt human subjects research.

OHRP defines engagement in guidance, stating:

“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.”

The guidance also states that institutions that receive an award through a grant, contract, or cooperative agreement directly from DHHS for non-exempt human subjects research (i.e., awardee institutions), are also considered engaged in research even when 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 Yale facilities, by Yale Principal or Sub-Investigators (as defined on the FDA 1572 or equivalent, or the delegation of responsibilities log), or in the facilities or involving the investigators of any entity whose research is under the auspices of the Yale HRPP requires review by a Yale-designated IRB. Exceptions to this requirement may be granted on a case-by-case basis (e.g., when Yale’s involvement in the research is limited to the provision of a common diagnostic procedure and associated reading or analysis).

The HRPP Director or designee, with the assistance of legal counsel as needed, are authorized to determine whether Yale is engaged in a particular research study. Investigators and other institutions may not independently determine whether Yale is engaged in a particular research study.

When Yale is engaged in research, the Institutional Official may choose to enter into an agreement to cede review to an external IRB. This Institutional Official can delegate this authority to appropriate designees.

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

1.9 Key Definitions

Human Subject Research. Human Subject Research means any activity that meets the definition of “research” and involves “human subjects” as defined by the Common Rule or other applicable regulations (e.g., FDA).

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

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.

Common Rule. The Common Rule refers to the “[Federal Policy for the Protection of Human Subjects](#)” adopted by a number of federal agencies. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in 45 CFR 46 Subpart A. For the purposes of this document, references to the Common Rule will cite the DHHS regulations. The Common Rule was updated in 2018, throughout this manual references to the “pre-2018 Common Rule” (or requirements) apply to studies approved or determined exempt prior to January 21, 2019 that have not been transitioned to comply with the 2018 Common Rule. References to the “2018 Common Rule” (or requirements) or the “revised Common Rule” apply to studies approved or determined exempt on or after January 21, 2019.

Pre-2018 Common Rule Definitions:

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 the purposes of these policies and procedures, 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.

Human subject. Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

- (1) Data through intervention or interaction with the individual, or
- (2) Identifiable private information.

Intervention. Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.

Interaction. Interaction includes communication or interpersonal contact between investigator and subject. *Please note that per OHRP, interaction includes indirect means of communication such as via completion of a web-based survey.*

Private Information. Private information includes 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 that 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. Identifiable information means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

2018 Common Rule Definitions:

Clinical Trial. Per the 2018 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).

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. [45 CFR 46.102(e)(1)]

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. [45 CFR 46.102(e)(2)]

Interaction means communication or interpersonal contact between investigator and subject. *Please note that per OHRP interaction includes indirect means of communication such as via completion of a web-based survey.*

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. [45 CFR 46.102(e)(5)]. *Note: This definition is within the 2018 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 [45 CFR 46.102(e)(6)]

Legally authorized representative means 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. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

Public health authority means an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

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

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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)]

*NIH issues determinations about whether NIH-supported or conducted activities qualify as [public health surveillance activities](#) deemed to be “not research” under the revised Common Rule. Investigators and institutions may not make their own determinations.

For the purposes of these policies and procedures, a “**systematic investigation**” is an activity that involves a 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. In accordance with OHRP guidance, the establishment of a research repository is also considered a systematic investigation intended to develop generalizable knowledge.

Food & Drug Administration (FDA) Definitions:

Research. 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\(b\)](#)]

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. 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 might be either a healthy individual or a patient. For research involving medical devices a human subject is also an individual on whose specimen an investigational device is used or tested or used as a control (regardless of whether the specimens are identifiable). [[21 CFR 50.3\(g\)](#), [21 CFR 312.3\(b\)](#), [21 CFR 812.3\(p\)](#)]

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

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

1. **[Human drugs](#)** – A drug is defined as a substance recognized by an official pharmacopoeia or formulary; a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance (other than food) intended to affect the structure or any function of the body; a substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process). The primary intended use of a drug product is achieved through chemical action or by being metabolized by the body.
2. **[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 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 its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o)."

The 21st Century Cures Act amended the FD&C Act to specifically exclude certain software functions from the definition of medical device. Summarized, these

include exclusions for software functions intended for administrative support of a health care facility; for maintaining or encouraging a healthy lifestyle; to serve as electronic patient records; for transferring, storing, converting formats, or displaying clinical laboratory tests or other device data and results and related information; and for displaying, analyzing, or printing medical information, for supporting or providing recommendations to a health care professional, and enabling the health care professional to independently review the basis for such recommendations. Additional information regarding the application of these exclusions is available on FDA's "[Guidances with Digital Health Content](#)" website.

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

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

4. **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.

5. **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.
6. **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.
7. **Mobile Medical Apps** - Mobile apps are software applications that can be executed on a mobile platform or a web-based software application that is tailored to a mobile platform but is executed on a server. Mobile medical apps are a subset of mobile apps that medical devices that meet the definition of a [medical device](#) and either are intended to be used as an accessory to a regulated medical device; or to transform a mobile platform into a regulated medical device.
8. **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".
9. **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).

1.10 Written Policies and Procedures

These Policies and Standard Operating Procedures (SOPs) for Human Research Protection detail the procedures, standards, and requirements for research with human subjects under the auspices of Yale and the requirements of the Yale HRP and IRB. This is not a static document.

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The policies and procedures are reviewed at a minimum of annually and revised by the Director of HRPP with input from the HRPP staff, Office of General Counsel, Institutional Official, and other applicable stakeholders.

Changes to the policies and SOPs proposed by the HRPP staff or members undergo a change management process. The proposed revisions are first reviewed by the HRPP change management advisory group consisting of representatives of different units within the HRPP Office. Their opinion along with the proposal is then reviewed by the HRPP leadership groups (Managers, Assistant and Associate Directors, and Advisors) at their respective meetings. The Director of the HRPP will ultimately approve all revisions.

The Yale 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. This manual is also available on the [Yale HRPP website](#). Changes to the manual are communicated to investigators and research staff, and IRB members and HRPP staff by way of email, change log on HRPP website, staff meetings, and other appropriate means.

1.11 Yale HRPP Structure

The HRPP consists of individuals, departments, and committees with responsibilities for human research protections such as the Institutional Official, the Director of the HRPP, HRPP staff, the IRB, the HRPP/IRB Leadership Committee, the Protocol Review Committees, the Biological Safety Committee, the Radiation Safety Committees, the Radioactive Drug Research Committee (RDRC), the Radioactive Investigational Drug Committee, the Institutional Conflicts of Interest Committee, the Provost’s Committee on Conflicts of Interest (COI Committee), Research Administration, the Office of the Provost, the Office of Sponsored Projects, the Office of Research Compliance, the Office of General Counsel, the Information Security Office, the Yale Center for Clinical Investigation, investigators, research personnel, 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.

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

1.11.1 Institutional Official

The ultimate responsibility of the HRPP resides with the Institutional Official (IO) of the HRPP. The IO is legally authorized to represent Yale. The IO is the signatory of Yale’s FWA and assumes the obligations of the FWA. At Yale, the Senior Associate Provost for Research Administration is the Institutional Official. The responsibilities of the IO include:

- Fostering, supporting, and maintaining an organizational culture that supports the ethical conduct of research involving human subjects and compliance with applicable regulatory and other requirements.
- Serving as the signatory authority and ensuring compliance with the terms of the University's FWA.
- Ensuring that the HRPP and IRB have the resources and support necessary to fulfill their mission and responsibilities. Such resources include, but are not limited to:
 - Staffing commensurate with the size and complexity of the research program.
 - Appropriate office space, meeting space, equipment, materials, and technology.
 - Resources for the production, maintenance, and secure storage of HRPP and IRB records.
 - Resources for overseeing the conduct of research, including audits and investigations.
 - Access to legal counsel.
 - Access to consulting reviewers as needed to ensure that the IRB has the appropriate expertise to review the research before it.
 - Training in human research protections and other relevant subject matter for researchers, IRB members, and staff to support the review and conduct of human research in accordance with ethical standards and applicable regulations and requirements.
- Appointing members of the IRB.
- Ensuring that the IRB functions independently by, among other mechanisms, being directly accessible to the IRB Chairs and members if they experience undue influence or if they have concerns about how the IRB is functioning.
- Oversight of the IRB.
- Determining when reliance upon an external IRB is acceptable and appropriate.
- Oversight over the conduct of research under the auspices of the Yale HRPP
- Taking action as necessary to ensure the protection of human subjects, the integrity of research and the HRPP, the autonomy and authority of the IRB, the proper conduct of research, and to ensure compliance with regulatory and other requirements. This includes the authority to suspend, terminate, or disapprove research, to sanction or restrict research privileges, and to disallow or restrict the use of research data. Such actions will be reported to the HRPP and IRB when appropriate so that the HRPP and IRB may take any necessary actions to ensure the protection of human subjects.

The HRPP Director, with the assistance of others as needed, performs an ongoing review of the HRPP, makes adjustments as needed based on the findings, and reports findings to the IO. In addition to evaluating the adequacy of resources (see above), the review includes evaluation of:

- Whether IRB membership remains appropriate or whether changes are needed (e.g., for expertise, due to attendance or performance issues, etc.);

- Whether there are any institutional or IRB member conflicts of interest that require management;
- The adequacy of the education provided to the IRB, HRPP staff, and the research community;
- The outcomes of the HRPP Quality Improvement activities and the plan for the upcoming year; and
- The adequacy of community outreach activities.

The IO completes the CITI Program training for Institutional/Signatory Officials. The HRPP Office 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 HRPP Director and IRB Chairs have access to the IO for any concerns or issues related to the HRPP or IRB.

In the performance of these duties, the IO has the authority to delegate responsibilities to others while maintaining primary responsibility for the program.

1.11.2 Director of the HRPP

The Director of the HRPP, also known as the Human Protections Administrator, is selected by and reports to the Institutional Official (IO) and is responsible for the oversight of and day-to-day operations of the HRPP. The Director's responsibilities include:

- Developing, managing, and evaluating policies and procedures that ensure compliance with state and federal regulations and Yale policies. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing the administration of the IRB.
- Advising the IO on key matters regarding human subjects research.
- Implementing the organization's HRPP Policies and Standard Operating Procedures.
- Overseeing the administration of the HRPP and IRB, including the supervision of staff.
- Overseeing the administration of 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 Yale HRPP and IRB.
- Assisting the IRB in its efforts to review research and ensure the protection of human subjects.
- Assisting investigators in their efforts to carry out the organization's research mission.
- Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program.

- Developing training requirements as required and as appropriate for IRB members, investigators, and staff, and ensuring that training is completed on a timely basis.
- Serving as the primary contact at Yale 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.
- Serving as an internal expert resource for questions and other matters regarding the protection of human subjects.

1.11.3 HRPP Staff

In addition to the leadership structure described above, the HRPP office is staffed by personnel with responsibilities in the following general areas: (1) HRPP Operations, (2) HRPP Review, (3) IRB Reliance & sIRB, (4) Regulatory, Compliance & Quality; (5) Yale Institutional Review Board; and (6) other areas of committee oversight (e.g., RDRC, RIDC, ICOI (in collaboration with the COI office), etc.). HRPP personnel 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. HRPP staff report to the HRPP Leadership Team.

1.11.3.1 HRPP Review


The HRPP Review team is part of the HRPP staff. The HRPP review consists of review of investigators' compliance with institutional requirements related to human subjects research. The review occurs prior to IRB review, regardless of whether the research study will be under purview of internal IRB or IRB external to Yale.

The relevant outcomes of the review that may affect IRB review are communicated to the reviewing IRB either via IRB electronic system or a separate communication.

1.11.4 Institutional Review Board (IRB)

Yale has multiple IRB panels the members of which are appointed by the Institutional Official (IO). The IRB prospectively reviews and make decisions concerning all human subjects research under the auspices of the Yale HRPP unless it has been determined that Yale is not engaged in the research or Yale has entered into agreement with an external IRB to serve as the IRB of record. The IRB are responsible for the protection of the rights and welfare of human research subjects, exercised through the review and oversight of human subjects research in compliance with applicable regulations, requirements, standards, and policies.

The IRB functions independently of, but in coordination with, other organizational committees and officials. The IRB, however, makes independent determinations whether to approve, require modification in, or disapprove research.

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Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the organization. However, no one at Yale may approve the implementation of human subjects research that has been disapproved or not yet been approved by the IRB of record, nor may anyone override an IRB suspension or termination of IRB approval.

1.11.5 Legal Counsel

The Yale HRPP consults with the Office of General Counsel (OGC) on the interpretation of human subjects regulations, 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.

1.11.6 Organizational Leaders

The Yale [Faculty Handbook](#) institutes rules for appointment process to Yale Faculty positions along with the permitted activities at different levels of the Faculty ranks (research, teaching, serving as advisers of dissertations, serving as the Principal Investigator on grants, etc.). The departments establish Faculty Affairs offices that are responsible for ensuring that incoming and existing Faculty meet and maintain requirements for their appointments such as medical and other professional licensures, training, insurance, etc. The department chairs are responsible for ensuring that investigators are qualified by training and experience to conduct human subjects research. The department chairs and the relevant Deans of Yale schools provide written permission for investigators who do not meet the established criteria for serving as principal investigators on research.

When requested, the HRPP provides lists of active research studies to the department chairs. The departments are responsible for establishing approval process for research activities involving their investigators prior to submission of grant application or the research protocol to the IRB. Yale Cancer Center requires approval from the leaders of the Disease Aligned Research Teams (DARTs) before accepting a study for a scientific review. When requested, the HRPP establishes processes to ensure an approval from the relevant department chair either by obtaining a written permission prior to accepting a study for review or creating a workflow in the HRP electronic system that routes the submission to the department.

1.11.7 Principal Investigators

The Principal Investigator (PI) is ultimately responsible for the protection of the human subjects participating in research they conduct or oversee. The PI is expected to abide by the highest ethical standards when developing a research plan and to incorporate the principles of the [Belmont Report](#). The PI is expected to conduct research in accordance with the IRB approved research plan and to personally conduct or oversee all aspects of the research. In addition to

complying with all applicable regulatory policies and standards, PIs must comply with organizational and administrative requirements for conducting research. The PI is responsible for ensuring that all investigators and research staff complete all organization required trainings as well as training for their specific responsibilities in any given research study. When investigational drugs or devices are used, the PI is responsible for ensuring an appropriate plan for their storage, security, dispensing, accounting, and disposal.

The IRB considers investigator qualifications when reviewing research and in doing so may rely upon sources of information that support that the investigators are appropriately qualified (e.g., for reliance, the relying organization; the Yale-held IND/IDE sign-off process, etc.). The IRB 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 PI for human subjects research under the auspices of Yale's HRPP must meet [the Faculty Handbook](#) criteria for serving as a Principal Investigator on sponsored projects. The Faculty Handbook specifies appointments that allow serving as the PI with permission from the Department Chair and the Dean or the Provost. The permission is documented on a Yale mandated 'PI Status Request Form' provided to the Office of Sponsored Projects at the time of the grant or contract proposal or, if the research does not include external funding, a 'Special Permission to serve as the PI' form submitted to the Yale HRPP.

Trainees, whether or not they are employees (such as postdoctoral fellows/associates, students, interns or residents), may apply to serve as the Principal Investigators on research projects only with the approval of a Yale faculty sponsor or mentor who meets the Faculty Handbook criteria to serve as the PI. Attestation from the faculty mentor must be submitted to the Yale HRPP at the time of the protocol submission.

Individuals 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.

Individuals with a history of compliance issues related to the conduct of research (e.g., recipients of an FDA Warning Letter) 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 indicates that the issues have been resolved, and similar considerations.

1.11.8 Other Related Units

Units within the Office of Research Administration (ORA) and several other Yale offices and committees outside of the ORA share the responsibility to oversee University research. They consider the rights and welfare of human subjects participating in Yale studies when developing and carrying out their core functions supporting the research, including their own compliance

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responsibilities. These entities are responsible for coordinating their core business processes and/or responsibilities with the University's human subject protection program.

1.11.8.1 Office of Sponsored Projects

The HRPP and Office of Sponsored Projects (OSP) coordinate efforts to help ensure the protection of human subjects in research and to support compliance with applicable rules and policies. OSP 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 OSP have the authority to approve funding proposals and to execute research agreements on behalf of the organization.

OSP ensures that required AAHRPP language (see Section 24) is included in contracts. OSP has access to the IRB submission to confirm that the contract and the consent documents are consistent in terms of costs to subjects and who covers cost of treatment of research related injury. The OSP and the HRPP office coordinate efforts when institutional certification that involves IRB review is required as a term of an award or by policy (e.g., NIH genomic data sharing). OSP and HRPP routinely coordinate reviews of terms of materials and data sharing during Data Use Agreements and Material Transfer Agreements negotiations to ensure consistency between these agreements and consent documents.

1.11.8.2 Office of Research Compliance

The Office of Research Compliance (ORC) provides support to the Office of Research Administration (ORA) and its mission. As such, ORC's role is to review and participate in the implementation of emerging regulatory requirements, and proactively monitoring regulatory compliance through assessments and responding to concerns expressed to the ORC.

1.11.8.3 Office of Export Controls

The Office of Export Controls oversees Yale Export Compliance Program and supports Yale faculty, staff, and students in meeting requirements related to export controls, such as equipment, technology, and information used by the Yale community in the conduct of research. The HRPP will coordinate with the Office of Export Controls when studies involving embargoed countries are submitted for review to ensure a sign-off is in place.

1.11.8.4 Pharmacy

Yale New Haven Investigational Drug Pharmacy is responsible for the receipt, storage, control, dispensing, and compounding of most investigational drugs used in research, whether conducted in inpatient or outpatient facilities. The manufacture/compounding of drug products not commercially available is coordinated by YNHHS IDS pharmacy. Waivers from use

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of the YNHH IDS pharmacy for handling investigational drugs will be considered on a case-by-case basis by both the IRB and when applicable, the institution, with information regarding the planned control of investigational product provided with the IRB application.

The Pharmacy is available to provide guidance to investigators in relation to the management of the study drugs.

1.11.8.5 Yale YCCI IND/IDE Management Office

[Yale Center for Clinical Investigation \(YCCI\) IND/IDE Management Office](#) provides a comprehensive, centralized resource for FDA submission of Investigational New Drug (IND) applications and Investigational Device Exemptions (IDEs). The Office reviews and approves all Yale proposals to be performed under a Yale-held IND, IDE, or EUA. The YCCI IND/IDE Management Office may refer proposals to the YCCI Oversight Committee for further adjudication or action. This group has been charged to provide general oversight of all proposed projects to be completed under an IND/IDE/EUA for feasibility, resources, budget, project management, monitoring and data management prior to full development of the IND or IDE application and protocol.

1.11.8.6 Radioactive Drug Research Committee (RDRC)

RDRC, an FDA regulated committee, reviews and approves human subjects research involving radiation exposure and the administration or use of investigational radioactive drugs which require neither an Investigational New Drug (IND) nor Food and Drug Administration (FDA) approval. This research is typically conducted at the Yale University PET Center. Among other responsibilities mandated by the FDA, the RDRC ensures that both the pharmacological dose to be administered to subjects and the radiation dose received by subjects are within limits set by the FDA. Approval decisions regarding research studies are communicated directly to the HRPP and IRB using the IRB electronic system.

1.11.8.7 Radioactive Investigational Drug Committee (RIDC)

RIDC reviews and approves human subject research protocols involving the use of FDA-approved radiopharmaceuticals, investigational radioactive drugs with an IND, amended IND or an FDA allowed IND exemption. The research that requires RIDC review is typically conducted at the Yale University PET Center or another Yale University facility under Yale University's NRC medical use license. RIDC is responsible for ensuring that that the radioactive materials administered are appropriate. The RIDC responsibilities include confirming that the underlying science and research protocol are of sound design; reviewing and approving the consent form language related to radiation; and evaluating radiation dosimetry. Approval decisions regarding research studies are communicated directly to the HRPP and IRB using the IRB electronic system.

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1.11.8.8 YNHH and YU Radiation Safety Committees (RSC)

YNHH RSC and YU RSC review scientific and safety aspects of research conducted under their respective NRC licenses and involving radioactive materials and/or subject exposure to external sources of radiation. The committees ensure compliance with appropriate radioactive material use licenses and radiation producing equipment permits and registrations. Approval decisions regarding research studies are communicated directly to the HRPP and IRB using the IRB electronic system.

1.11.8.9 Conflict of Interest Committee (COIC)

The Conflict of Interest Committee collaborates with the HRPP in the review of protocol-specific conflict of interest disclosures to ensure that conflicts are either reduced, managed or eliminated. The COIC communicates all plans for conflict management to the HRPP Office and notifies the office about changes in individual investigators' disclosures that can be potentially related to human subject research protocols.

1.11.8.10 Institutional Conflict of Interest Committee (ICOIC)

The Institutional Conflict of Interest Committee is charged with the review of institutional conflicts of interest in human research. If the ICOIC determines that an ICOI exists in relation to human subjects research, it will decide upon appropriate actions to eliminate or manage the ICOI, and it will report the ICOI along with those decisions to the President, HRPP, and other designated offices or individuals. The HRPP ensures that any actions are communicated to the IRB of record.

1.11.9 Relationship Among Components

The Research Compliance Committee will meet to ensure a dialogue is maintained between the various individuals and offices with responsibilities for research compliance at Yale University. Membership is comprised of the list of individuals below with the Senior Associate Vice Provost and Institutional Official as Chair. The committee will act in an advisory capacity to the Vice Provost for Research, monitoring the effectiveness of existing programs, developing new or revised policies as changes in requirements occur, and disseminating updates to the research community.

- Chief Research Compliance Officer
- Director, Institutional Compliance Program
- Director, Human Research Protection Program
- Director, Research Integrity
- Executive Director, Office of Sponsored Projects
- Director, Conflict of Interest Office

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- Director, Sponsored Projects Financial Administration
- Associate General Counsel, Office of General Counsel
- Other representatives as appropriate

1.11.10 Study-Specific Coordination

In addition to IRB approval, PIs may need to obtain and document the approval, support, or permission of other individuals and departments or entities impacted by the research as well as approval by other oversight committees, including, but not limited to:

- Yale Cancer Center Protocol Review Committee
- Pediatric Protocol Review Committee
- Nursing Committee
- Institutional Biosafety Committee
- Yale or Yale New Haven Radiation Safety Committee
- Radioactive Drug Research Committee
- Radioactive Investigational Drug Committee

When applicable, a letter of support, collaboration, permission, or approval from the designated authority, should be included in the Initial Study Application to the IRB. The application will be reviewed by the HRPP Review team within the HRPP Office to ensure that all necessary letters are included. When appropriate, the HRPP will establish workflows using the HRPP electronic system that allow for electronic routing to the ancillary committee or designated authority for approval or acknowledgment. A complete list of the ancillary committees, timing of the required approvals (whether the approvals must occur prior to, simultaneously, or following IRB approval), and instructions on how to obtain them are included in the Investigator Manual.

The HRPP and the IRB may request review by or consultation with any of the above listed or other organizational committees or components even when such review or consultation is not required by policy.

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2 Quality Assurance

Yale HRPP 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 HRPP and applicable parties which may include, but are not limited to, Office of General Counsel, Department Chairs, Yale Center for Clinical Investigation, and Investigational Pharmacy, if applicable should be notified in advance, whenever possible, of upcoming audits or inspections of research whether the study is reviewed by the Yale IRB or an external IRB on Yale's behalf. HRPP representatives may participate in entrance and exit interviews and otherwise observe or support the audit or inspection. Likewise, Yale representatives may assist in the development of any responses to audits or inspections.

When research is under the oversight of the Yale IRB, all reports from external monitors, auditors, or inspectors that find noncompliance must be submitted to the IRB for review. The IRB Chair or designee 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 IRB to determine what additional actions are necessary, if any.

When Yale is engaged in research reviewed by an external IRB, all reports from audits or inspections that find noncompliance must be submitted to the HRPP for review. The HRPP may require corrective and preventive actions (CAPA), a follow up review, or other actions as needed to ensure the protection of human subjects and to support compliance.

Reports indicative of any negative actions by a government oversight office regarding research conducted at or by Yale including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated (classification as "OAI" is typically made after the FDA has the opportunity to review any responses to a 483), FDA Restrictions Placed on IRB or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections must be immediately reported to the HRPP/IRB office by submission of Reportable New Information (RNI) via the IRB electronic system regardless of whether the research is reviewed by an internal or external IRB. See Section 22 for more information.

2.2 Investigator Compliance Reviews (aka Post-Approval Monitoring)

For human subjects research studies conducted under the auspices of Yale School of Medicine, the Yale Center for Clinical Investigation (YCCI) and HRPP support a joint compliance program to

conduct compliance reviews. For all other human subjects research under the auspices of the Yale HRPP, compliance reviews are conducted by the HRPP regulatory, compliance, and quality (RCQ) team or designated individual(s). Compliance reviews may be directed (for cause) or routine (not for cause). On occasion, other internal or external staff, may conduct compliance reviews of human subjects research conducted under the auspices of Yale. Studies selected for routine reviews are determined based on a risk assessment of objective criteria. Directed or routine reviews may include a full compliance review or targeted review. Generally, high-risk studies will receive a full compliance review and medium/low-risk studies will receive a targeted or limited review. Investigator self-assessments may be requested as an additional means to monitor compliance. Generally, self-assessments will be requested for studies identified as low-risk. Additionally, the 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 oversight. The subcommittee may be composed of IRB members and 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 Yale policies, and to identify areas for improvement, and to provide recommendations based on existing policies and procedures. Results of compliance reviews will be reported to the investigator along with recommendations and any required actions. Findings will be escalated to the HRPP Director and other Yale leadership, as appropriate. Any IRB 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 HRPP Director and the IRB of record.

If issues are identified that indicate possible misconduct in research, the matter will be referred to the Research Integrity Office.

Compliance reviews may include:

- Requesting progress reports from investigators
- Examining investigator-held research records and records held by pharmacy or other ancillary services
- Reviewing source documentation
- Reviewing the recruitment process and materials
- Reviewing consent materials and the documentation of consent
- Observing the consent process and other research activities
- Verifying HIPAA authorization
- Interviewing investigators and research staff
- Interviewing research subjects

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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

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

Review activities may include:

- Review of the 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 IRB 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 IRB databases to evaluate whether all required fields are completed accurately
- Verifying IRB 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 IRB review process
- Reviewing the workload of the IRB and HRPP staff
- Other review activities as appropriate

The HRPP Director will review the results of IRB compliance reviews with the IRB, including IRB Chair(s), and the Institutional Official at least annually. If substantive deficiencies are identified at any time, a corrective action plan will be developed by the HRPP Director and approved by the IO. The HRPP Director 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 HRPP Director and IO in consultation with designated individuals 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

- 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 HRPP Director will meet regularly throughout the year with the 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, IO, and other designated individuals 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 HRPP Director will report those issues or trends to the appropriate parties (e.g., the IO, the IRB Chair, Compliance) and, if appropriate, a proposed CAPA plan.

In addition to the above, the HRPP Director is responsible for tracking internal data and metrics that are informative when considering HRPP and IRB efficiency, effectiveness, workload, and resources. Tracking of specific metrics may be delegated by the HRPP Director, as appropriate. Metrics reports will be provided to the Director and other appropriate parties throughout the year.

3 Education & Training

3.1 IRB Chairs, Members, and Staff

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

In addition to CITI and HIPAA Privacy training, all new IRB members must complete an orientation regarding their roles and responsibilities in the review of research prior to their participating as a voting member of the IRB. Orientation is conducted by an IRB Chair, or designee, and may be scheduled individually or in groups, as necessary. Members may be provided with supplemental materials to support the learning/orientation objectives. IRB Chairs are also asked to complete the CITI IRB Chair Course.

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, Yale 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

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 HRPP Director or designee.

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

The Director 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 IRB members, alternates, and staff. Continuing failure to complete training may result in a member's service being discontinued or not renewed.

3.2 Investigators and Research Staff

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

All individuals affiliated with Yale must complete a Compliance Assessment through the Training Management System (TMS) on annual basis or when their engagement in human subjects research changes. The requirements for training will be assigned based on the responses on the assessment:

- Individuals engaged in human subjects research must have a valid Human Subject Protection Training, completed within the previous three years. Acceptable courses include CITI training and others that are listed on the HRPP website.
- Individuals engaged in conduct of social behavioral or biomedical clinical trials must have a valid Good Clinical Practice Training, completed within the previous 3 years (does not replace need for the Human Subject Training referenced above). Acceptable courses include CITI training and others that are listed on the HRPP website.
- Investigators from HIPAA covered entities must complete HIPAA training if the research includes collection or interacting with the protected health information (does not replace the need for Human Subjects Training or Good Clinical Practice training referenced above).

In addition, the IRB or Yale leadership can require supplemental training for the PI or research team members for certain types of studies. The supplemental training requirement will be communicated directly to the PI.

Investigators and Research Staff are responsible for complying with any additional training requirements that are applicable to their research (e.g., sponsor or funding agency requirements) and maintaining documentation of the training.

Continuing Education

Examples of continuing education offerings that would satisfy the continuing education requirement include:

- The Yale Human Subject Research Resource and Education Program, which is a seven module, web-based educational offering that outlines the ethical foundations underlying the responsible conduct of research. Learning objectives include critical points that must be considered by investigators when preparing a protocol, conducting research, and when completing or terminating a research study. The roles of the Institutional Review Board, government agencies, research sponsor, and other entities providing oversight of human research are also described.

- Large group educational sessions that are offered by the HRPP and YCCI on topics affecting protocol design, conduct and review. Education topics are determined by the IRB Chairs, Human Research Protection Program (HRPP) Director or designee, or as requested by researchers. Course offerings are available through the Yale training website, <http://www.yale.edu/training/>.
- The Collaborative Institutional Training Initiative (CITI), which was developed by bioethicists and other human research professionals, offers a large and diverse selection of human research educational modules.
- OHRP human research protection foundational training.

Initial training is considered current for a period of 3 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

In addition to the basic requirements described above, Yale will periodically provide training on topics relevant to human subject protections, regulations, policies and standards, and IRB 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 or Yale Center for Clinical Investigation.

Verification of Training

Compliance with training requirements is assessed at the time of initial submission for each investigator and research staff member listed in the electronic submission. The submission will not be forwarded to the IRB for review unless training has been completed. Principal Investigators are responsible for ensuring that research team members who are not listed in the electronic system maintain current training.

Training is also verified at the time of continuing review and with 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.

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 (See definitions in Section 1.9).

Consultation with the HRPP Office is encouraged. The HRPP Office provides investigators with a checklist and guidance that delineate research from other types of activities such as quality improvement (QI) projects or journalistic activities. Because the analysis can be complex, individuals with any questions regarding the applicability of the regulations to their activities can request a determination that an activity does or does not involve research. Such requests should be submitted in the IRB electronic system for a formal determination or by sending the proposal materials via email to the HRPP office for consultation. An IRB Analyst or other higher level HRPP staff will review the materials and issue an official determination letter when submissions are received via electronic system. The HRPP staff (IRB Analyst or above) will respond to an email consultation request with advice whether proposed activity constitutes human subject research necessitating IRB review. Yale New Haven Hospital provides support with reviews of QI activities proposed at the Yale New Haven Hospital.

Similarly, the responsibility for the initial determination of whether research involves “human subjects” rests with the investigator. The HRPP Office provides investigators with a worksheet to help determine whether an activity is Human Research and how it is regulated (DHHS vs. FDA). 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. It should be noted that this definition differs significantly from de-identified in accordance with HIPAA standards. FDA regulations do not incorporate the concept of “identifiability” in the evaluation of whether an activity is a clinical investigation (or research) subject to FDA regulations. For example, the use of de-identified human specimens to evaluate the safety or effectiveness of a diagnostic device is considered human subjects 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 in the IRB electronic system, or by sending the research proposal materials via email to the HRPP office for consultation. The HRPP will issue an official determination letter when submissions are received via electronic system. The HRPP staff will respond to an email consultation request with advice whether proposed activity constitutes human subject research necessitating IRB review.

Note: With the implementation of the revised Common 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 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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5 Exempt Determinations

All human subjects research under the purview of the Yale HRPP must be approved by Yale before it may begin. Determinations of exempt status must be made by an experienced IRB member, IRB and HRPP staff reviewer, or appropriately trained personnel delegated by the IRB to grant exemptions. Yale may also choose to accept an exempt determination made by an external IRB, the Yale HRPP will consider such requests 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 exempt 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](#). Investigators are expected to design exempt studies so that risks to participants are minimized and justified by the anticipated benefits of the research; where prospective participants are informed about the research and voluntarily agree to participate; participant privacy and confidentiality is protected commensurate with confidentiality risks including appropriate data security; and subject selection is equitable. To be eligible for exemption, the research must involve no more than minimal risk to subjects.

Ethical requirements also extend to incidental findings arising in the course of research. Researchers should be prepared to respond to any issues that arise in the course of exempt research to ensure the protection of research participants. For example, observational studies may encounter situations of imminent risk to participants, and tissue-based research may identify risk factors for disease. Researchers should consider the types of incidental findings which could arise in a given project, whether it would be possible to contact participants and then identify appropriate responses, if any. Exemption status also does not obviate other obligations of the investigator such as State-mandated reporting requirements for abuse, communicable disease or other applicable state reporting requirements.

The individual(s) making the determination of exemption will determine whether the research plan sufficiently protects human subjects from an ethical standpoint and may require additional protections for subjects in keeping with ethical principles.

5.1 Limitations on Exemptions

The following limitations on exemptions apply to research conducted or supported by HHS:

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For research subject to the pre-2018 requirements, including research subject to DOJ regulations:

Children: The exemption for research involving survey or interview procedures or observations of public behavior (#2) 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.

Prisoners: Exemptions do NOT apply. IRB review is required.

For research subject to the revised Common Rule (2018 requirements):

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 policy, research activities not regulated by the FDA (see Section 5.3 for FDA Exemptions) in which the only involvement of human subjects is determined to be in one or more of the following categories may be determined exempt:

For research subject to the pre-2018 Common Rule requirements, including research subject to DOJ regulations:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as
 - (i) research on regular and special education instructional strategies, or
 - (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
 - (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

- (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under category 2, if:
 - (i) the human subjects are elected or appointed public officials or candidates for public office; or
 - (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

NOTE: To be eligible for this exemption, all of the materials have to already be in existence at the time the research is proposed for an exempt determination.

5. Research and demonstration projects which are conducted by or subject to the approval of federal department or agency heads, and which are designed to study, evaluate, or otherwise examine:
 - (i) Public benefit or service programs;
 - (ii) Procedures for obtaining benefits or services under those programs;
 - (iii) Possible changes in or alternatives to those programs or procedures; or
 - (iv) Possible changes in methods or levels of payment for benefits or services under those programs.

The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).

The research demonstration project must be conducted pursuant to specific federal statutory authority, there must be no statutory requirements of IRB review, the research must not involve significant physical invasions or intrusions upon the privacy of subjects, and the exemption must be invoked only with authorization or concurrence by the federal funding agency.

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 FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

For research subject to the revised Common Rule (2018 requirements):

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.*
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 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.

Like most organizations, the Yale HRPP does not utilize exempt categories 7 & 8 for the storage, maintenance and secondary research use of identifiable data and/or biospecimens.

5.3 FDA Exemptions

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

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 16.10 for detailed discussion of this exemption.

2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [\[21 CFR 56.104\(d\)\]](#)

5.4 Procedures for Exemption Determination

To request an exempt determination, investigators must submit the following materials via the IRB electronic system:

1. A completed Exemption Request Form, indicating the applicable exemption category;
2. The study protocol (not required if Exemption Request Form is submitted);
3. Any study materials such as recruitment materials, information sheets, consent forms, assessments, questionnaires, or surveys;
4. Letter(s) of permission from any non-Yale sites; or, when applicable, documentation of IRB approval or exemption from the external site; and
5. Verification of current CITI training for all members of the research team.

If the research clearly qualifies for exemption, the assigned reviewer will issue an exemption determination letter to the investigator via the IRB electronic system. When a study qualifies

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for exempt status, the HRPP staff or the exempt reviewer may also choose to send the study to the convened board for review because, for example, the review could benefit from the variety of perspectives and expertise that convened board review brings. The reason for the referral to the convened board should be documented in the IRB electronic system or the IRB minutes. If the research does not clearly qualify for exemption, or if participants would benefit from continued IRB oversight, the reviewer may also refer the study for expedited review or to a meeting of the convened IRB for review. The reviewer also may request clarifications from the Principal Investigator via the IRB electronic system. The permissible exemption category is documented in the IRB electronic system by the assigned reviewer. 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.

Once a protocol is determined to be exempt, it is not reviewed again by the IRB unless certain changes are made to the protocol. Exempt determinations do not have a termination date. Minor modifications to the protocol, such as addition of Yale study personnel, minor changes to study materials, and slightly increasing study enrollment numbers, do not need to be submitted as formal Modifications in the IRB electronic system for exempt studies. Only major changes, which would impact the original exemption category, such as a change in Principal Investigator, addition of a vulnerable study population, or major change in research questions or study procedures, must be submitted to the IRB for review and approval via a Modification application in the IRB electronic system.

The exempt determination must not be assumed by the investigator without formal written determination from the IRB or qualified reviewer. No human subjects' research may commence until such written exemption determination is provided by the IRB/staff/qualified reviewer to the investigator. There is no continuing IRB review process for exempt research.

Investigators conducting research involving human participants (exempt or otherwise) are required to report Unanticipated Problems Involving Subjects or Others (UPIRSOs) and Adverse Events in accordance with Yale HRPP policy. See Sections 17 and 20 for more information.

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 5 calendar days). [45 CFR 46.108(a)(3)(iii)]

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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 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)]

Yale applies the Belmont Report to all research reviewed and approved by the Yale IRB, regardless of risk or review level. In addition to applying the Belmont Report to exempt research, the individual making the determination of exemption will determine whether to require additional protections for subjects, as deemed appropriate.

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6 IRB Reliance

When engaged in multi-site research, research involving external collaborators, or research that is otherwise under the jurisdiction of more than one IRB, Yale acknowledges that each organization is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. Yale may choose to review the research in its entirety, only those components of the research Yale is engaged in, rely on the review of another qualified IRB, or make other arrangements for avoiding duplication of effort. When Yale is the prime awardee on an HHS grant, it will ensure that at least one IRB reviews the research in its entirety.

When relying upon another IRB or when serving as the reviewing IRB for an outside organization or external investigator, a formal relationship must be established between Yale and the outside organization or investigator through an IRB Authorization Agreement, Unaffiliated Investigator Agreement, a Memorandum of Understanding, or other such written agreement. The written agreement must be executed before Yale HRPP 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, in policies and procedures, or other written materials. The reliance agreement or procedures should indicate which organization is responsible for obtaining any applicable approvals from DHHS when the research involves pregnant women, fetuses, and neonates; or children; or prisoners. Reliance agreements should also address which organization is responsible for ensuring continued IRB oversight of active studies until study closure or mutually agreed upon transfer of the studies to another IRB if the Reliance Agreement is terminated.

Yale HRPP staff utilize a worksheet to ensure that reliance agreements and any accompanying materials address all requirements and are consistent with Yale HRPP's standards. To support compliance, Yale HRPP will make every effort to ensure as much consistency as possible across reliance agreements.

Requests for Yale 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 following the process described on [the HRPP website](#). Requests to cede review to an external (non-Yale) IRB must be made via Yale HRPP electronic system.

Yale 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. In collaboration with the other

participating organizations, Yale will determine on a study-by-study basis whether the SMART IRB SOPs or alternative procedures will be utilized to implement the reliance.

6.1 Yale Serving as Reviewing IRB

Generally, Yale IRB does not serve as the IRB of record for an external organization unless Yale is also engaged in the research or has a master agreement in place with the external organization. Yale HRPP staff evaluate the following factors, and others as appropriate, when considering a request for the Yale IRB to serve as the IRB of record for a particular study or studies:

1. The terms of the external organization's FWA;
2. Prior experience with the organization and investigators;
3. The accreditation status of the external organization's HRPP;
4. The compliance history of the organization and investigators (e.g., outcomes of prior audits or inspections, corrective actions);
5. The research activities conducted by or at the external organization;
6. The willingness of the external organization to accept Yale's reliance terms and procedures;
7. The ability of the organizations 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 organization 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 Yale IRB with the proposed research, subject population, and applicable regulations;
 - d. The familiarity of the Yale IRB with the relevant local context considerations of the external organization; and/or
 - e. The willingness or ability of the external organization 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.

When the Yale IRB serves as the reviewing IRB for another organization, the requirements and procedures outlined throughout this manual apply unless an alternative procedure has 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. Management and documentation of scientific review, other ancillary reviews, and institutional permissions for research;

2. Training requirements and verification of qualifications and credentials for external investigators and staff;
3. For-cause and not-for-cause compliance reviews;
4. The disclosure and management of conflicts of interest. In all cases, any COIs and CMPs identified and developed by the relying organization will be communicated to the reviewing IRB. The reviewing IRB will determine the acceptability of the plan in accordance with their policies and procedures;
5. Review and management of matters such as site-specific consent language, HIPAA (e.g., authorizations, waivers, alterations), noncompliance, unanticipated problems, and federal reports;
6. Ensuring concordance between any applicable grant and the IRB application/protocol.
7. Procedures for and type of IRB review (e.g., expedited, convened) of additional sites after the research protocol is IRB-approved;
8. Procedures for submission and review of interim reports and continuing review materials; and/or
9. The communication of IRB determinations and other information to external investigators and organizations.

6.2 External IRB Review of Yale Research

All non-exempt human subject research (or exempt research for which limited IRB review takes place pursuant to 45 CFR 46.104(d)(2)(iii) or (d)(3)(i)(C)) that Yale is engaged in must be reviewed and approved by the Yale IRB or an external IRB that Yale has agreed to rely upon prior to the initiation of the research. See Section 1.8 for information regarding engagement.

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

- Advarra IRB and WIRB-Copernicus Group (WCG) IRB for studies authorized to use an external IRB
- NCI's Adult CIRB for NCI research involving adult subjects
- NCI's Pediatric CIRB for NCI research involving children

Research that falls within the above parameters must be registered with Yale prior to submission to the external IRB following the procedures outlined in Section 6.3. Post-approval requirements are summarized in Section 6.4.

Yale may also choose to enter into an agreement to rely upon other external IRBs, most commonly when required as a condition of a grant or contract. Investigators should submit reliance requests as early in the grant/contract process as possible by completing a submission in the HRPP electronic system and submitting it for review of compliance with institutional requirements and authorization to use the external IRB.

Yale HRPP staff evaluate 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 that will be conducted at or by Yale;
7. The risks and complexities of the proposed research;
8. The proposed reliance terms and procedures including the procedures for collaborative management of matters such as conflicts of interest, 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.

When reliance on a non-accredited IRB is proposed, the evaluation may also take into consideration one or more of the following based upon the risks of the research, the research activities that Yale will be involved in, and Yale's familiarity with the IRB:

1. When the research is minimal risk (or the activities that Yale is involved with are minimal risk), a statement of assurance from the proposed IRB that its review will be consistent with applicable ethical and regulatory standards, and that it will report any regulatory investigations, citations, or actions taken regarding the reviewing IRB, and, when applicable, to the organization's FWA;
2. An attestation about, or summary of, any quality assessment of the reviewing IRB such as evaluation by an external consultant or internal evaluation of compliance using the FDA's self-evaluation checklist or AAHRPP's self-evaluation instrument;
3. The willingness of the external IRB to accommodate requests for relevant minutes and other records of the proposed study and/or to copy Yale's HRPP office on correspondence such as determination letters and notices of suspensions or terminations of IRB approval;
4. The willingness of the external IRB to accommodate a request for someone from the relying organization to serve as a consultant to the IRB or to observe the review of the proposed study; and/or
5. An assessment of the external IRB's policies and procedures.

The external IRBs that serve as the IRB of record for Yale research have the same authority as the Yale IRB and all determinations and requirements of the external IRBs are equally binding.

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Investigators must be familiar with and comply with the external IRB's policies and procedures and any additional requirements or procedures outlined in the IRB reliance agreement or companion materials (e.g., reliance SOPs). Yale will support compliance with the terms of reliance agreements by providing investigators with information relevant to their responsibilities, such as a copy or summary of the agreement, an information sheet, or reliance SOPs.

Regardless of which IRB is designated to review a research project, Yale is responsible for the conduct of the research in which it engages. Research reviewed by external IRBs remains subject to review, approval, and oversight by Yale and must adhere to all applicable policies, procedures, and requirements, including those of the Yale HRPP.

6.3 Registration of Studies Reviewed by External IRBs

Investigators must register studies that will be reviewed by an external IRB by submitting basic information about the research to the HRPP office. When submitting a request for approval to use an external IRB, the PI or designee must submit the following to the Yale HRPP office via the HRPP electronic system:

1. Request to Use External IRB form;
2. All required study-related documents (e.g., protocol, consent forms, investigator's brochure, recruitment materials, etc.)

The HRPP office will review the information and verify that CITI training, COI review, and any other applicable approvals or requirements have been completed and will determine the need for relaying local context information to the reviewing IRB in accordance with the reliance agreement. When applicable, and when the external IRB is not responsible for reviews of requests for waivers or alterations of HIPAA authorization (e.g., studies reviewed by the NCI CIRB), the HRPP staff will forward requests for waiver or alteration of HIPAA authorization and any relevant materials to the internal IRB Chair or a designated expedited reviewer for review. The HRPP staff will notify the investigators once the proposed research has been cleared for submission to the external IRB via an electronic system notification about the HRPP Authorization Letter. Once approved by the external IRB, investigators must submit a copy of the approval notice to the HRPP office via the electronic system.

6.4 Post-Approval Requirements

Instances of reportable information must be submitted directly to the designated external IRB in accordance with the external IRB's reporting requirements. The Yale HRPP will be notified by the external IRB regarding its determinations. Investigators must promptly report to the Yale HRPP any determinations of serious or continuing noncompliance or unanticipated problems that the external IRB made for the Yale site, and any notifications of suspension or termination of the study from the external IRB (See Sections 17, 18, & 19 of this manual).

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Changes in PI and, when applicable, the addition of other research team members must be submitted to the HRPP office via the electronic system prior to the new PI or research team member assuming any study responsibilities. The HRPP office must verify CITI training, COI review, and any other applicable requirements.

Any of the following issues must be reported immediately (asap once aware) to the Yale HRPP office by phone or email:

- Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated (classification as “OAI” is typically made after the FDA has the opportunity to review any responses to a 483), FDA Restrictions Placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections;
- Any litigation, arbitration, or settlements initiated related to human research protections; and/or
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding Yale’s HRPP.

See Section 22 for more information.

Investigators are reminded that other Yale reporting requirements, such as to Compliance, Privacy, and applicable ancillary committees remain applicable in addition to HRPP reporting requirements.

6.5 NIH Single IRB (sIRB) for Multi-Site Research

In June 2016, the National Institutes of Health (NIH) released a final policy requiring domestic awardees and domestic sites of NIH-funded multi-site research to use a [single IRB](#) (sIRB) for review of non-exempt human subject research unless an exception is granted. This policy is intended to streamline the IRB review process and reduce inefficiencies and redundancies while maintaining and enhancing subject protections. The NIH policy does not apply to career development, research training, or fellowship awards,) nor does it apply to research sites outside of the U.S. However, sIRB may still be required for domestic sites under the [Cooperative Research](#) provisions of the revised Common Rule.

Exceptions to the policy are rare. Information regarding exception requests is available on NIH’s [Single IRB](#) website.

6.6 Selection and Designation of a sIRB

Yale’s investigators submitting applications for NIH-funded multi-site research must plan for use of an sIRB plan at the time of the funding proposal (grant application or contract proposal), and, if applicable, may request direct cost funding to cover additional costs related to the

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requirements of the NIH policy. The sIRB can be the IRB at one of the participating sites or an independent, fee-based IRB. When the sIRB is named in the proposal or JIT time, the IRB must have agreed to take on this responsibility in advance. Requests for the Yale IRB to serve as the sIRB should be directed to the HRPP office. The HRPP Director will consult with others within the organization as needed and make a recommendation to the IO or designee for consideration. Requests for Yale to rely upon an external IRB as the sIRB should be submitted as early in the process as possible by submitting a reliance request following the instructions posted on [Yale HRPP website](#).

6.7 Reliance Agreements for sIRB Studies

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

Reliance Agreements should describe 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. Reliance Agreements should also address which organization is responsible for ensuring continued IRB oversight of active studies until study closure or mutually agreed upon transfer of the studies to another IRB if the Reliance Agreement is terminated. When IRB certification requirements apply (e.g., for NIH Genomic Data Sharing), the agreement or written procedures should indicate who is responsible for meeting the certification requirements. Similarly, the Reliance Agreement or written procedures should indicate which organization is responsible for obtaining any applicable approvals from DHHS when the research involves pregnant women, fetuses, and neonates; or children; or prisoners.

The institution that is awarded the funding for the research or the sIRB 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.

7 Research Previously Approved by Another IRB

When an investigator transfers human subjects research to Yale that was previously approved by another IRB, the investigator must:

- Submit the research to the Yale HRPP for IRB review or determination of exemption; or
- Submit a request for Yale to rely upon the existing IRB of record (such requests must be approved by both organizations)

Research determined to be exempt at the previous institution will be reviewed according to the procedures in Section 5. All other research must be submitted as if it were undergoing initial review and the remaining research activities will be reviewed using the appropriate review procedures, expedited or convened. Research activities under the auspices of the Yale HRPP cannot commence until all necessary approvals are in place including approval by the internal IRB or an IRB reliance agreement is executed (and the transferred activities are approved by the IRB of record).

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

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8 HRPP Business Continuity

In the event of an emergency or disaster (e.g., public health or weather-related), the policies and procedures in this manual may be modified as appropriate for the situation. Such modifications may include alternative meeting procedures, alternative procedures for the submission and review of modifications, alternative procedures for prompt reporting, and any other changes necessary to ensure appropriate ongoing oversight and conduct of research. Because procedural modifications may vary based on the nature of the event, these cannot be anticipated and described in this manual. Instead, such procedural modifications will be recorded in an addendum to the manual, note-to-file, or other appropriate means of documentation and communicated to the research community. This documentation will be maintained in accordance with applicable record retention requirements.

Yale’s HRPP Business Continuity Plan (BCP) is available in Part II of this manual. As noted in this document, the HRPP BCP addresses the necessary actions required to continue to conduct essential functions of research involving human subjects and to resume normal operations as quickly and efficiently as possible after an emergency or disaster.

9 Yale Institutional Review Board

Yale has established multiple Institutional Review Boards (IRBs) to ensure the protection of human subjects in research it engages in.

Although Yale has authorized a number of IRB panels to fulfill the review and oversight function of the Yale IRB, all panels follow the same policies and procedures. Therefore, for the purposes of this manual, all IRB panels of the Yale IRB will be referred to as the IRB. Likewise, the terms IRB Chair and Vice-Chair refer to all Chairs and Vice-Chairs.

Research initially reviewed by any of the Yale IRB panels can be subsequently reviewed by any other Yale IRB panel.

9.1 IRB Authority

Under U.S. federal regulations and Yale Policy, the Yale IRB has 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 of the revised Common Rule for which limited IRB review is a condition of exemption (under 45 CFR 46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7), and (8));
2. To require that informed consent is obtained and documented in accordance with regulatory and policy requirements unless the IRB determines that the criteria for the waiver or alteration of such requirements have been satisfied and approves the waiver or alteration. 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. **For research subject to the revised Common Rule (2018 requirements):** 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, except as described in Section 11.5;

When research is subject to other regulations (e.g., pre-2018 Common Rule, FDA, DOJ) or requirements (e.g., grant or contract terms) that require continuing review, 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, this authority extends to exempt research;
5. To observe, or have a third party observe, the consent process;

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6. To observe, or have a third party observe, the conduct of the research; and
7. In consultation with the HRPP Director and IO, determine whether data or specimens gathered without IRB approval or in association with serious or continuing noncompliance may be published or used for research purposes.
8. To oversee the conduct of human subjects research that qualifies for exempt status and to take action as needed to ensure the protection of human subject and the integrity of the research.

No research involving human subjects may be conducted without IRB approval or determination of exemption and no research may commence until all required Institutional approvals (including IRB) are obtained. Other institutional bodies may review any human subjects research protocol and may have the right to disapprove or terminate approval of a research protocol that has been approved by the IRB of record. However, no one at the University may approve the implementation of human subjects research that has been disapproved or not yet been approved by the IRB, nor may anyone override an IRB suspension or termination of IRB approval.

9.2 Roles and Responsibilities

9.2.1 Chair of the IRB

The IO, in consultation with the HRPP Director, appoints a Chair and Vice Chair of the IRB to serve for renewable 1-year terms. Any change in appointment, including reappointment or removal, requires written notification.

The IRB Chair should be a highly respected individual, 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 Chair. 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 Chair is responsible for conducting IRB meetings and expedited reviews and may serve as signatory for correspondence generated by the IRB.

The IRB Chair is 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 Chair may designate other experienced IRB members to perform duties such as expedited reviews and other IRB functions. The IRB Chair provides feedback about IRB member performance to the HRPP Director.

The performance of the IRB Chair will be reviewed on an annual basis by the HRPP Director and designated staff members. As part of the annual review process, the IRB Chair may also be asked to complete a self-evaluation. The results of the annual review will be shared with the IO along with any related recommendations. Feedback will also be provided to the Chair. If the Chair is not acting in accordance with the IRB's mission, following policies and procedures, has an undue number of absences, or is not fulfilling the responsibilities of the Chair, they may be removed. The IO may also take other appropriate action (e.g., requiring additional training).

9.2.2 Vice Chair of the IRB

The Vice Chair serves as the Chair of the IRB in the absence of the Chair and has the same qualifications, authority, and duties as the Chair.

The performance of the IRB Vice Chair will be reviewed on an annual basis by the HRPP Director and designated staff members. As part of the annual review process, the Vice Chair may also be asked to complete a self-evaluation. The results of the annual review will be shared with the IO along with any related recommendations. Feedback will also be provided to the Vice Chair. If the Vice Chair is not acting in accordance with the IRB's mission, following policies and procedures, has an undue number of absences, or is not fulfilling the responsibilities of the Vice Chair, they may be removed. The IO may also take other appropriate action (e.g., requiring additional training).

9.2.3 IRB Members

The role of an IRB member involves careful review of research protocols with emphasis on human subject protections issues and in accordance with applicable regulations, policies and procedures, and ethical standards.

Member responsibilities include:

- 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 they have 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 designated HRPP staff and the IRB Chair. If

a member's availability changes and they are no longer able to regularly attend IRB meetings or will be absent for an extended period of time, they should inform the designated HRPP staff and IRB Chair, who will inform the IRB Manager. The Manager will assess the situation, including the availability of the alternate when applicable, and make recommendations to the HRPP Director and IRB 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 an annual basis by the HRPP Director, the IRB Chair, and may include other designated HRPP staff. As part of the annual review process, IRB members may also be asked to complete a self-evaluation. The results of the annual review will be shared with the IO along with any related recommendations. Feedback will also be provided to each IRB member. Members who are not acting in accordance with the IRB's mission, not following policies and procedures, have an undue number of absences, or are otherwise not fulfilling the responsibilities of membership, may be removed by the IO or his/her designee.

9.2.4 Alternate 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 regard 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 Chair to conduct expedited reviews.

9.2.5 Subcommittees of the IRB

The IRB Chair, in consultation with the HRPP Director or designated HRPP staff, 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 Chair. Any such subcommittee cannot approve research or issue determinations that require review by the convened IRB.

9.3 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 Yale 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.
- 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, pregnant women, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons) 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.

- As applicable, the IRB includes at least one nurse as a voting member (applicable to IRBs responsible for the review of nursing research initiated by a nurse from a Magnet Nursing facility).

At the discretion of the IO and HRPP Director, HRPP staff may be appointed as IRB members or alternates.

Individuals from the Yale Office of Sponsored Projects, Business Development Office, or Office of Cooperative Research 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 HRPP Director or designee review the membership and composition of the IRB to determine if it continues to meet regulatory and organizational requirements.

9.3.1 Appointment of Members to the IRB

When the need for a new IRB member or alternate is identified, the HRPP Director seeks out qualified candidates and informs the IO. Any member of the Yale community may recommend candidates for IRB membership. Recommendations may also be made by persons external to Yale (e.g., an unaffiliated IRB member). Once a qualified candidate has been identified, the HRPP Director will elevate the appointment recommendation to the IO.

Appointments are made for an annual term. Any change in appointment, including reappointment or removal before the end of a member's term, requires written notification. Members may resign by verbal or written notification to the HRPP Director, IRB Chair, and/or other designated HRPP staff.

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

9.4 Liability Coverage for IRB Members

Yale insurance coverage applies to employees and any other person authorized to act on behalf of Yale for acts or omissions within the scope of their employment or authorized activity.

9.5 Use of Consultants

When necessary, the IRB Chair or the HRPP Director or designee 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 IRB Office will ensure that all relevant materials are provided to the consulting reviewer prior to the convened meeting or expedited review.

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The HRPP Director 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.

9.6 Reporting and Investigation of Allegations of Undue Influence

The IRB functions independently. Attempts to coerce or otherwise unduly influence the actions of the IRB are forbidden by policy. 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.

If an IRB Chair, member, or staff person feels that the IRB has been unduly influenced by any party, they shall make a confidential report to the HRPP Director, IO, or can make a confidential or anonymous report using the Yale University Hotline, either [online](#) or by calling the toll-free number (at 877-360-YALE). 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 the Vice Provost for Research or another designee within the Office of the Provost for investigation and any necessary action.

The reports made to Hotline (either online or telephone) are received and managed by an independent, third-party reporting service provider and not by University employees.

10 IRB Actions, Failure to Respond, Appeals

10.1 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 under the 2018 requirements. An action of disapproval can only be taken at a convened IRB meeting.

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.

Modifications Required for Approval (*also known as approved with conditions or conditional approval*). The research, proposed modification to the previously approved research, or other item is approved but modifications must be made and/or information verified before the approval becomes effective.

The IRB may approve research as modifications required if, given scope and nature of the modifications, the IRB is able to, based on the assumption that the requirements will be satisfied, make all of the determinations required for approval (i.e., approval criteria and any applicable special determinations). Any time the IRB cannot make one or more of the determinations required for approval, the IRB may not approve the study as modifications required.

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 as modifications required, the requirements will be documented in the IRB minutes for research reviewed at a convened meeting or in the IRB electronic system for research reviewed under an expedited review procedure.

When the convened IRB approves research with modifications required, the IRB may designate the IRB Chair, an IRB member, or other qualified individuals (e.g., HRPP staff) 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

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approves research with conditions, the original expedited reviewer (and/or other qualified individual(s)) will receive the response materials.

After verification, the following will be documented in IRB records and written communication to the investigator:

1. The date when the IRB determined that the criteria for approval were satisfied (i.e., the "approval date")
2. The date when verification was made that all IRB conditions have been satisfied (i.e., the "effective date"), and
3. For initial approval and continuing reviews, the date by which continuing review must occur (i.e., the "expiration date")

Partial Approval or Approval with Limitations or Restrictions. This action may be taken when the IRB only approves some but not all components of the research while other components of the research that require modification or clarification cannot begin or continue until approved by the IRB. For example, the IRB could determine that a study may begin but that children cannot be enrolled until the investigator submits, and the IRB approves, a plan for assent; the IRB could stipulate that the approval for the local site only includes adult subjects; the IRB could approve one phase of the research but require that a modification is submitted before future phases begin; or the IRB could limit the research responsibilities of an investigator due to a COI.

Defer. This action is taken by the IRB when modifications are required of the nature or amount that the IRB cannot 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 deferral is documented in the IRB minutes and is communicated to the investigator in writing.

When the convened IRB defers approval, the responsive materials from the investigator will be provided to the convened IRB for review at a subsequent meeting. When an expedited reviewer is unable to take an action of approved or modifications required (e.g., because of significant issues with the protocol that cannot easily be remedied), the review will be referred for full committee 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).

Suspend. Suspension of IRB approval is a directive of the convened IRB, IRB Chair, or IRB Vice Chair to temporarily stop some or all previously approved research activities. The IRB Chair/Vice 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. See Section 12 for more information.

Terminate. 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. See Section 12 for more information.

118 Determination (*also known as Approval in Principle*). Per HHS regulations at [45 CFR 46.118](#), there are circumstances in which a sponsoring department or agency may require certification of IRB approval as a condition of submitting for or releasing funds but before definitive plans for the involvement of human subjects have been developed (e.g., grants in which the procedures involving human subjects are dependent on preliminary activities such as the completion of animal studies or development of instruments). In these circumstances, the IRB may grant “approval in principle” without having reviewed the as yet undeveloped procedures or materials. The IRB Chair or designee will review the available information (i.e., the grant or proposal and any supplemental information provided by the investigator) and, if appropriate, will provide certification of IRB approval in principle. Any approvals in principle will note that IRB approval must be obtained before any activities involving human subjects may commence.

Additional Actions. In addition to the above actions, the IRB may **acknowledge** reports and other items that do not 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 Yale IRB before human research activities involving the collaborating organization or personnel may commence.

10.2 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 request(s) in a timely manner may lead to the protocol being withdrawn (if never initially opened) or administratively closed by the IRB. Investigators will be contacted by the IRB prior to withdrawal or administrative closure, reminding them of the outstanding request by the IRB.

10.3 Reporting IRB Actions

All IRB actions are communicated to the investigator, and/or designated contact person for the research study, via the publication of a letter in the IRB electronic system within ten (10) working days, whenever possible, of the review. When applicable, a stamped copy of the

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approved consent form, parental permission form, and/or assent form will also be published. For IRB actions of modifications required for approval or deferral, 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 by providing the HRPP Director and IO with access to IRB minutes and the report of expedited reviews in the IRB electronic system. The Director also ensures that the IO and other appropriate parties are informed of important, relevant information (e.g., a determination of serious noncompliance) in a timely manner.

10.4 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. 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/or other supportive materials via the IRB electronic system. 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.

The IRB may also independently decide to reconsider its decisions at any time (e.g., when additional information becomes available).

11 IRB Review Process

Prior to IRB review, the HRPP Review team will confirm compliance with institutional requirements related to human subjects research. The Yale 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:

- Exempt Review (see Section 5)
- Expedited Review
- Review by Convened IRB

11.1 Expedited Review

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

- **For research subject to the revised Common Rule (2018 requirements):**
 - When the research activities involve only procedures appearing on the [federal register list](#) of categories of research eligible for expedited review **and** confirmed by the reviewer(s) to involve no more than minimal risk. If the reviewer determines that the research involves more than minimal risk, the reviewer must document the rationale for the more than minimal risk determination and the research must be reviewed by the convened IRB.
 - Research for which limited IRB review is a condition of exemption under 45 CFR 46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8).
- **For research subject to the pre-2018 Common Rule, or FDA or DOJ regulations or other requirement that requires reviewer determination of minimal risk:**
 - When the research activities involve only procedures appearing on the [federal register list](#) (or when applicable, the [FDA list](#)) of categories of research eligible for expedited review **and** 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

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.

11.1.1 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:

- The acceptability of the risk-to-benefit analysis (i.e., the change does not increase the level of risk);
- The research design or methods (adding procedures that are not eligible for expedited review (See Section 11.1) would be considered more than a minor change);
- Any other factor which would warrant review of the proposed changes by the convened IRB.

Minor changes also include the addition of sites to a protocol approved by the convened IRB so long as the investigator(s)/site(s) do not have a conflict of interest, potential compliance concerns (e.g., a 483 that has not been adequately resolved), or any other investigator or site-specific concerns (e.g., qualifications, facilities, or resources to safely conduct the research).

In addition, if a study is transitioned from the pre-2018 Common Rule to comply with the 2018 requirements, the IRB may consider an investigator modification of the consent form to be consistent with the 2018 requirements to represent a minor change to the research. If such a determination is made, the IRB may use the expedited review procedure to evaluate the consent form changes, as permitted under §46.110(b)(1)(ii).

11.1.2 Categories of Research Eligible for Expedited Review

Yale applies the categories of research eligible for expedited review, which were published in the Federal Register on November 9, 1998 (Common Rule: notice [63 FR 60364-60367](#); FDA: notice [63 FR 60353](#)).

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, nonpregnant 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 nondisfiguring 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 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. 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. 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 under the oversight of the Yale IRB 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 *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 sites under the oversight of the Yale IRB 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 sites under the oversight of the Yale IRB 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.)

11.1.3 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 experienced members and alternate members of the IRB. Designated reviewers must be professionally competent (i.e., experienced with and having demonstrated the ability to apply IRB review requirements and with appropriate scientific or scholarly expertise) to conduct expedited reviews.

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 applicable worksheets to guide the review and applicable checklists to document the IRB findings. When a reviewer determines that research subject to the revised Common Rule (the 2018 requirements) falls within the expedited categories but may involve more than minimal risk, the reviewer will document the rationale for that determination in the electronic system 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.

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 worksheets (e.g., Eligibility for Review Using the Expedited Procedure, Criteria for Approval) to assess the criteria for approval. Specific IRB findings (e.g., waiver of consent, waiver of documentation of consent, Subpart D determinations for research involving children) are documented via applicable checklists. For initial and continuing reviews, the documentation will include the category(ies) under which the research qualifies for expedited review in the IRB electronic system.

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

11.1.4 Informing the IRB

Members of the IRB will be apprised of all expedited review approvals, including limited IRB reviews conducted using expedited review procedures, by means of a report made available in the IRB electronic system. Any IRB member can request to review the materials for any study by contacting the IRB Office.

11.2 Convened IRB Meetings

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

11.2.1 IRB Meeting Schedule

The IRB meets on a regular basis throughout the year. 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 [Yale IRB website](#). Special meetings (referred to as “On Demand” meetings) may be called as needed by a Chair, IRB Manager, HRPP Director, or designated HRPP staff.

11.2.2 Preliminary Review

Prior to finalizing the agenda, the HRPP staff will perform a preliminary review of all submissions for determination of completeness and accuracy. Only complete submissions will be placed on the IRB agenda for review. The investigator will be informed via the IRB electronic system or 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.

The HRPP staff may use worksheets and checklists to guide their review of the agenda items prior to the meeting to identify any potential deferrable issues and applicable regulatory determinations. The HRPP staff performing a preliminary review, the IRB Manager, and the Chair will meet prior to the IRB meeting to discuss the agenda items. The discussion includes review of the required IRB findings, any identified issues, correspondences with the investigators and feedback from the reviewers.

11.2.3 Primary Reviewers

After it has been determined that a submission is complete, HRPP staff, 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 9.5). 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 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 worksheets

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

When it can be anticipated that the primary reviewer may be absent from the meeting, a new primary reviewer will be assigned if possible, providing that they have the necessary expertise and sufficient time to review the materials in advance of the meeting. 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.

11.2.4 Materials received by the IRB

All required materials need to be submitted to the IRB office prior to the published agenda closure deadlines for inclusion on the IRB agenda. On occasion, when a review is time-sensitive, the IRB 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 HRPP staff in consultation as needed with the IRB Chair or IRB Manager as needed. All IRB members receive the IRB agenda, prior meeting minutes, applicable business items, and research submission materials generally 5-7 business days before the scheduled meeting to allow sufficient time for review. A time-sensitive item may be added to the agenda less than 5-7 business days in advance if circumstances warrant and the HRPP staff have contacted the IRB members and verified that they will have sufficient time for review.

All IRB members have access in the IRB electronic system to all materials submitted for all studies on the agenda, which include the following, as applicable:

- The complete protocol
- The application or submission form (e.g., initial, continuing review, modification request, interim report)
- The proposed and/or previously approved Consent/Parental Permission/Assent Form(s)
- 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 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 IRB office or the investigator. Any additional information should be provided to the other members.

Primary reviewers have access to applicable reviewer worksheets, which serve as a guide for the review and a tool for summarizing recommendations prior to board discussion.

11.2.5 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 initial review or when there is significant new information that may affect the risk profile, a physician or pharmacist 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, HRPP staff will document the departure and notify the IRB Chair if a quorum is not present. An annotated agenda is used as by the HRPP staff and/or IRB Chair to monitor quorum and to temporarily document attendance and quorum until the minutes are prepared and finalized. For meetings held by videoconference, attendees will visually or audibly confirm their presence in order to count toward quorum. Recused members are placed in the virtual waiting room by the HRPP staff and brought back into the meeting once discussion and vote are taken on the agenda item. Members inform the IRB Chair if they must leave the meeting at any time prior to its end, and quorum is re-evaluated by the IRB Chair to ensure continuation of the meeting or adjournment if quorum is lost.

In addition to the required attendance of at least one “non-scientist” member, it is generally expected that at least one scientific member, one unaffiliated member, and one member who represents the general perspective of participants (one individual can serve in more than one capacity) 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). For IRBs with responsibility for the review of nursing research from a Magnet Nursing facility, a nurse member or nurse alternate member should be present and in voting status at the majority of IRB meetings.

When the IRB regularly reviews research that involves subjects vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, 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.

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.

11.2.6 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 Chair reviews and approves the minutes. Minutes are then posted to the applicable IRB meeting space. IRB members are instructed to review the minutes from the prior meeting and inform the IRB Chair if there are any revisions to be made. If there are no changes to be made, the minutes will be accepted as presented and considered final. If revisions are necessary, the minutes will be amended and re-reviewed and approved by the IRB Chair.

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). The Primary 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 worksheets as a guide, when applicable. 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.

11.2.7 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.

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 IRB Manager. 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.

11.3 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 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. **For research subject to the pre-2018 Common Rule, or FDA or DOJ regulations:** 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 vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
For research subject to the revised Common Rule (2018 requirements): 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, individuals with impaired decision-making capacity, 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, pregnant women, mentally disabled persons, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

11.3.1 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;
3. **Identify the anticipated benefits** to be derived from the research, both direct benefits to subjects and possible benefits to society, science and others;
4. **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. The IRB considers blood limits for adults and children in the assessment of risk. See “Reference Guide: Blood Limit Guidelines for Adults and Pediatric Research” for additional guidance.

11.3.1.1 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, an ancillary review committee, departmental review, or review by consultants or ad hoc reviewers, as requested by the IRB. When scientific or scholarly review is conducted by an individual or entity external to the IRB, documentation of the outcome of that review should be provided to the IRB for review and consideration.

11.3.2 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 vulnerable populations or subjects vulnerable to coercion or undue influence such as children, prisoners, pregnant women, mentally disabled persons, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons;
- The scientific and ethical justification for excluding classes of persons who might benefit from the research; and

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- The inclusion/exclusion criteria, and the procedures/materials intended for use for the identification and recruitment of potential subjects.

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

11.3.2.1 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 11.4 for a discussion of IRB review of advertisements and for a discussion of IRB review of payments. See PART II of this manual for detailed information regarding acceptable recruitment practices at Yale.

11.3.3 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 14 for a detailed discussion on informed consent.

11.3.4 Data and Safety Monitoring

For research that is more than minimal risk, the investigator submit a data and safety monitoring (DSM) plan. A DSM plan may also be required for certain minimal risk research. The plan 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 DSM plan and may require establishment of a DSMB, DMC, or other methods to enhance the monitoring and management of participant 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.

11.3.5 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**.

11.3.5.1 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.

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.

11.3.5.2 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”

11.3.5.3 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, 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. In some cases, the IRB may also require that a Certificate of Confidentiality is obtained to protect data from compelled disclosure (See Section 35).

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](#). The investigator is responsible for ensuring that systems used for processing or storage of research data meet Yale's Minimum Security Standards as required by [Yale Information Security policies](#).

11.3.6 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 15.

11.4 Additional Considerations

11.4.1 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 in the electronic system record.

11.4.2 Period of Approval

At the time of initial review and at continuing review, the IRB will make a determination regarding the period of approval.

For research subject to the pre-2018 Common Rule, or FDA or DOJ regulations: The IRB will conduct continuing review of research at intervals appropriate to the degree of risk but not less than once per year.

For research subject to the revised Common Rule (2018 requirements): The IRB will 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, except as described in Section 11.5.

In some circumstances, a review interval shorter than one-year (e.g., semi-annually, quarterly, or after accrual of a specific number of participants) may be required (see below). The electronic system record, including meeting minutes for convened board, will reflect the IRB's determination regarding the period of approval.

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 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 "Modifications Required to Secure Approval". When continuing review is required, the expiration date of the initial approval period, which is the date by which the first continuing review must occur, may be as late as one year after the effective date of initial IRB approval.

The use of the effective date of IRB approval to determine the latest permissible date for continuing review *only applies to the first continuing review*. For all subsequent continuing reviews of a research study, the date the convened IRB or the date that the expedited reviewer conducts continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review (when continuing review is required).

The approval date and approval expiration date, when applicable, 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 IRB electronic system sends reminders to the investigator prior to the study's expiration date, notifying them that the study is due for a continuing review or when approval has expired.

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.

11.4.3 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;

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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);
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 that is subject to continuing review, the reason for more frequent review must be documented in the minutes or the electronic system record.

11.4.4 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 have occurred since previous IRB review.

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 or may require such verification at the time of any other review (e.g., continuation, modifications, interim reports) or when a complaint, concern, or allegation is received.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken (see Section 18 on Noncompliance).

11.4.5 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 the consent process may not be/is not being conducted appropriately (e.g., prior investigator noncompliance, etc.).

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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 HRPP Director, or designee from the HRPP Regulatory, Compliance, and Quality group, 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.

11.4.6 Investigator Qualifications

The IRB relies upon Yale departmental processes (e.g., credentialing) to determine whether investigators and members of the research team are appropriately qualified to conduct the research. The IRB may review credentials, curriculum vitae, resumes, or other relevant materials to inform this determination.

11.4.7 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).

11.4.8 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 Chair or convened IRB will make a final determination as to whether any COI is adequately addressed by management or disclosure, protects the human subjects in the research, and allows the research to be approved. Likewise, when there is an institutional COI, the IRB Chair or convened IRB 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).

11.4.9 Advertisements and Recruitment Materials

The IRB must review and approve all advertisements and recruitment materials prior to posting, use, or distribution. See Part II of this manual for additional information. 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 on potential subjects 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;
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://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.

11.4.10 Payments to Research Subjects

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 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. The IRB may ask for 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.

Yale 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). Please see [3417 PR.01 Human Research Study Participant Remuneration](#) for additional information. 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.

11.4.10.1 Lotteries and Raffles

If subjects will be entered into a lottery as potential compensation for participation, the informed consent document must include a description of the lottery or raffle process, the odds of winning, and how winners will be notified.

11.4.11 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.

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 participation.

11.4.11.1 Psychology Subject Pool

Studies intending to recruit students in Introductory Psychology for course credit must conform to both IRB and Psychology Subject Pool requirements. Additional consent requirements are required by the IRB, including clearly indicating the ability to meet course requirements in other ways as agreed to between the IRB and the Psychology Subject Pool Coordinator. See <https://psychology.yale.edu/resources> for related information.

11.4.12 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 Yale Office of General Counsel for the interpretation and application of CT law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. Details on the most relevant state laws are described in section 29 of this manual.

11.5 Continuing Review

For research subject to the pre-2018 Common Rule, FDA or DOJ regulations, and any research where continuing review is required by applicable regulations, policy, or other requirements:

The IRB will conduct continuing review of research at intervals appropriate to the degree of risk but not less than once per year. The date by which continuing review must occur will be recorded in the IRB electronic system and on initial and continuing review approval letters. There are no exceptions to the requirement for continuing review in the pre-2018 Common Rule, or in FDA or DOJ regulations.

For research subject to the revised Common Rule (2018 requirements): The IRB will 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, except as described below. When applicable, the date by which continuing review must occur will be recorded in the IRB electronic system and on initial and continuing review approval letters.

Unless an IRB determines otherwise, continuing review of research subject to the 2018 Common Rule (the revised Common 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;
- 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.

Yale IRB may determine that continuing review is required for any research protocol that falls within the above criteria. 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. Recommended by Federal guidance (e.g., OHRP recommends that IRB's require continuing review of research that falls within expedited categories 8(b) and 9);
4. The research involves topics, procedures, or data that may be considered sensitive or controversial;
5. The research involves particularly vulnerable subjects or circumstances that increase subjects' vulnerability;

6. An investigator has minimal experience in research or the research type, topic, or procedures; and/or
7. An investigator has a history of noncompliance.

When the Yale 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.

When the Yale IRB determines that continuing review is not required, the IRB electronic system will send an automatic notification on the anniversary of the review reminding an investigator about the investigator's obligation to submit modifications to the IRB for review and approval and to close the study when the research no longer involves human subjects.

11.5.1 Continuing Review Process

As a courtesy to investigators, the IRB electronic system and office staff when necessary will send out multiple reminder notices 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 should submit the following for continuing review, as applicable to the research:

1. The Continuing Review Application (this serves as the progress report);
2. The current Investigator's Brochure, device manual, or other updated risk information (if not already on record);
3. The most recent report from the DSMB or DMC;
4. For sponsor-investigators, the most recent annual report or progress report to the FDA and/or funding agency;
5. Any proposed modifications to the research including any changes to materials;
6. Any new literature relevant to the potential risks or benefits of the research since the last IRB approval; and
7. Any previously un-submitted reports identified while completing the Continuing Review Application.

Currently approved documents and historical information is available to the IRB and IRB members in the electronic system. For studies initially approved in the IRB legacy system, the HRPP staff can access the historical information and provide it to the IRB reviewers per request. IRB office staff attend the convened meetings. 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.

11.5.2 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:

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

11.5.3 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 11.2.4 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 Reviewer is responsible for reviewing the complete materials submitted for continuing review and any relevant historical information such as modifications approved since the last IRB review. The Primary Reviewer can use a reviewer worksheet to facilitate the review and discussion at the meeting. At the meeting, the Primary Reviewer assists the Chair by providing a summary of the research, their evaluation of the research and continuing review materials, and recommendations.

11.5.4 Expedited Review

In conducting continuing review under expedited procedures, the IRB Chair or designated reviewer receive all of the previously noted materials. The reviewer will use the review worksheets 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.

For research subject to the pre-2018 Common Rule, or FDA or DOJ regulations:

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, except in the limited circumstances described by expedited review categories (8) and (9) (see Expedited Review Categories in Section 11.1). 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.

For research subject to the revised Common Rule (2018 requirements):

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
- 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 11.1).

When continuing review is not required (See Section 11.5) for research subject to the 2018 Common Rule and the IRB reviewer determines that continuing review is required, the reviewer shall document the rationale in the study record.

11.5.5 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 10.

If an IRB member conducting expedited review believes that continuation of the research should be disapproved, they will refer the continuing review to the convened board for review. If the IRB has significant concerns the IRB may vote to suspend or terminate the research (See Section 12 for a detailed discussion of suspensions and terminations).

If a research study receives Modifications Required to Secure 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

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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.

11.5.6 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 IRB electronic system and office staff sends a notification to the investigator noting the expiration of approval and instructions that all research activities must stop. If the investigator fails to respond to the notification and does not submit continuing review materials or a closure report within 30 days, the study will be administratively closed.

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.

11.5.6.1 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.

11.6 Modification of an Approved Protocol

Investigators may wish to modify or amend approved research. **Investigators must obtain IRB approval before making any changes, no matter how minor, in approved research** unless the change is necessary to eliminate an apparent 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.

11.6.1 Procedures

Investigators proposing to modify a study must submit a Modification Request and all supporting documents identified in the form via the IRB electronic system 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

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investigators/personnel may not assume any study responsibilities involving human subjects or their identifiable data until the IRB has approved their participation.

The HRPP 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.

11.6.2 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 also available to IRB members. The Primary Reviewer may use a review worksheet 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 Chair in leading the 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 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.

11.6.3 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.

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Expedited reviewer(s) may consult a reviewer worksheet 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 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.

11.6.4 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 10.

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 12 for a detailed discussion of suspensions and terminations).

11.6.5 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 "Modification Request" via IRB electronic system along with any new or revised materials, and documentation of sponsor approval, if applicable.

The only time a protocol 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.

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11.7 Closure of Research Studies

The completion or early termination of the study is a change in research activity and must 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 provide 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).

For multi-center research, the study may be closed once all research activities (as above) are complete at Yale 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 the Continuing Review application.

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.

12 Suspensions, Terminations, and Investigator Holds

12.1 Suspension/Termination

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 17 for a discussion of unanticipated problems and Section 18 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, Vice President for Research, Dean, Ancillary Committees, HRPP Director] has the authority to suspend or terminate the organization's approval for 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.

Suspension of IRB approval is a directive of the convened IRB, IRB Chair or Vice Chair, or designee to temporarily stop some or all previously approved research activities. The IRB Chair, Vice Chair, or designee 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. Temporary suspensions by the Chair, Vice Chair, or designee 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 items 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.

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 to the IRB in person (e.g., via videoconference) 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 21 for a 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 21 for a discussion of reporting requirements.

12.2 Investigator Hold

An investigator may request an investigator hold when the investigator wishes to temporarily or permanently stop some or all approved research activities. Such a hold is initiated by an investigator but must be immediately reported to the IRB when related to the safety, rights, or welfare of subjects or others so that the IRB can consider whether any additional actions are necessary to protect subjects. Investigator holds are not equivalent to IRB suspensions or terminations. Examples of situations in which a PI may decide to put his/her research study on a voluntary hold include the following: as a result of a review or monitoring of study data, upon recommendation from Data and Safety Monitoring Boards or Committees, prior to or during an investigation of an allegation of noncompliance, following adverse events or an unanticipated problem involving risks to subjects or others (UPIRSO).

Studies under an investigator hold remain subject to all IRB, University, and regulatory requirements, including the requirements for continuing review and for reporting issues or information as outlined in this manual.

12.2.1 Procedures

Investigators must submit a memo and any supporting materials via the IRB electronic system to inform the IRB of the hold within five (5) business days of placing the study on hold when the hold is related to safety, rights, or welfare. The memo and materials should include:

1. A statement that the investigator is voluntarily placing a study on hold;
 - a. The reason(s) for the hold;
 - b. A description of the research activities that will be stopped;

- c. Proposed actions to be taken to protect current participants; and
- d. Any actions that will be taken prior to IRB approval of proposed changes in order to eliminate apparent immediate risk of harm.

Upon receipt, HRPP staff notify the IRB Chair or designee and place the research on the next available agenda for review;

The IRB Chair or designee will follow the procedures for the review of reportable information, including assessing whether the issue or information represents an unanticipated problem involving risk to subjects or others and whether serious or continuing non-compliance occurred. When reporting to a regulatory agency is required, the procedures outlined in Section 21 of this manual will be implemented.

The IRB Chair or designee, in consultation with the investigator, determines whether any additional procedures need to be followed to protect the safety, rights, and welfare of current participants;

The IRB Chair or designee, in consultation with the investigator, determines whether and how currently enrolled subjects will be notified of the hold;

Prior to lifting the hold, the investigator must seek approval from the IRB so that the IRB may consider whether subjects are appropriately protected and if the research remains approvable.

12.3 Protection of Currently Enrolled Participants

Before a study hold, 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

13 Documentation and Records

Yale prepares and maintains adequate documentation of the Yale 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.

13.1 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 13.2);
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 2018 revised 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 [the Common Rule] (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;
11. Federal Wide Assurances;
12. Federal IRB Registrations; and
13. Documentation of complaints and any related findings and/or resolution.

13.2 IRB Protocol Files

The IRB maintains a separate file for each protocol (including expanded access), HUD, emergency use, or report it receives for review in the IRB electronic system under a unique identification number assigned by the system. Emergency use notifications/requests may be kept outside of the electronic system. 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;
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 under the revised Common Rule as described in Section 11.5;
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. IRB reviewer checklists;
9. Documentation of scientific or scholarly review (if available);
10. Documentation of the type of IRB review. For exempt determinations and expedited review, this will include the category or basis under which the review is allowed;
11. 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;
12. **For research subject to the pre-2018 Common Rule, or FDA or DOJ regulations:** For expedited review, documentation of the risk determination and period of approval. For research reviewed by the convened board these determinations are recorded in the minutes;

13. **For research subject to the revised Common Rule (2018 requirements):** 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. For research reviewed by the convened board the risk determination and period of approval, when applicable, are recorded in the minutes.
14. Documentation of all IRB review actions;
15. Notification of expiration of IRB approval to the investigator;
16. Notification of suspension or termination of research;
17. Letters to investigator informing them of IRB review outcomes;
18. IRB correspondence to and from investigators related to the protocol;
19. All other IRB correspondence related to the research;
20. For studies evaluating the safety or effectiveness of medical devices, documentation of the device determination (exempt, non-significant risk, significant risk);
21. Reports of unanticipated problems involving risk to subjects or others; and
22. Any statements of significant new findings provided to subjects.

13.3 The IRB Minutes

Draft minutes of IRB meeting proceedings are written and approved by the Chair. Approved minutes are generally available for review by members the next regularly scheduled IRB meeting. Once accepted by the members, a copy is available to the IO. Changes may not be made to finalized minutes without re-review by the IRB Chair 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 HRPP staff, investigators, and study coordinators

Note: The vote on each action will reflect the numbers of members present for the vote on that item. The minutes will indicate the names of members who count toward quorum but who were not present for the vote.

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. When both a member and an alternate are present, the minutes will reflect if and when the alternate substituted for the member. Generally, the member votes, but an alternate may substitute when appropriate (e.g., the member has a conflict of interest, the alternate has needed expertise, etc.);
4. Business Items discussed, and any education provided;
5. Actions taken, including separate deliberations, actions, and votes for each submission undergoing review by the convened IRB;
6. 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;
7. Basis or justification for actions disapproving or requiring changes in research;
8. Summary of controverted issues and their resolution;
9. 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;
10. **For research subject to the revised Common Rule (2018 requirements):** The rationale for requiring continuing review of research that otherwise would not require continuing review as described in Section 11.5;
11. Risk determination for initial reviews will be recorded in the minutes. For continuing reviews and modifications, the risk determination will be recorded when the risk level is altered;

12. Justification for deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document;
13. 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;
14. Study-specific findings supporting that that the research meets each of the required criteria when the requirements for documentation of consent are waived;
15. Study-specific findings supporting that the research meets each of the criteria for approval for vulnerable populations under any applicable Subparts;
16. Exempt/significant risk/non-significant risk device determinations and the basis for those determinations;
17. Determinations related to conflicts of interest and acceptance or modification of conflict management plans;
18. 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;
19. Review and determinations related to interim reports (e.g., unanticipated problems or safety reports, serious or continuing noncompliance, suspensions or terminations, etc.);
20. An indication that the list of research approved under expedited review procedures, including limited IRB reviews conducted using expedited procedures, since the time of the last such report was made available to the members;
21. 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
22. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.

While IRB reviewers may enter or upload notes or other supporting documentation (e.g., checklists, worksheets) into the IRB electronic system in advance of IRB meetings to help them prepare for discussion, the IRB minutes serve as the official record of the convened IRB's deliberations, determinations, and actions. There is no expectation that reviewer notes and meeting minutes match as notes reflect the informal thoughts of a single individual before hearing the commentary and viewpoints of other members. Any substantive disconnect between a reviewer's proposed findings or concerns and the final IRB findings that resulted in the discussion of controverted issues will be recorded in the IRB minutes.

13.4 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 Yale or Yale New Haven Health System.
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.
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 and experienced in working with children, pregnant women, adults with impaired decision-making capacity, and other vulnerable populations or other subjects vulnerable to coercion or undue influence commonly involved in Yale's research;
7. Role on the IRB (Chair, Vice-Chair, 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.

13.5 Documentation of Exemptions

Documentation of verified exemptions consists of the reviewer's citation of a specific exempt category in the electronic system and written concurrence that the activity described in the investigator's request satisfies the conditions of the exempt research as detailed in Section 5. When an exemption includes limited IRB review under the revised Common Rule (2018

requirements), 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 manual.

13.6 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.

13.7 Access to IRB Records

IRB protocol files are secured in the IRB electronic system with administrative access controlled by the IRB office. Likewise, investigators control access to investigator records in the electronic system. All other IRB records (e.g., membership rosters) are kept secure in a limited access file on Yale's servers.

Ordinarily, access to IRB records is limited to the IO, HRPP Director, HRPP staff, IRB members, authorized organizational officials with a legitimate business need to access records, 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 posted on the HRPP website and provided to regulatory agencies, accreditation bodies, and persons or offices outside of Yale with a legitimate need (e.g., Sponsor through a contractual agreement). A memorandum documenting compliance with pertinent federal rules and regulations, IRB membership requirements, and with Yale's Federalwide Assurance is available and will be provided to sponsors and others upon request.

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

13.8 Record Retention

In order to comply with the requirements of OHRP and FDA, IRB records for research not subject to HIPAA are maintained for at least three (3) years after completion of the research or the exemption determination. IRB records for research subject to HIPAA that include documentation required for and related to the disclosure of PHI for research (e.g., waiver of authorization for a study by the IRB/privacy board) are maintained for 6 years from the completion of research or the exemption determination.

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 six (6) years.

At any time, the Office of the General Counsel may instruct the HRPP to preserve IRB records for institutional purposes such as an investigation or another legal process. Such instructions supersede any retention period listed above, and documents subject to such instructions must be preserved until the Office of the General Counsel instructs otherwise. Otherwise, after the noted times, IRB records may be securely destroyed.

14 Obtaining Informed Consent from Research Subjects

The requirement to obtain the legally effective informed consent of individuals before involving them in research is one of the central protections provided for by the federal regulations and Yale's HRPP. Investigators are required to obtain legally effective informed consent from a subject or the subject's LAR unless the requirement has been waived by the IRB of record. When informed consent is required, it must be sought prospectively, and properly documented. Except as provided in Sections 14.10, 14.11, and 14.12 of these procedures, informed consent must be documented using a written consent form approved by the IRB.

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 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. 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. The process of 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. See Section 14.10 for an exclusion for certain screening and recruitment activities.

If someone other than the principal investigator obtains consent, the investigator needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. It is the PI's responsibility to ensure that consent delegates are knowledgeable about the research to be conducted and the consent process and have the expertise to be able to answer questions about the study including those regarding risks, procedures, and alternatives. The Yale IRB application solicits information regarding investigators who will obtain consent; proposed changes to the investigators authorized to obtain consent must be submitted to the Yale 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 following procedures describe the requirements for obtaining consent from subjects in research conducted under the auspices of Yale. When the Yale 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).

14.1 General Requirements

Except as provided elsewhere in this manual:

For research subject to the pre-2018 Common Rule, or FDA or DOJ regulations:

No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative 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.

For research subject to the revised Common Rule (2018 requirements):

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
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.

14.2 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 who are not fluent in English, informed consent must be obtained in a language that is understandable to the subject (or LAR/guardian). In accordance with this policy, the Yale 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. For studies involving Yale New Haven Hospital patients, interpreter services that may be used include the Yale New Haven Hospital Interpreter Service, hired interpreters approved by Yale New Haven Hospital Interpreter Services, or use of telephone interpretation services. Study personnel who are fluent in the language of the subject may conduct research conversations with the participant once they have been approved by Yale New Haven Hospital Interpreter Services. They do not serve as interpreters because they are not interpreting third party communication.
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.

14.3 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.”*

Who may serve as LAR is determined by state law. Connecticut law does not specifically address informed consent by LARs of incapacitated persons for participation in clinical research, except for protected persons who have court appointed guardians with the granted level of supervision dependent on the severity of the protected person's intellectual disability. A protected person is a person for whom a guardianship is granted by court (CT statute, Sec. 45a-669).

Connecticut state statutes ([Sec. 45a-677](#)) prohibits court appointed guardians to consent on behalf of the protected person to ‘the performance of any experimental biomedical or behavioral medical procedure or participation in any biomedical or behavioral experiment, unless it (A) is intended to preserve the life or prevent serious impairment of the physical health of the protected person, (B) is intended to assist the protected person to regain the protected person's abilities and has been approved for the protected person by the court, or (C) has been (i) approved by a recognized institutional review board, as defined by 45 CFR 46, 21 CFR 50 and 21 CFR 56, as amended from time to time, which is not a part of the Department of Developmental Services, (ii) endorsed or supported by the Department of Developmental Services, and (iii) approved for the protected person by such protected person's primary care physician.’

For other incapacitated persons for whom there is no guardianship granted by court, the applicable guidelines for determining the most appropriate surrogate for research are based upon the guidelines that apply in the clinical setting.

Absent a participant-designated or state-specified legally authorized representative for research decision-making, investigators may engage and IRBs may approve as surrogates individuals who would normally provide consent for medical care under prevailing, commonly accepted clinical practices. Participant assent also must be obtained whenever possible.

When the Yale 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 sought (local context information) and applied.

LARs should be well informed regarding their roles and responsibilities when asked to provide surrogate 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 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.

Further discussion and procedures for assessment of capacity and inclusion of adults with impaired decision-making capacity in research are described in Section 15.7.

14.4 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**;
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 will 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. Contact information for the research team for questions, concerns, or complaints.
9. Contact information for someone independent of the research team for problems, concerns, questions, or input.
10. 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;

11. **For research subject to the revised Common Rule (2018 requirements):** 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.
 12. For **FDA-regulated studies**, a statement that notes the possibility that the Food and Drug Administration may inspect the records;
 13. 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."

NIH Policy requires a similar statement for clinical trials that fall within the scope of their registration & dissemination policy.
- 14.5 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;
 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;

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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. **For research subject to the revised Common Rule (2018 requirements):**
 - a. 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;
 - b. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions;
 - c. 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).

14.6 Yale Requirements

In addition to the federal elements of consent described above, Yale has defined specific additional information that must be included in consent documents when applicable to the research under Yale HRPP purview (e.g., language related to research procedures at Yale PET Center). A list of these requirements along with research situations with board preferred language is provided in a document titled ‘Consent Glossary - Glossary of preferred and required terms for consent forms’ posted in the IRB’s electronic system ([IRES IRB Library](#)) for investigator and reviewer reference.

14.7 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

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and may not be removed. The consent document cannot provide the participant the option of having the data 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 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. Investigators wishing to use third-party vendors to conduct the review of public records must ensure that the vendor is listed by name in the HIPAA Research Authorization signed by the participant and appropriate agreements e.g., Business Associate Agreement, are in place between Yale and the vendor.

14.8 Documentation of Informed Consent

Except as provided in Sections 14.10, 14.11 and 14.12 of this manual, 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. **For research subject to the pre-2018 Common Rule, or FDA or DOJ regulations:** A written consent document that embodies the basic and required additional elements of informed consent. The consent form may be read to the subject or the subject's LAR, but the subject or LAR must be given adequate opportunity to read it before it is signed;
For research subject to the revised Common Rule (2018 requirements): 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 LAR;
or
2. A short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's LAR (**For research subject to the revised Common Rule:** and that the key information required by Section 14.1 #5 was presented first to the subject, before other information, if any, was provided). When this method is used:
 - a. The oral presentation and the short form written document should be in a language understandable to the subject; and
 - b. There must be a witness to the oral presentation; and
 - c. The IRB must approve a written summary of what is to be said to the subject (the approved full consent document may serve as this summary); and
 - d. The short form document is signed by the subject;
 - e. The witness must sign both the short form and a copy of the summary; and
 - f. The person actually obtaining consent must sign a copy of the summary; and
 - g. A copy of the summary must be given to the subject or representative, in addition to a copy of the short form.

When the short form procedure is used with subjects who do not speak or read English, or who are not fluent, (i) the oral presentation and the short form written document should be in a

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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. An adult family member of the research participant can also serve as a witness if there is no reasonable concern that the proposed witness is not acting in the best interest of the participant. Neither the individual obtaining consent nor any member of the research team can serve in that role.

Unless already available in the IRB electronic system, 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 IRB. Short forms available in the IRB electronic system do not need to be submitted for IRB review and approval. In all cases, the possible inclusion of non-English speaking participants or participants who are not fluent in English in research and the use of a short form must be described in the protocol application and approved by the IRB.

For studies that invoke HIPAA, where a compound authorization is used, the short form includes language indicating that HIPAA requirements have been included in the oral presentation. The short form may also be used in concert with a HIPAA Research Authorization Form (RAF) and acknowledged by the IRB in its role as the Privacy Board. Translated HIPAA RAFs available on the [HIPAA Privacy Office website](#) do not need to be submitted for acknowledgment. In instances in which a translated RAF is not available, the HRPP staff will make a determination to waive the requirement for written authorization.

14.9 Special Consent Circumstances

Federal regulations and guidance recognize the need for flexibility in the consent process and documentation of consent, particularly to support equitable selection of subjects and access to research that may offer benefit. The following content is intended to help investigators navigate certain circumstances that may impact how consent is obtained and documented but is not exhaustive. Investigators are encouraged to contact the HRPP/IRB office with any questions they have about obtaining and documenting consent.

14.9.1 Consent Process Conducted Remotely

When the consent process cannot be conducted in person at the study site, an alternative method may be used as long as the method is approved by the IRB. Whether in-person or remote, consent may only be obtained when the prospective participant (or the representative) has sufficient opportunity to consider whether or not to participate in the study.

When it is not feasible to conduct the consent process in-person, the following process can be implemented:

- The IRB approved consent form can either be mailed, emailed, or faxed to the individual ahead of the discussion.
- A call (via phone or another audio and video conferencing software that meets HIPAA privacy requirements and is approved by Yale ITS for use with high-risk data) or a telehealth visit using MyChart app supported by EPIC will be scheduled between the investigator and the potential participant to review the consent discussions.
- All individuals on the call will be asked to identify themselves. The researcher must ensure that the participant has access to the consent form during the discussion. *

When an alternate consent process occurs, documentation of the process should be done as follows:

- The consent discussion must be documented in the study records (and medical record if appropriate) with the date when the consent process took place.
- If the participant agrees to participate, the participant signs and dates the consent document and returns the signed consent to the study team as a scanned document via email or fax, delivered in-person or via mail.
- See section [14.9.2](#) if utilizing e-consent.
- Once the research team receives the signed informed consent document from the participant, the investigator who conducted the consent process signs and dates the document using the current date. Under the signature line, the investigator documents that consent was obtained over the telephone or video conferencing, and includes the date of the discussions, and the date the signed consent was received. For example, "Discussed with [participant or LAR name] via [telephone or videoconferencing] on [insert date] and received signed consent form on [insert date]."
- The signed document is appended to the participant's research record (and medical record when applicable) and a copy must be provided to the participant.
- No research activities may occur until the proof of signed consent form is received by the investigator.

*If the participant cannot print the consent form provided electronically, a witness, who is not otherwise connected with the clinical investigation, must be present during the discussion. After the discussion, the participant must be asked for a verbal confirmation that their questions have been answered and that they would like to participate in the trial. They will be asked for a verbal confirmation that they signed and dated a blank piece of paper with a written statement that they voluntarily agree to participate in the protocol, noting both the Protocol 'NUMBER' and brief protocol title. After signing and dating that statement, the participant will send a photograph of the signed and dated statement by fax, text message, or email to the investigator; or will return the document to the investigator by mail at a later date, or in-person visit. The trial records will include a signed and dated attestation by the witness who participated on the call that the participant confirmed their agreement to participate in the trial and signed the document referenced above.

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14.9.2 Electronic Informed Consent (eIC)

The ethical obligation to obtain informed consent for participation in research is fundamental; however, U.S. regulations do not specify a particular method for the informed consent process. Recognizing the increased interest in using electronic informed consent (eIC) to replace or supplement the traditional paper-based process, OHRP and FDA issued [joint guidance](#) on the topic in 2016. Per the guidance, eIC refers to *“the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent.”* Investigators planning to use eIC should review the guidance in advance to ensure that the eIC process and platform meet OHRP and FDA (as applicable) expectations.

Investigators proposing to use eIC should submit copies of all forms and informational materials (e.g., video content, hyperlinked webpages) that the potential subject will review during the eIC process. If the eIC includes questions or other methods to gauge subject comprehension, these should also be provided. Investigators are responsible for periodically reviewing any linked to materials to ensure that the content remains available and is unchanged. Any changes to the eIC or any of the supplemental information must be submitted to the IRB for review and approval.

Whether the eIC process takes place in person or remotely, the responsibility for obtaining informed consent remains with the investigator and any appropriately delegated study team members. When the eIC process takes place remotely and is not witnessed by the investigator or study team members, the eIC generally should include a method to ensure that the person electronically signing the eIC is the subject or their LAR, when applicable. Exceptions to this general rule may be acceptable in certain circumstances (e.g., minimal risk research).

As with any other form of consent, the eIC process must allow for sufficient time for the potential subject to consider whether to participate and must include a mechanism for potential subjects to ask questions and have them answered. A copy of the eIC must be provided to participants, including copies of any supplemental materials. The copy provided to participants may be hardcopy or electronic.

Electronic signatures must be compliant with applicable legal requirements, including those of the jurisdiction where the research is to be conducted, and the FDA’s requirements, when applicable. Per University Procedure [1101 PR.06 Approval Authority](#), there is not a single approved electronic signature service for University-wide use. For non-FDA regulated research, investigator may propose use of existing services such as RedCap.

14.9.3 Enrollment of persons who are not fluent in the English language

- 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. The translated consent document or compound authorization document must be approved by the IRB before use with participants. 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 document 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 14.8. For FDA regulated research, FDA expects that an investigator promptly obtains and submits a translated copy of the IRB-approved long consent form to the IRB for review. Once approved by the IRB, the translated form is to be provided to the subjects as soon as possible. For other, non-FDA regulated studies, if more than two (2) study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

- 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-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

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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. People serving as interpreters for subjects in research studies at Yale New Haven Hospital (YNHH) must be approved by YNHH Interpreter Services. Information on available Language Services is posted on the websites for [Yale New Haven Health \(YNHH\)](#) and [YNHH, Smilow](#).

14.9.4 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) has the ability to understand the concepts of the study and evaluate the risks and benefits 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 14.11.

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 videotape.

14.9.5 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.

14.10 Waiver or Alteration of Informed Consent

General Waiver or Alteration:

For research subject to the pre-2018 Common Rule, or FDA or DOJ regulations:

An IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

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

For research subject to the revised Common Rule (2018 requirements):

An IRB may waive the requirement to obtain informed consent, provided the IRB finds and documents that the below criteria are satisfied. An IRB **may not** waive or alter broad consent under the revised Common Rule, nor may it waive consent for the storage, maintenance, or secondary research use of identifiable biospecimens if an individual was asked to provide broad consent and refused.

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. An IRB **may not** omit or alter any of the general requirements for informed consent (See Section 14.1).

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.

Public Benefit or Service Programs Waiver or Alterations

For research subject to the pre-2018 Common Rule or DOJ regulations:

(Note: this option is not available to research subject to FDA regulations)

In addition, an IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

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.

For research subject to the revised Common Rule (2018 requirements):

An IRB may waive the requirement to obtain informed consent, provided the IRB finds and documents that the below criteria are satisfied. An IRB **may not** waive or alter broad consent under the revised Common Rule, nor may it waive consent for the storage, maintenance, or secondary research use of identifiable biospecimens if an individual was asked to provide broad consent and refused.

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”) (See Sections 14.4 and 14.5), provided that the IRB finds and documents that the below criteria are satisfied. An IRB **may not** omit or alter any of the general requirements for informed consent (See Section 14.1).

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
- e. The research could not practicably be carried out without the waiver or alteration.

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14.10.1 Screening, recruiting, or determining eligibility

For research subject to the revised Common Rule: 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.

*(Note: The provisions described in this section do not apply to research subject to the **pre-2018 Common Rule** or to **DOJ-regulated research**. These provisions do not appear in FDA regulations, however, the FDA does not consider records review or oral communication with potential subjects prior to obtaining consent to be part of a clinical investigation, therefore waivers are not required. See [FDA Draft Guidance](#) for more information.)*

14.11 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 informed consent form and the principal 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) will 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

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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 research subject to the **pre-2018 Common Rule or to FDA or DOJ** regulations.

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.

14.12 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 14.12.2.1 and 14.12.2.2 below. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

14.12.1 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, a legally competent adult with one of the following relationships to the subject: spouse; parent; child (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.

14.12.2 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:
 - 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 with paragraph 7.e. of this section.
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 researchers 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.

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.

14.12.2.1 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 14.12.2 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 14.12.2 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\(b\)](#).

14.12.2.2 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](#)

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[50](#), and (ii) found and documented **and** reported to the OHRP that the conditions required Section 14.12.2 have been met relative to the research.

14.13 Consent for Future Use of Research Data/Biospecimens

Yale did not adopt the broad consent provisions and does not grant exemption determinations under categories 45 CFR 46.104 (d) (7) Storage or maintenance for secondary research for which broad consent is required or (8) Secondary research for which broad consent is required. Currently, such proposals will be evaluated against approval criteria, including any necessary waivers of consent. However, the Yale HRPP acknowledges that investigators may wish to include consent elements to allow for storage and future use of identifiable research data and/or biospecimens. Inclusion of consent language addressing the storage and possible secondary research use of data/biospecimens does not serve as actual informed consent for the future research but can be used in support of a request for a waiver of consent for the future research. Permission for future research should be presented as an opt-in within the consent form unless maintenance and future use of data/biospecimens is essential (e.g., for a research repository). This approach is consistent with HIPAA requirements (See Section 27.7) and NIH’s requirements for genomic data.

When investigators propose secondary research involving the use of identifiable private information and/or biospecimens and permission for future use was addressed in the original consent, the investigators should include documentation of the IRB approval for the storage or maintenance of the information or specimens and a copy of the consent form and/or other materials. The Yale IRB will review the information provided with the aid of a worksheet to ensure that all requirements are satisfied. The outcome of the IRB’s review will be communicated to the investigator in writing following the procedures described elsewhere in this manual.

14.14 Posting of Clinical Trial Consent Forms

For research subject to the revised Common Rule (2018 requirements):

*(Note: The provisions in this section **do not apply** to research subject to the **pre-2018 Common Rule** or to **FDA or DOJ regulations**.)*

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

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

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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.

At this time, two publicly available federal websites that will satisfy the consent form posting requirement have been identified: [ClinicalTrials.gov](https://clinicaltrials.gov) and a docket folder on Regulations.gov (Docket ID: [HHS-OPHS-2018-0021](https://www.regulations.gov/docket/HHS-OPHS-2018-0021)). Additional federal websites that would satisfy the revised Common Rule's clinical trial consent form posting requirement might be identified in the future.

[Yale Center for Analytical Sciences](#) provides guidance to Yale investigators regarding trial registration, reporting, and record updates requirements for clinical trials where Yale serves as the Responsible Party. Verification of compliance with these requirements, as applicable, is confirmed at the time of IRB initial and continuing review, and study closures.

15 Vulnerable Subjects in Research

When participants in research conducted under the auspices of Yale 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 applicable regulatory requirements for the protection of subjects are met and that appropriate additional protections for vulnerable subjects are in place.

15.1 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\(a\)](#)]. Emancipated minors are considered adults for the purpose of this policy.

According to Connecticut (CT) 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, Yale IRB defines children as persons who are under eighteen years of age. Because CT law does not specifically address consent of children with majority status to research, Yale 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 Connecticut, the research must comply with the laws regarding the legal age of consent in the relevant jurisdictions. Legal counsel may 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).

Emancipated Minor: A minor who is to be treated as an adult for purposes of this policy. An emancipation order allows a minor to consent to "medical, dental or psychiatric care, without parental consent, knowledge or liability." In Connecticut, minors aged sixteen or seventeen or their parents may petition the Superior Court for Juvenile Matters or the Probate Court for emancipation orders. Conn. Gen. Stat. §46b-150. The court may declare the minor emancipated if (1) the minor has entered into a valid marriage, whether or not that marriage has been terminated by dissolution, (2) the minor is on active duty with any of the armed forces of the United States of America, (3) the minor willingly lives separate and apart from his/her parents or guardian, with or without the consent of the parents or guardian, and that the minor is managing his/her own financial affairs, regardless of the source of any lawful income, or (4) the court determines "for good cause" that emancipation is in the "best interest" of the minor, any child of the minor, or the parents or guardian of the minor. Conn. Gen. Stat. §46b-150b. A minor may also be considered emancipated under common law under similar circumstances.

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 Connecticut, a guardian is judicially appointed parental rights for a child including (A) the obligation of care and control; and (B) the authority to make major decisions affecting the child's education and welfare, including, but not limited to, consent determinations regarding marriage, enlistment in the armed forces and major medical, psychiatric or surgical treatment.

NOTE: For research conducted in jurisdictions other than Connecticut, the research must comply with the laws regarding guardianship in all relevant jurisdictions. Legal counsel may 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\(c\)\]](#). In addition, any individual who satisfies the above definition and who is receiving care in a medical treatment setting will be considered a prisoner for purposes of this policy. For

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purposes of this policy, the definition of prisoner does not include individuals on probation or parole, or supervised by electronic monitoring devices.

NOTE: CT statute defines a prisoner as ‘any person in the custody of the Commissioner of Correction or confined in any institution or facility of the Department of Correction until released from such custody or control, including any person on parole’ (CGS 325 Sec. 18-84). Therefore, the research plan, from recruitment to retention to privacy protections for these individuals, should be carefully designed by the researcher and receive heightened scrutiny from the IRB to ensure that no procedures compromise the safety or status of these participants or otherwise negatively affect their well-being.

15.2 Involvement of Vulnerable Populations in Research

When the 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 and 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

Non-exempt DHHS-conducted or supported research that involves any of these populations must comply with the requirements of the relevant subparts. Research regulated by the FDA includes equivalent protections and obligations when research involves children ([Subpart D](#)). Research conducted, supported, or otherwise regulated by other federal departments or agencies may or may not be covered by the subparts. See sections 42-47 of this manual for additional information on department or agency requirements.

In its FWA, Yale 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.

15.3 Procedures

The following policies and procedures apply to all research involving vulnerable populations (subjects vulnerable to coercion or undue influence) under the oversight of the Yale IRB

regardless of funding. Subsequent sections address additional procedures and requirements that apply to specific populations.

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 inclusion of vulnerable population(s) in the research and the safeguards proposed by the investigator, taking into consideration the following factors, as applicable to the research:
 - a. Whether inclusion of vulnerable populations is ethically and scientifically appropriate;
 - b. Whether the proposed plans, including the settings and circumstances, for the identification and recruitment of subjects, and for obtaining consent or parental permission, ensure equitable selection of subjects and promote voluntariness;
 - c. Whether the proposed research confers any direct benefit, whether the benefit is available outside of the research, and whether access to the benefit may unduly influence participation by vulnerable populations;
 - d. Whether any costs or plans for subject reimbursement or compensation, may exclude or unduly influence participation by vulnerable populations;
 - e. Whether the provisions for privacy and confidentiality adequately protect vulnerable populations; and
 - f. Other relevant considerations as appropriate for the population(s) and the circumstances of the research
5. The IRB will determine whether the inclusion of the vulnerable population(s) is appropriate and whether the proposed plan adequately safeguards the rights and welfare of these subjects. When appropriate, the IRB may restrict or disallow the inclusion of vulnerable subjects or may require modifications to the research plan to enhance protections or to monitor the effectiveness of protections. For example, the IRB could require review more than annually, periodic HRPP QA/QI reviews, independent routine monitoring, or the use of a research subject advocate or consent monitor.

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.

Continuing Review

1. 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);
2. 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 and when applicable, whether the research continues to satisfy the requirements of subpart B, C, or D of 45 CFR part 46.

15.4 Research Involving Pregnant Women, Human Fetuses and Neonates

The following applies to all research involving pregnant women, human fetuses, and neonates reviewed by the Yale IRB. DHHS-specific requirements are noted in the appropriate sections.

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.

15.4.1 Research Involving Pregnant Women or Fetuses

15.4.1.1 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. See Supplemental Guidance: Reproductive Risks and Contraception for additional guidance.

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;
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 15.1) 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.

15.4.1.2 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.
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 15.1) who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 15.6.2;
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.

15.4.2 Research involving Neonates of Uncertain Viability or Nonviable Neonates

15.4.2.1 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:

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.

15.4.2.2 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:

1. The IRB determines that:

- a. 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
 - b. 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.

15.4.3 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 Yale policies).

15.4.4 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.

15.4.5 Research Not Otherwise Approvable

15.4.5.1 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.

15.4.5.2 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.

15.5 Research Involving Prisoners

15.5.1 Applicability

For research not conducted or supported by DHHS, where the risk to prisoners is no more than minimal (as defined in Section 15.5.2), no additional safeguards are required under these policies and procedures. However, the 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 is subject to the revised Common Rule, qualifies for exemption, and only incidentally includes prisoners (See Section 5)), the requirements outlined in this section apply.

The investigator must promptly secure approval from the State of Connecticut Department of Corrections Research Committee, if applicable, and any other involved entity (e.g., relevant state correctional facility oversight body for research conducted outside Connecticut, juvenile offender facility, Federal Bureau of Prisons) before conducting research procedures with prisoners.

15.5.2 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.

15.5.3 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.

15.5.4 Review of Research Involving Prisoners

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, videoconference, 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\(a\)](#)).

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).

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).

Expedited Review

1. Research **involving interaction** with prisoners may be reviewed by the expedited procedure if a determination is made that the research involves no greater than minimal risk for the prison population being studied and the research falls within the categories of research eligible for expedited review. Whenever possible, the prisoner representative will be consulted to verify that they agree that the research is minimal risk and to conduct (if designated by the IRB Chair as an expedited reviewer) or participate in the expedited review as a consultant. Review of modifications and continuing review will follow these same procedures;

2. Research **that does not involve interaction** with prisoners (e.g., records review) may be reviewed by the expedited procedure if a determination is made that the research involves no greater than minimal risk for the prison population being studied. Review by a prisoner representative is not required. The prisoner representative may review the research as a reviewer (if designated by the IRB Chair as an expedited reviewer) or consultant. Review of modifications and continuing review will follow these same procedures.

15.5.5 Incarceration of Enrolled Subjects

If a subject becomes a prisoner while enrolled in a research study that was not reviewed according to prisoner research requirements and procedures, all research interactions and interventions with, and obtaining identifiable private information about, the now incarcerated prisoner-participant must cease until the requirements of the IRB policy have been satisfied with respect to the relevant protocol unless there is a safety concern. In that case . the investigator must promptly notify the IRB and the IRB shall:

1. Confirm that the subject meets the definition of a prisoner;
2. 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.
3. 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.
4. 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.

15.5.6 Additional Duties of the IRB

In addition to the responsibilities of the IRB described in other sections of this manual, the 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;
 - 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. Prisoners cannot be a particular focus of such research, and the research must present no more than minimal risk and no more than inconvenience to the prisoner-subjects
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

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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.

15.5.7 Certification to DHHS

Under [45 CFR 46.305\(c\)](#), institutions engaged in 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 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, regardless of whether the institution has chosen to extend the applicability of its FWA and Subparts B, C, and D to all research. Certification is not required for exempt research that only incidentally includes prisoners (see Section 5).

When Yale is responsible for submitting certification to OHRP, the HRPP/IRB office will do so using the web-based certification form available on OHRP's website. The certification form must be accompanied by the "research proposal" which OHRP defines as including:

- the IRB-approved protocol, including consent forms;
- any IRB application forms required by the IRB; and
- any other information requested or required by the IRB to be considered during IRB review.

DHHS-conducted or supported research involving prisoners as subjects may not proceed until OHRP reviews the certification and issues its authorization on behalf of the Secretary.

15.6 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.


15.6.1 Allowable Categories

In addition to the IRB's normal duties, non-exempt 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:

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 15.6.2.
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 15.6.2.
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 15.6.2.
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.
 - 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:

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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 15.6.2.

15.6.2 Parental Permission and Assent

15.6.2.1 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 14.

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/checklist when a study receives expedited review, and in meeting minutes when reviewed by the convened committee and communicated to the investigator.

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 14.10; 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 appropriate mechanism would depend upon the nature and purpose of the activities

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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 14.8.

15.6.2.2 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 for research that meets the provisions for a general waiver in Section 14.10.

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 them 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 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.

Documentation of Assent

When the IRB determines that assent is required, it 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 is up to the child whether to participate and that it is 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.

15.6.2.3 Children Who are Wards

Ward: A child who is placed in the legal custody of the State or other agency institution, or entity, consistent with applicable Federal, State, or local law. 21 CFR §50.3(q). For example, children under the protection of a court, child protective services, or under the care of a non-parental relative would be considered to be wards.

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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 15.6.1), **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*.

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.

NOTE: All research protocols designed to enroll children who are wards of the State of Connecticut must obtain approval from the Connecticut Department of Children and Families Institutional Review Board (DCF IRB).

15.7 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 Yale investigators and the IRB with the development and review of research involving adults with impaired decision-making capacity.

15.7.1 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 them); (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.

15.7.2 Decision-Making Capacity

“Decision-making capacity” refers to a potential subject’s ability to make a rationale 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;
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. 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.

15.7.3 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 audiotaping 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.

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 14.3). 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.

15.7.4 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;
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.

15.8 Yale Students, Fellows, Trainees and Employees

When Yale students, fellows, trainees and employees are specifically targeted for participation in human subjects research, their participation will be treated in a manner commensurate with their special status. Such individuals are vulnerable to coercion and undue influence and, in the case of undergraduate students, may be minors. Additional safeguards must be implemented to protect their rights and welfare (45 CFR §46.111(b) and 21 CFR §56.111(b)), as described below.

The Yale employment or educational setting may be coercive to potential participants if they perceive that continued employment, academic standing, or other benefits are dependent upon their participation in research. Similarly, potential participants in a subordinate position to an investigator may feel undue pressure to participate in research. Researchers must

acknowledge that recruiting their own students, fellows, trainees or employees to participate in research may place these individuals in a compromised position, and should be mindful of their ability to influence others when directly recruiting their own students and/or employees as research participants. Investigators should pay particular attention to the circumstances surrounding the research and whether the student, fellow, trainee or /employee may feel pressure to participate in research because of his/her relationship with the investigator. Recruitment methods and activities must be conducted to assure the potential participant that his/her job, promotion, or course grade, for example, are not dependent upon his/her participation in the research. In cases where very personal or private information is collected during the study, researchers must have compelling scientific justification for including their students or staff due to privacy concerns. The IRB must review and approve the recruitment plan. In addition, approval from the appropriate School must be obtained when the investigator intends to conduct recruitment among students e.g., researchers specifically focusing on Yale School of Medicine students must obtain an approval from the departmental committee created to review and approve research targeting medical students. Similarly, investigators who wish to send a mass email to faculty, staff, and students about their research must obtain specific departmental approvals from Provost Office, Office of Public Affairs, Internal Communications, Yale College Dean's and other applicable parties, depending on the targeted audience.

A student shall not be required to enroll in University research as a research participant as part of a course requirement. Similarly, an employee shall not be required to enroll in employer-initiated research as a condition of employment.

15.8.1 Students as Research Subjects

Investigators enrolling their own, or purposefully enrolling their institution's, students or trainees in research must:

1. Not directly interact for recruitment purposes with students, fellows and trainees who report directly to the investigator unless one of the special situations applies (see Special Situations below);
2. Ensure that students understand that they may choose not to participate in the research and that their decision will not affect their grade/class standing;
3. Avoid using class time to recruit or engage in the research;
4. Limit the use of extra credit as compensation; it should not significantly increase a student's overall grade;
5. Provide students with an equal alternative to participation, which should be comparable in terms of effort, time commitment, and credit given;
6. Outline procedures in the research protocol to ensure that students will not be subject to undue influence or coercion and to ensure that each student's privacy will be respected.

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15.8.2 Employees as Research Subjects

Investigators enrolling their own or, or purposefully enrolling their institution's, employees in research must:

1. Not directly interact for recruitment purposes with employees that report directly to the investigator unless one of the special situations applies (see Special Situations below);
2. Engage in recruitment and consent activities outside of the presence of the employee's supervisor(s) whenever possible;
3. Ensure that employees understand that they may choose not to participate in the research and that their decision will not affect their employment or performance evaluation;
4. Outline procedures to ensure that employees will not be subject to undue influence or coercion and to ensure that each employee's privacy will be respected;
5. Ensure that steps are taken to avoid informing supervisors whenever possible of employees who decline participation;
6. Conduct the research procedures out of sight of other employees whenever possible. For example, surveys or questionnaires could be given to employee participants to complete online or at home and mail back to the investigators instead of asking all employee participants to convene in a room on-site, which could identify them as research participants to their superiors and co-workers.

Investigators recruiting their research sponsor's employees in research must, in addition to the aforementioned requirements, ensure that all data given to the employer is either in the aggregate or is stripped of all identifiers so that the employee participant's identity is protected.

15.8.3 Students or Employees as Subjects of non-Yale-Conducted Research

External investigators conducting research projects that do not involve Yale faculty but involve recruitment targeted specifically at members of the Yale community as a defined group must obtain approval from the appropriate official responsible for the group to be recruited. Review by a Yale Institutional Review Board (IRB) is not required when the University is not engaged in the research.

15.8.4 Special Situations/Exceptions

Permitted Convenience Sampling

While convenience sampling of an investigator's own students or staff is generally prohibited of the investigator, students or staff may elect to participate in research if they approach the

research team and initiate enrollment on their own behalf. In such cases, the enrollment and consent process should not be conducted by the investigator, but should be conducted by someone on the research team who is “at arm’s length” to the potential participants whenever possible.

Convenience sampling may also be approved by the IRB in cases where the IRB determines that 1) the study qualifies as no greater than minimal risk; 2) adequate steps have been taken to minimize potential coercion or undue influence; and 3) any harms that may arise in the research would not be exacerbated by the academic or employment relationship.

Waiver of Prohibition Against Requiring Enrollment in Educational Research

The IRB can waive the prohibition against requiring student participation in educational research on a case-by-case basis when an investigator can demonstrate that participation is educational and integral to fulfilling course requirements, or that full class participation is essential for study integrity, or when the study qualifies for exemption under 45CFR §46.104(d)(1): Educational Research.

Recruitment Through the Psychology Subject Pool

Studies intending to recruit students in Introductory Psychology must conform to both IRB and Psychology Subject Pool requirements. The Psychology Subject Pool Committee requires that the proposed research be educational for the students and consistent with course goals. Additional consent requirements are required by the IRB, including clearly indicating the ability to meet course requirements in other ways as agreed to between the IRB and the Psychology Subject Pool Coordinator.

Recruitment of non-Yale Students or Employees

Yale investigators seeking to recruit students or employees from another institution for participation in Yale research must respect the institution’s policies or practices with regard to such recruitment and seek appropriate institutional permission before initiating recruitment activities.

16 FDA-Regulated Research

FDA regulations apply to research that involves an 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 FWA, IAA, or an award or contract, then the Common Rule must also be applied. When research involving investigational test articles is conducted in countries other than the U.S., applicable law and requirements of the country must be followed.

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 Yale IRB.

16.1 Definitions

Additional FDA definitions are available in Section 1.9 Key Definitions.

Bioavailability. Bioavailability (BA) is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action. Bioavailability studies, including determining when an IND is required, are regulated under [21 CFR 320](#).

Bioequivalence. Bioequivalence (BE) is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended-release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. For drug products that are not intended to be absorbed into the bloodstream, bioequivalence may be assessed by scientifically valid measurements intended to reflect the rate and extent to

which the active ingredient or active moiety becomes available at the site of drug action. Bioequivalence studies, including determining when an IND is required, are regulated under [21 CFR 320](#).

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 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\(d\)](#)]

Emergency Use Authorization. FDA's Emergency Use Authorization (EUA) authority is intended to help strengthen the nation's public health protections against chemical, biological, radiological, and nuclear (CBRN) threats, including infectious diseases, by facilitating the availability and use of medical countermeasures (MCMs) needed during public health emergencies. Under the FD&C Act, when the DHHS Secretary declares that an EUA is appropriate, FDA may authorize unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when certain criteria are met. Products authorized under an EUA are not subject to IRB oversight unless used to obtain research information; then an IND/IDE is required.

Human Cells, Tissues, or Cellular or Tissue-based Products (HCT/P's) – HCT/P's means articles containing or consisting of human cells or tissues that are intended for implantation,

transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.

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

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

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
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\(m\)](#)]

16.2 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\(d\)](#)]

16.3 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:
 - 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 Yale 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 Investigational Drug Service or pharmacy service .
 - c. Investigational drugs and devices must be labeled in accordance with federal and state standards.
 - d. All devices received for a study must be stored in a locked environment under secure control with limited access. When applicable, proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device, and the disposition of remaining devices at the conclusion of the investigation.
10. The investigator shall furnish all reports required by the sponsor of the research including adverse events, progress reports, safety reports, final reports, and financial disclosure reports.
11. The investigator will permit inspection of research records by the sponsor, sponsor representatives, HRPP and IRB representatives, the FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under regulation, organizational policy, or contractual agreement.

16.4 Digital Health

Certain medical and decision support software have been excluded from the definition of medical device under the 21st Century Cures Act and thus are not subject to FDA's regulations. These include exclusions for software functions:

- Intended for administrative support of a health care facility, including the processing and maintenance of financial records, claims or billing information, appointment schedules, business analytics, information about patient populations, admissions, practice and inventory management, analysis of historical claims data to predict future utilization or cost-effectiveness, determination of health benefit eligibility, population health management, and laboratory workflow;
- Intended for maintaining or encouraging a healthy lifestyle and unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition;
- Intended to serve as electronic patient records, including patient-provided information, to the extent that such records are intended to transfer, store, convert formats, or display the equivalent of a paper medical chart, so long as—
 - such records were created, stored, transferred, or reviewed by health care professionals, or by individuals working under supervision of such professionals;
 - such records are part of health information technology that is certified under section 300jj–11(c)(5) of title 42; and
 - such function is not intended to interpret or analyze patient records, including medical image data, for the purpose of the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition
- Intended for transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results, findings by a health care professional with respect to such data and results, general information about such findings, and general background information about such laboratory test or other device, unless such function is intended to interpret or analyze clinical laboratory test or other device data, results, and findings; and
- Not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system; and
 - Is intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines);
 - Is intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition; and
 - Is intended for the purpose of enabling such health care professional to independently review the basis for such recommendations that such software

presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient.

Additional information regarding the application of these exclusions is available on the FDA website referenced below.

Research involving software excluded from the definition of medical device will be evaluated by the Yale IRB in accordance with any other applicable regulations (e.g., the Common Rule, HIPAA) and the criteria outlined in this manual.

Other digital health products may be subject to FDA regulations and will be evaluated accordingly. FDA has provided a website listing of [Guidances with Digital Health Content](#) to help the regulated community understand FDA's interpretation and application of the regulations and to describe when FDA will practice enforcement discretion in regards to certain requirements such as those for pre-market review and for device reports. Investigators are encouraged to consult these guidances in advance of their submission to the IRB and to consult directly with the FDA as needed. Investigators may contact the IND/IDE Management Office for assistance

16.5 Human Cells, Tissues, or Cellular or Tissue-based Products (HCT/P's)

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

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

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

16.7 Cannabis and Derivatives

Cannabis and its derivatives, including cannabidiol (CBD), are classified by the FDA as drug products, [not as dietary supplements](#). In most circumstances, research involving the administration of Cannabis and/or its derivatives must be conducted under an IND and comply with FDA's quality requirements. Additional requirements apply when the product is classified as "Marihuana", which is a Schedule 1 controlled substance. Investigators are strongly encouraged to consult with the FDA's [Botanical Review Team](#) (BRT) when planning a study involving the use of Cannabis and/or its derivatives to ensure that the study conforms with regulatory requirements and avoid delays in Yale's review and approval of the research. Investigators are also encouraged to review the information on FDA's website: [FDA and Cannabis: Research and Drug Approval Process](#). Yale investigators should consult with Yale Environmental Health and Safety Policy, "Policy on the Use of Controlled Substances in Research."

16.8 Clinical Investigations of Articles Regulated as Drugs or Devices

16.8.1 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 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 (Note: Investigator's Brochures (IBs) should not be used to validate an IND or IDE because one IB may be used for multiple INDs or IDEs).

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 whether the study must be submitted to the FDA, using the criteria below.

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

The Yale Center for Clinical Investigation (YCCI) provides a comprehensive, [centralized resource for FDA submission of IND applications and IDEs](#). This unit provides guidance on whether an IND is required, answers questions about the submission process, and assists researchers in complying with the regulatory requirements associated with IND and IDE applications. The IND/IDE office should be consulted before a research study is ready to move into human trials.

16.8.2 IND Exemptions

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

1. [21 CFR 312.2\(b\)\(1\)](#): 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
 - 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.

2. [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](#)
3. [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.
4. [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\(d\)\(3\)](#)].
5. [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.
6. 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;
 - 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]

16.8.3 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 “510k” 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.

16.8.4 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 16. 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):
 - 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.

16.9 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 (or alternate institutional committee) approve the use of a 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.

16.9.1 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.

16.9.2 IRB Review Requirements

A Humanitarian Use Device (HUD) may only be used in a facility after an IRB (or alternative institutional committee) has approved its use, except in certain emergencies.

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 an FDA-approved IDE before starting the clinical investigation of a Significant Risk device.

16.9.3 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 Yale 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 via the electronic submission system:

1. Application Form – HRP-593 - Humanitarian Use Device Template;
2. A copy of the HDE approval letter from the FDA;
3. A description of the device, such as a device brochure;
4. The product labeling;
5. The patient information packet for the HUD;
6. The proposed clinical consent process;
7. Other relevant materials (e.g., training certificates) as identified in the Application Form

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.

While the use of an HUD must initially be reviewed and approved by the fully convened IRB, the IRB may decide to use expedited review procedures for subsequent and continuing reviews since the initial review would have been performed by the full board, and use of the HUD within its approved labeling does not constitute research, according to FDA guidance. The fully convened IRB will determine at initial review whether or not subsequent and continuing reviews of the use of the HUD may be expedited in the future, provided no unanticipated problems have occurred with its use. Continuing review must be completed at least annually unless the IRB requires a shorter time frame.


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 via Modification application in the IRB electronic system 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.

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 via the IRB electronic system include:

The Continuing Review application with the following supplemental documents uploaded within the submission, as applicable:

1. The most recent periodic report to the FDA by the HDE holder;

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2. The current patient information packet, if applicable;
3. The current consent, if applicable;
4. Other materials as identified on the Continuing Review application; and
5. Any other new relevant information or materials

16.9.4 Emergency Uses of HUDs

Unapproved 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 provider must comply with the HDE holder’s requirements for certification of the emergent need for the HUD. Within 5 business days after the emergency use of the device, the provider must provide, via email, written notification of the use to the Yale IRB Chair including the identification of the patient involved, the date of the use, and the reason for the use. [\[21 CFR 812.124\]](#) The relevant departmental designee at YNHH must also be informed by the provider of the use and inventory adjusted appropriately thereafter. The HRPP notifies the IND/IDE management office upon receipt of the provider’s notification.

Off-label Use of HUDs - 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 indications, the physician should consult with the HDE holder and IRB in advance whenever 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 requirements, as appropriate given the specifics of the situation.

16.10 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 16.10.

16.10.1 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 policies and procedures.

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. Convened IRB review is 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, the Yale HRPP, and YCCI, to determine the

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appropriate access mechanism and ensure that proper regulatory procedures are followed. The FDA provides information about the procedures and requirements for expanded access on a [website](#), including a link to FDA's [contact information](#).

Please contact the [IND/IDE Management Office](#) for assistance regarding the appropriate mechanism for [expanded access](#) submission, which varies depending on therapeutic area and product type.

16.10.1.1 Expanded Access to Investigational Drugs for Individual Patients

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

Sponsor or Manufacturer Approval:

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

FDA Approval:

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

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

by the convened IRB. This alternative review procedure is referred to as a “concurrence review” in FDA guidance; however, the IRB Chair must review the same materials and make the same determinations as the convened board would. IRB Chair review 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 to the FDA within 15 days of the FDA’s authorization. For more information on emergency use, see Section 16.10.

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

IRB Review:

Unless the conditions that permit an emergency use exemption (see Section 16.10.1.2) 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 the IRB electronic system:

1. A completed Yale HRP-503X Protocol for Expanded Access Programs (EAPs) template 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.

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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.

Yale 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 must submit the request for external use in IRES IRB 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.

16.10.1.2 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 16.10.1.2.1 below.

Approval from the FDA and the Sponsor/Manufacturer 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.

A copy of reports or amendments submitted to the FDA and any related correspondence must be submitted to the IRB office.

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

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a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state or local law.

16.10.1.2.1 Emergency Use Exemption from Prospective IRB Approval

Under FDA regulations at [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 the conditions described below are satisfied and that the emergency use is reported to the IRB within 5 working days. Any subsequent use of the investigational drug in the facility requires IRB approval. 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 it appears likely that the investigational drug may need to be used again, the IRB may request that a study application is submitted which would cover future uses.

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 16.10.1.3), 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 business days** after an emergency exemption is used. If time permits, the prescribing clinician should notify one of the Chairs of the IRB in writing of his/her intent to utilize an investigational drug for a therapeutic or diagnostic reason and obtain Chair concurrence at least 24 hours prior to the planned date of the first administration of the drug.

Review by the IRB Chair for such use is specific and limited to the individual patient. If, in the clinician's opinion, immediate use of the test article is required to preserve the patient's life, and if time is not sufficient to obtain prospective IRB Chair review, the clinician should make the determination and proceed.

The clinician must provide the following information by email to the Chair for the emergency use of the investigational drug:

- assurance from the prescribing clinician that the use is NOT part of a project that is currently awaiting IRB approval;
- assurance that the use of the drug(s) or biologic is primarily to treat a patient with a specific, clinically urgent condition, and that the patient is not a research subject;
- a brief written statement explaining the rationale for the use of the investigational drug;
- a copy of the consent form that will be used by the prescribing clinician to obtain informed consent from the patient or the patient's legally authorized representative/surrogate; and
- a formal statement that the prescribing clinician has received from the manufacturer (or distributor) of the investigational drug approval for its use for the purpose outlined in the consent document.

The IRB Chair (or a Chair-designated IRB member) 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 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\(c\)](#).

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

16.10.1.3 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 business days** when an emergency consent exception is invoked. The prescribing clinician performing the intervention submits the written material noted above by email for review and evaluation by the IRB Chair. The IRB Chair will review the report and documentation of the independent physician evaluation to verify that circumstances of the emergency exception conformed to FDA regulations.

16.10.2 Expanded Access to Investigational and Unapproved 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 Yale HRPP, to ensure that proper regulatory procedures are followed. Additional guidance on Expanded Access can be obtained by contacting the [IND/IDE Management Office](#).

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

16.10.2.1 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);
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 16.10.2.3), 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. 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 IRB office and submit the following via the IRB electronic system. Note that the Office of Sponsored Projects will be notified of the submission for any applicable contract review.

The IRB submission includes:

1. A completed Yale HRP-503X Protocol for Expanded Access Programs (EAPs) 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; and
4. A copy of the draft informed consent document.

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

Yale 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 must submit requests for IRB Reliance for Compassionate Use protocols via the electronic IRB submission system.

Post-Approval Requirements

Once obtained, the investigator is to submit IRB approval to the relevant YNHH Vice President or Service Line director for YNHH review and approval. If the device is approved for use at YNHH, an individual shall be designated in the relevant department to control the inventory, dispensation and chain of custody of the device(s). This individual must be notified of any use by the investigator, prior to use for a planned procedure and as soon as possible thereafter in the event of an emergency use. The request must be reviewed and approved in writing by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

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.

16.10.2.2 Treatment Use of Investigational/Unapproved Medical Devices

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

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

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

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

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

IRB Review:

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

To request IRB approval for treatment use, investigators should contact the IRB office and submit the following via the IRB electronic system. Note that the Office of Sponsored Projects will be notified of the submission for any applicable contract review.

The IRB submission includes:

1. A completed Yale HRP-503X Protocol for Expanded Access Programs (EAPs) 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; and
4. A copy of the draft informed consent document.

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

Yale 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

Once obtained, the investigator is to submit IRB approval to the relevant YNHH Vice President or Service Line director for YNHH review and approval. If the device is approved for use at YNHH, an individual shall be designated in the relevant department to control the inventory, dispensation and chain of custody of the device(s). This individual must be notified of any use by the investigator, prior to use for a planned procedure and as soon as possible thereafter in the event of an emergency use. The request must be reviewed and approved in writing by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

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.

16.10.2.3 Emergency Use of Investigational Devices

[FDA does not consider the single-patient emergency use of an investigational or unapproved device to constitute research](#). 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 and IRB approval are not required, FDA expects providers planning the emergency use of an investigational device to obtain as many of the following as possible:

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

At Yale, 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 email the description of the use and supporting documentation for review by the IRB Chair. The IRB Chair 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.).

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The Office of Sponsored Projects will be notified by the HRPP of the submission for any applicable contract review.

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.

Providers are reminded that they must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved devices, such as notifying the relevant YNHH Vice President or Service Line director of the emergency use of the device.

16.11 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.

The [Yale Center for Clinical Investigation](#) (YCCI) prepares Medicare coverage analyses for Medicare qualifying clinical trials involving the provision of billable clinical procedures and for all qualifying trials under the auspices of the Yale School of Medicine.

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

16.11.2 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](#).

17 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 UPIRSOs).

This section provides definitions and procedures for the reporting of UAPs to the Yale IRB. 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 6.4.

In conducting its review of protocol deviations, 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 UAP.

17.1 Definitions

Unanticipated problems involving risk to participants or others. Unanticipated problems involving risks to subjects or others (UAPs) 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

UAPs also encompass Unanticipated Adverse Device Effects, as defined below, information that sponsors are required to report to the FDA in IND Safety Reports under [21 CFR 312.32](#) and Serious Adverse Events (SAEs) that occur in Bioavailability (BA) and Bioequivalence (BE) studies.

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 the procedures involved 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, whether or not considered related to the subject’s participation in the research. Adverse events encompass both physical and

psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

Serious Unexpected Suspected Adverse Reaction (SUSAR). For research subject to FDA's IND regulations, a Serious Unexpected Suspected Adverse Reaction refers to any suspected adverse reaction to study treatment, including active comparators, that is both serious and unexpected. Sponsors, or sponsor-investigators, are responsible for determining whether an event meets all three components of this definition (i.e., serious & unexpected & suspected adverse reaction), and thus must be reported to the FDA in an IND Safety Report. Investigators are encouraged to consult [FDA draft guidance](#) (2021) and [final guidance](#) (2012) for information regarding FDA's terminology and its application to safety reporting requirements.

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\(s\)](#)].

17.2 Procedures

17.2.1 Reporting

Adverse events in FDA-regulated clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. Unless specifically required by the IRB for a given protocol, the Yale IRB does not accept reports of adverse events that are not also an unanticipated problem involving risks to subjects or others (UAP).

Investigators must report the following events or issues to the IRB as soon as possible but within **5 business days** after the investigator first learns of the event using the "Reportable New Information" (RNI) form in the IRB electronic system.

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

Examples of UAPs 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 (SAE) 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 UAP;
7. IND Safety Reports from sponsors that meet the criteria for reporting to the FDA under [21 CFR 312.32](#). Such reports must be accompanied by confirmation that the sponsor has submitted the report to the FDA. For more information on IND safety reporting, see FDA's guidance "[Safety Reporting Requirements for INDs and BA/BE Studies](#)";
8. Any SAE that occurs in a Bioavailability (BA) or Bioequivalence (BE) study
9. Unanticipated Adverse Device Effects (UADEs);
10. 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. In general, 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.
11. 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.

12. Sponsor or lead investigator/coordinating center-imposed suspension or termination of some or all research activities;
13. An unanticipated event related to the research that exposes subjects or others to potential risk but that does not involve direct harm;
14. A breach of confidentiality or loss of research data (e.g., a laptop or thumb drive is lost or stolen);
15. 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;
16. 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.

17.2.2 Review Procedures

1. Upon receipt of the RNI form, the HRPP staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information. If during pre-review it is determined through clarification with the PI that the report does not in fact meet the submission criteria as defined above (i.e., concerns an adverse event that is not serious (or life-threatening), unexpected, or related to participation in the study or does not present an unexpected risk to subjects or others), then review by the IRB Chair or other qualified designee will not proceed. The PI will be notified by the HRPP staff that the submission criteria was not met and educated regarding the required submission criteria.
2. **For IND Safety Reports and UADEs**, the IRB Chair or designated reviewer receives and reviews the report and determines whether (1) the report can be accepted as submitted without any further action needed to ensure the protection of subjects who are enrolled at sites for which the Yale IRB is the IRB of record; or (2) if review by the convened IRB is warranted to determine whether additional actions are necessary. If needed, the Chair or designee may request additional information from the investigator, sponsor, or others. It is FDA's position that, in general, information that must be reported to the FDA in an IND Safety Report or as an UADE are UAPs, therefore the IRB does not need to determine whether the reported problem is a UAP.

3. **For reports other than IND Safety Reports and UADEs**, the IRB Chair or designated reviewer receives and reviews the report and makes an initial determination as to whether the event represents an UAP. If needed, the Chair or designee 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).
 - a. If the reviewer determines that the problem does not meet the definition of an UAP, they will determine 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 reviewer notes in the electronic system and communicated to the investigator.
 - b. If the reviewer determines that the event may be an UAP, the report will be referred for review by the convened IRB. The convened IRB will determine whether the event is a UAP and whether any additional actions are necessary to ensure the protection of human subjects. If needed, the IRB may request additional information from the investigator, sponsor, or others. The results of the review will be recorded in the IRB minutes and communicated to the investigator.
4. 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 implementing 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;
 - 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. For studies approved by an external IRB cross-reference Section 6 of this manual for reporting requirements.

All events that may represent UPIRSOs should be promptly reported (in accordance with the timeframes as described above), regardless of whether they occur during the conduct of the study or after the study has closed at Yale, or whether they involve a subject who has withdrawn from or completed study participation. The IRB may make a late reporting notation to all UPIRSOs reported outside the timeframes as outlined above, and repeated incidences of late reporting may constitute continuing noncompliance. If changes to the research or consent process are proposed as a result of the event, or if additional information will be provided to current and/or past subjects, an amendment request also must be submitted for IRB review.

When the IRB determines that an event is an UAP, the HRPP staff will follow the procedures for reporting to regulatory agencies, sponsors, and organizational officials in Section 21. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions. IND Safety Reports, UADE Reports, and any other reports that have already been reported to the federal oversight agency (e.g., by a Sponsor, Coordinating Center, sIRB, or the institution where research occurred (e.g., the VA) do not also need to be reported by Yale.

18 Noncompliance

This section provides definitions and procedures for the reporting and review of known or suspected noncompliance for research under the oversight of the Yale 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 6.4.

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.

18.1 Definitions

Noncompliance is defined as any failure to follow:

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

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

Serious Noncompliance is defined as noncompliance that increases risk of harm to subjects; adversely affects the rights, safety, or welfare of subjects; or adversely affects the integrity of the data or the research.

Major Protocol Deviation is a protocol deviation that was done without prospective IRB approval and resulted in a potential increase of risk or harm to subjects.

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

Apparent Noncompliance describes an event that appears to constitute noncompliance, but the IRB has not yet made a formal assessment of the event.

18.2 Reporting

Investigators and their study staff are required to report instances of possible serious and/or continuing noncompliance and major protocol deviations to the IRB within **5 business days** of discovery using the RNI form in the IRB electronic system.

Additionally, anyone may report concerns of possible noncompliance to the HRPP or IRB 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. Retaliation, coercion or undue influence against an individual for having made in good faith an allegation of noncompliance with human research regulations or policy is a violation of University policy and an offense subject to University disciplinary procedures. Concerns about possible retaliation or harassment must be reported to the IRB.

If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report noncompliance, he or she may contact the HRPP Director, IRB Manager, Chair or other designee directly to discuss the situation informally.

Principal investigators are also required to report results of audits or inspections conducted by sponsors, other external entities such as the Food and Drug Administration (FDA), or internal oversight committees, which indicate noncompliance. Investigators are not required to report instances of noncompliance that occur at other sites unless a Yale investigator serves as the lead Principal Investigator, Yale serves as the IRB of record or Yale serves as the coordinating center for a multi-center study.

18.3 Review Procedures

1. Upon receipt of the RNI, the HRPP staff designee 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 HRPP Director, IRB Manager, or assigned HRPP staff may develop a written report summarizing the available information and will upload the report into the IRB electronic system. If the information provided suggests that subjects may be at risk of harm without immediate intervention or that research misconduct may have occurred, the HRPP Director, IRB Chair, and, when appropriate, the IO and/or Research Integrity Office, will be notified so that they can take any necessary steps to ensure the safety of subjects or investigate the matter.
2. The IRB Chair or designated reviewer 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 reviewer may request additional information from the investigator or others. When circumstances warrant, the HRPP Director, IRB Manager, or HRPP staff designee may bypass this step and assign the report for convened board review. If participants are at immediate risk of harm and may be placed at further risk while awaiting the outcome of a convened IRB meeting, the IRB Chair(s) or designee has the authority to place one or all aspects of a study on-hold pending the decision of the convened IRB.
3. If the reviewer determines that the event or issue is not noncompliance, or is noncompliance but not serious or continuing, they 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 reviewer may refer the matter to the convened IRB for review. The results of the review will be recorded in the electronic system and communicated to the investigator.

4. If the reviewer determines that the event or issue may be serious or continuing noncompliance, the report will be referred for review by the convened IRB. The convened 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 outlined 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:
 - 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, Research Integrity Officer)
 - 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 designee will follow the procedures for reporting to regulatory agencies,

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sponsors, and organizational officials in Section 21. 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 10.4.

18.4 Apparent IRB Noncompliance

When there has been noncompliance on the part of the IRB (e.g., repeated failure to make a required determination), the HRPP Director or designee will gather the relevant facts and if determined to be potentially serious or continuing report the matter, with any recommendations, to the IO. The IO may take actions as needed to further investigate the matter (e.g., a directed audit) prior to determining whether the apparent noncompliance is serious or continuing. The IO may also require corrective and preventive actions as warranted to remedy the matter and prevent recurrence. Serious or continuing noncompliance on the part of the IRB will be reported as necessary following the procedures outlined in Section 21.

19 Complaints

The HRPP & 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 oversight of the Yale IRB report complaints unable to be resolved by the investigator using the Reportable New Information (RNI) form via the IRB electronic system. All complaints, including those resolved by the investigator, should be summarized at the time of continuing review in the Continuing Review submission, when continuing review is applicable.

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 6.4.

Investigators are encouraged to contact the HRPP Director or designee, IRB Chair, or IRB Manager when they are having difficulty resolving a complaint or concern, and whenever circumstances warrant (e.g., immediate attention is needed).

When the HRPP or IRB office is the direct recipient of complaints or concerns, the staff will do the following:

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., Research Compliance, Risk Management, Patient Relations, Privacy) to assist with information-gathering or resolution.

For research under the oversight of the Yale HRPP, an HRPP staff member will consider the complaint or concern and take any reasonable steps necessary to investigate and/or resolve the issue, if possible and appropriate. Based on the nature of the complaint, the report and any related information will be provided to the IRB for review in accordance with the procedures

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for Other Reportable Information, UPIRSOs, or potentially serious or continuing noncompliance. HRPP staff, IRB Chairs, and designated reviewers may refer any complaint for review by the convened IRB. The IRB minutes, or in-system documentation of expedited reviews, will reflect the action(s) taken.

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

20 Other Reportable Information

When research is under the oversight of the Yale IRB, in addition to UAPs, 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 **5 business days** of discovery using the RNI submission 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 6.4.

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);
 - a. For device studies subject to FDA's IDE regulations, any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency must be reported to the sponsor and the IRB of record **no later than 5 business days** after the emergency occurred.
2. Trends which may indicate that subjects may be at increased risk or that the integrity of the research is in jeopardy (i.e., trends in deviations);
3. Monitoring, audit, and inspection reports indicating noncompliance in accordance with Section 2.1 of this manual;
4. Notice of:
 - a. Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated (classification as "OAI" is typically made after FDA has had the opportunity to review the responses to a 483), FDA Restrictions Placed on IRBs or Investigators, and any corresponding compliance actions taken under non-US authorities related to human research protections.
 - b. Any litigation, arbitration, or settlements initiated related to human research protections.
 - c. Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding human subjects research conducted at or by Yale or Yale's program for the protection of human research participants.

NOTE: The above events (5.a, b, and/or c) must be reported to the HRPP/IRB office by phone or email **as soon as anyone becomes aware**, with the formal submission within the 5-day timeline as noted above. See Section 22 for more information.

5. Sponsor or coordinating center reports;
6. Data Safety Monitoring reports, including reports from DSMBs, DMCs, and others;
7. Enrollment or inclusion of vulnerable populations not previously approved by the IRB for the study (e.g., prisoner, pregnant woman, neonate, child, adult with impaired decision-making capacity);
8. 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);
9. Holds, suspensions, or terminations of a study, in part or in full, by an investigator, sponsor, or others;
10. Changes that impact the ability of the PI to conduct or supervise the study, temporarily or permanently;
11. Changes that impact the qualifications of investigators or research staff members such as actions taken by regulatory authorities, licensing boards, or credentialing committees;
12. New information that may impact the rights, welfare, or willingness of subjects to continue in the research.

20.1 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 HRPP Director, IRB Chair, and, when appropriate, the IO and/or Research Integrity Office, will be notified so that they can take any necessary steps to ensure the safety of subjects or investigate the matter.
2. The IRB Chair or designated reviewer receives and reviews the report and if the report may represent an UAP or noncompliance, reviews the report as described in Section 17 or 18. When circumstances warrant, the HRPP Director or IRB Manager may bypass this step and assign the report for convened board review.
3. If the reviewer determines that the event or issue is not noncompliance or an UAP, 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 electronic system and communicated to the investigator.

21 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. Yale 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.

IND Safety Reports, UADE Reports, and any other reports that have already been reported to the applicable federal oversight agency (e.g., by a Sponsor, Coordinating Center, or sIRB) do not also need to be reported by Yale. The Yale IO and any other appropriate parties will be informed of such reports by the HRPP Office when the matter involves local subjects or significantly impacts the conduct of the research at Yale.

21.1 Procedures

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

The HRPP Director or designee is responsible for preparing reports in accordance with the instructions of the Federal department or agency (e.g., [OHRP](#), [FDA](#)). The PI, in collaboration with Sponsored Projects, will report to the applicable Sponsor and/or funding agency, as applicable.

The HRPP Director or designee sends a copy of the report to:

1. The IRB Chair
2. The IO
3. Yale OGC
4. Federal departments or agencies, as follows:

- a. OHRP, if the research is conducted or supported by [DHHS](#), or if an engaged institution's FWA has been voluntarily extended to all non-exempt human subjects research
- b. If the research is conducted or supported by a Common Rule Dept. or Agency other than DHHS, the report is sent to the party identified by the Dept. or Agency. A list of contacts is available on OHRP's [Reporting Incidents](#) webpage.
- c. If the study is conducted or supported by a federal dept. or agency that has not adopted the Common Rule, and reporting is required, the report is sent to the party identified by the dept. or agency.
- d. FDA, if the study is subject to FDA regulations.

Reports are not submitted to federal departments or agencies such as OHRP or FDA unless the research is subject to federal regulations or another mandate that necessitates such reporting.

5. Sponsor, if applicable
6. Principal Investigator, when applicable
7. Others as deemed appropriate by the IO

The HRPP Director ensures that all steps of this policy are completed generally within 30 business days of the determination unless otherwise required by the funding agency. For more serious actions, the Director expedites reporting. If additional time is needed to gather facts, or determine corrective actions, a preliminary report will be submitted generally within 30 business days, to be followed by a final report as described above.

22 Reporting to AAHRPP

Yale's HRPP is accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). In addition to the information that Yale routinely provides to AAHRPP in annual reports and the re-accreditation application, AAHRPP requires that any of the following are reported to AAHRPP as soon as possible, but generally within 48 hours after the organization or any researcher (if the researcher is notified rather than the organization) becomes aware:

- Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA Restrictions Placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections;
- Any litigation, arbitration, or settlements initiated related to human research protections; and/or
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding Yale's HRPP.

The HRPP Director (or designee) is responsible for ensuring that such reports are made to AAHRPP and for informing appropriate organizational officials while maintaining the confidentiality of information as appropriate (e.g., information protected by Attorney/Client Privilege or otherwise deemed confidential). Investigators, research staff, HRPP staff, IRB members, and other organizational officials or offices (e.g., the IO, Compliance, OGC, etc.) are responsible for informing the HRPP/IRB office as soon as they become aware of any of the above so that these reporting obligations may be fulfilled.

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;
 - 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 Connecticut and the policies of Yale
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., COI, RDRC, RDIC, 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, as applicable;
23. Report unanticipated problems, deviations, complaints, noncompliance, suspensions, terminations, and any other reportable events to the IRB and the organization, as required by regulations and policy;
24. Notify the IRB if information becomes available that suggests a change to the potential risks, benefits, merit, or feasibility of the research;
25. Obtain IRB review and approval before changes are made to the research unless a change is necessary eliminate apparent immediate hazards to the subject(s);
26. Seek HRPP or IRB assistance when in doubt about whether proposed research requires IRB review;
27. Retain records for the time-period and in the manner described to and approved by the IRB and as required by required by regulations, agreements, and policies;

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

23.1.1 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.

Principal Investigators are responsible for consulting and complying with University policies as well as federal and state laws and regulations related to data retention including but not limited to HIPAA, FDA, DHHS, medical records, and funding agency or sponsor requirements as applicable. Records must be maintained for at least as long as the longest record retention period applicable to a given set of research records.

University human research records, which must be maintained, include the following:

- Primary source data collected or created in the course of the research project;
- Consent forms signed by the participant;
- Biological samples and associated data; and
- Tabulations or other manipulations of the data created for the purpose of data analysis

Secondary copies of the data and interim data manipulations are not required to be maintained but are nonetheless subject to University policies related to record retention and protection.

Principal Investigators who are leaving the University and wish to transfer University human research records to a new institution may request approval to transfer the identifiable records or biological samples. Such requests require that ethical, regulatory, and professional obligations are respected, including:

- Obtaining IRB approval from the new institution for use and/or storage of the data or biological samples.
- Recording disclosure of any PHI in accordance with HIPAA policy 5003 Accounting for Disclosures.
- Upholding any intellectual property rights of the University and research team members as co-owners of the data.
- Consideration of expectations of research participants as delineated in the informed consent document(s).
- Access and audit rights of the sponsor are exercised and maintained in a manner consistent with established agreements and legal or regulatory requirements.
- Ensuring adequate continuation of patient care in clinical trials.

To initiate a data or bio specimen transfer, the Investigator must submit a written request to the Department Chair, or designee and the IRB which includes a description of the data which is to be transferred; such as lab note books, primary data scoring records, primary diagnostic information, computer files, consent documents, tissue samples etc. The request for transfer must be approved by the Department Chair and the IRB. Requests to transfer the data or copies of the data or portions of biological specimens will be approved when the following criteria are satisfied:

- When the requestor is not the PI, then the PI approves that copies of the data, or portions of biological specimens may be transferred.
- If the requestor is the PI and the original data and/or specimens is requested for transfer, then provisions must be in place to permit Yale, federal and/or sponsor auditors access to the data and related research information at the new institution as

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needed to conduct audits related to research compliance and adherence to federal and state law and to any governing research contract(s) with the research sponsor.

- Other University research or clinical requirements are satisfied.
- If the records include biological specimens, a material transfer agreement may be required. Investigators should consult Grant and Contract Administration to determine if an agreement is necessary.
- If the data includes PHI as defined by HIPAA, and the data will not be stripped of identifiers to qualify as a de-identified or as a limited data set or if the transfer will occur without prior patient/subject authorization then the investigator must provide documentation of the disclosure in the accounting for disclosure log maintained at Yale.
- If the data/tissue will be maintained as a repository at an institution external to Yale, then IRB approval and oversight must be transferred to the new institution.

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.

23.2 Investigator Concerns

Investigators who have concerns or regarding the conduct of research at Yale, Yale’s HRPP or IRB(s), or the external IRBs Yale relies upon should convey them to the HRPP Director, the IO or other responsible parties (e.g., supervisor, Dean, Department Chair), when appropriate. The recipient of the concern will consider the issue, and when deemed necessary, seek additional information and convene the parties involved to form a response for the investigator or make necessary procedural or policy modifications, as warranted. In addition, the IRB Chair and IRB Manager are available to address investigators’ questions, concerns, and suggestions.

Anyone with concerns may also make a confidential or anonymous report using the Yale University Hotline, either [online](#) or by calling the toll-free number (at 877-360-YALE).

Consistent with Yale policies, there will be no retaliation against employees, faculty, students, staff, etc. who report concerns in good faith.

24 Sponsored Research

It is Yale policy that any sponsored research conducted under the auspices of Yale 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 Responsibility

Contracts and other funding agreements with sponsors will be reviewed for the following by the Office of Sponsored Projects, with consultation with the HRPP/IRB Office, as necessary:

1. All sponsor contracts have a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate.
2. In studies where sponsors conduct research site monitoring visits or conduct monitoring activities remotely, the sponsor contracts have a written agreement with the sponsor that the sponsor promptly reports to Yale 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 Yale, including the time frames for providing routine and urgent reports.
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 Yale 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.

25 Conflict of Interest in Research

It is Yale's 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

Pursuant to the Yale University Policy on [Conflict of Interest](#), Yale maintains a Conflict of Interest Committee (COI Committee). Yale IRB will collaborate with the COI Committee to ensure that disclosed COI of investigators and research team members (investigators) are identified and managed before the IRB completes its review of any research application. When research is under the oversight of an external IRB, the conflict of interest procedures outlined in the reliance agreement or related materials are followed. Investigators who disclose interests to external IRBs should ensure that the disclosures are consistent with COI disclosures to Yale.

25.1.1 Procedures

25.1.1.1 Disclosure of Researcher COI

For IRB purposes, investigator conflict review occurs at the time of new study submission, continuing review, with the addition of a new investigator, and whenever an investigator updates their Yale COI disclosure indicating a new or changed interest. HRPP management reviews the disclosure for potential COI and notifies the HRPP designee via submission of an RNI (for internal studies) in the electronic system whenever a submission requiring conflict review is identified. The HRPP designee reviews the investigators' disclosures and notifies the IRB Chair when one or more investigators has an interest that requires evaluation by the IRB. The designee will provide the IRB Chair with a written summary describing the conflict and advise on any conflict management that is necessary. The IRB Chair may decide on the necessity of conflict management or disclosure to subjects, or schedule conflict review by the convened IRB. The Chair's decision regarding any management or disclosure that is necessary to address a conflict of interest is provided to the convened IRB when the relevant protocol submission is reviewed by the board. The conflict management plan or disclosure requirement is

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communicated to the principal investigator by the IRB. Compliance with IRB requirements will be a condition for IRB approval or continued approval of the research.

The HRPP designee notifies the COI office of the IRB action taken. Alternatively, the IRB Chair may also refer the conflict review to the COI Committee and defer the research study review until the COI Committee review 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 conflict management plans (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 introduces undue influence on subjects or bias to the research;
3. Whether the COI might adversely affect the integrity or credibility of the research or the research program; and
4. 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. The IRB may also determine that an interest that the institution does not generally treat as a COI presents a conflict of interest to the research that requires management for the protection of human subjects.

With regard to the CMP issued by the COI Committee, the IRB shall either affirm the CMP or 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 Committee.

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

1. Disclosure of the COI to subjects through the consent process;

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2. Modification of the research plan or safety monitoring plan;
3. Limitation of the investigator’s conduct under the protocol, such as restriction from determining subject eligibility or consenting subjects;
4. Monitoring of research by a third party;
5. Disqualification of the conflicted party from participation in all or a portion of the research;
6. Appointment of a non-conflicted PI;
7. Divestiture of significant financial interests; and/or
8. 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 themselves from the deliberations and vote by leaving the room or virtual meeting space.

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 HRPP designee, who reviews the disclosure and determines if a COI exists. To protect the privacy of members, the specific details of the conflict will only be provided to management and 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 has a conflict and reminds members of conflicts at convened meetings as needed to ensure recusal. HRPP staff may consult with the designee 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 (See Yale University Policy on Conflict of Interest for a definition of 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.

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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 or virtual meeting space 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 is placed in the virtual waiting room for discussion and voting.

IRB members with a conflicting interest are excluded from being counted toward quorum for the particular review for which they have a conflict. Recusals of members with COIs are recorded in the minutes.

25.3 Institutional Conflict of Interest

The Institutional Conflict of Interest Committee (ICOIC) is responsible for the implementation of the policy on institutional conflict of interest. The Committee is appointed by the President and charged with the review of Significant External Relationships and Leadership Significant Financial Interests to assess whether they present institutional conflicts of interest in human research. If the ICOIC determines that an ICOI exists in relation to human subjects research, it will decide upon actions to eliminate or manage the ICOI, and it will report the ICOI along with those decisions to the President and Human Research Protections Program (“HRPP”). The ICOIC policy is available in PART III Policies.

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

Yale University 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 Yale University and provide them the opportunity to provide input, seek information, and express concerns. The following procedures describe how Yale University fulfills that responsibility.

26.1 Outreach Resources and Educational Materials

1. The HRPP office dedicates a section of the website to research participants entitled “Research Participants.” This website includes links to resources and information such as “Rights as a Research Participant”, “Informed Consent”, “Voluntary Participation”, “Reporting Concerns”, and relevant research-related links including links to other Yale offices that provide community outreach information and programs (e.g., the Yale Center for Clinical Investigation which provides education and training to the public regarding clinical trials by collaborating with community partners to understand public preferences, perceptions, and attitudes about research and conducting focus groups, etc.).
2. The HRPP website includes information regarding how to contact the YALE HRPP 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.
4. Yale University, through the Yale HRPP, Yale Center for Clinical Investigation, Yale Bioethics Center, etc.) provides presentations and educational information related to research to the community. This includes providing education and training to the public regarding research by collaborating with community partners to understand public preferences, perceptions, and attitudes about research and conducting focus groups.
5. Yale University holds an annual “Research Day” to which members of the public are invited.

26.2 Evaluation

Yale University evaluates outreach activities and makes changes when appropriate. This typically occurs annually. In order to formally evaluate its outreach activities, the HRPP Director 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 HRPP website.
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.

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.

The Yale HIPAA Privacy Office (<https://hipaa.yale.edu/>) houses the Yale policies and procedures related to HIPAA compliance at Yale University.

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

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

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

Genetic Information. Genetic information means, with respect to an individual, information about: (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.

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

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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.

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.

Yale's internal IRB and, when mutually agreed, the external IRBs it relies upon, fulfill 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 considered by the convened IRB, 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 (See Section 11.1). [45 CFR 46.110](#) and [21 CFR 56.110](#) permit an IRB to use an expedited review procedure to review minor changes in previously approved research. 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, because this type of modification may be 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;
4. A brief description of the PHI for which use or access has been determined to be necessary by the IRB to be necessary;
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.

Yale will not release PHI to investigators or other third parties without individual authorization, proper documentation of an IRB or Privacy Board approval of a waiver or alteration of the requirement, or in case of limited data set, an executed Data Use Agreement.

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 Yale, the HIPAA authorization can be documented separately from the research consent form, using HIPAA Research Authorization Form, or combined with the consent document. When Yale cedes IRB review to an external IRB but the Privacy Board functions have been not been delegated to that external IRB, HIPAA authorizations are submitted to the Yale IRB office to verify that the appropriate template is used without inappropriate substantive modification.

Once executed, a signed copy must be provided to the individual providing authorization. Signed authorizations must be retained by the covered entity 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 “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, 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.

27.5 Activities Preparatory to Research

Under the preparatory to research provision of the Privacy Rule, a covered entity may permit a 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.

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The covered entity must obtain from the investigator representations, either in writing or orally, 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. Therefore, if the researcher is not a workforce member or business associate of the covered entity, then the researcher may contact potential subjects only pursuant to a partial waiver of authorization from the cognizant IRB or privacy board, or pursuant to the Authorization of the subject.

At Yale, researchers seeking access to PHI for preparatory reviews (for projects in development) should sign the Yale Request Form For Access To Protected Health Information For Research Purpose (Form 5032, <https://hipaa.yale.edu/policies-procedures-forms>). This form should be provided to the record holder and a copy retained with the research record. To identify potential participants using PHI without individual authorization, investigator must request a partial waiver of authorization for screening purposes to the IRB of record or Yale IRB, if the Privacy Board function has not been delegated.

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.

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At Yale, the attestation option referenced above is accomplished by the investigator submitting a signed Yale University Request Form For Access To Protected Health Information For Research Purposes (Form 5032, <https://hipaa.yale.edu/policies-procedures-forms>) to the record holder. The copy must be retained with the research record.

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 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 can be a stand-alone document or may be incorporated into the authorization for the establishment of a database or repository or for the primary study unless the research involves the use or disclosure of psychotherapy notes. Authorizations for the use or disclosure of psychotherapy notes can only be combined with another authorization for a use or disclosure of psychotherapy notes.

If the authorization for future research is combined with the authorization for the primary study, the authorization must clearly differentiate between the authorization for the primary study and the authorization for the unspecified future research activities and allow 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.

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 form 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 effect 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:

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, 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 individual and is not otherwise capable of being translated to identify the individual. The covered entity may not use or disclose the code or other means of record identification for any other purpose and may not disclose its method of re-identifying the information.

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

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, PHI 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;
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 through [Office of Sponsored Projects](#).

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

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be restored upon conclusion of the clinical trial. Language accommodating this exclusion is included in the applicable Yale authorization 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 Yale, individuals may revoke authorization by telling the study staff or by writing to the Principal Investigator of the study. Withdrawal of authorization may be stored with the subject’s medical record.

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.

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 themselves; 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.

Further information on accounting disclosures for Yale is available in HIPAA Policy 5003: Accounting for Disclosures, <https://hipaa.yale.edu/policies-procedures-forms>.

28 IRB and HRPP Billing

Yale Human Research Protection Program charges a fee for institutional (HRPP fee) and IRB review (IRB fee) of externally supported human subject research protocols (exclusions listed below apply). These fees are consistent with the practices of many IRBs and peer research institutions. The fees collected provide support for the Human Research Protection Program (HRPP) and IRB operations otherwise not recovered by traditional indirect cost rate and overhead assessment. Uses of IRB fees include but are not limited to:

- Subsidizing IRB Committee membership, staff training, and continuing education requirements.
- Supplying informatics and technology related to the HRPP.
- Hiring and developing new staff to meet the demands and the expectations of the research community for both the IRB and HRPP.
- Financial support for the operations and implementation of new initiatives within the HRPP.

28.1 HRPP/IRB Fees Principles and Practices

Research applications submitted to the HRPP office will be reviewed for compliance with institutional requirements and triaged to IRB for ethical review (either internal or external IRB).

Applicable review fees will be sent to the Department of the Principal Investigator upon review of the study. These fees are **non-negotiable** and **non-refundable**.

- The HRPP/IRB review fees are assessments of actual costs associated with each review conducted by the IRB. These fees are Institutional fees independent from the clinical activity.
- HRPP/IRB review fees are not contingent upon a signed executed Clinical Trial Agreement (CTA).
- HRPP/IRB review fees are not assessed overhead and therefore payments should not be combined or co-mingled with clinical payments because clinical payments for clinical activities are assessed overhead.
- HRPP and IRB review fees must be listed in CTA as a separate invoiceable flat fee for local and external review, for each service category (i.e., initial review, renewal, minor amendment, major amendment, and closure). The budget must clearly indicate that the IRB fees are not limited in term or number.
- HRPP/IRB fees should not be incorporated as part of Study Startup costs invoiced by Clinical Institution billing for Study fees because Study Startup fees are assessed overhead.
- HRPP/IRB review fees will be reimbursed at prevailing rates.

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- The payment terms in the contract must include language that in the event that the study is submitted to an external IRB (non-Yale IRB) for IRB Review:
 - Sponsor will cover the costs charged by such external IRB directly, and
 - Sponsor will pay the HRPP administrative fee to Yale for the institutional oversight responsibilities retained by the HRPP.

28.2 Responsibility

IRB fees are regarded as a contractual responsibility of the benefactor funding the study. They are an essential part of the clinical study budget.

HRPP Office:

- The HRPP Office is responsible for invoicing the department for review fees,
- HRPP will create a journal entry for review fees to the Chart of Accounts (COA) related to the study and provided by the investigator at the time of the protocol submission,
- The HRPP will maintain a database of charges and receipts.

Department (Business Office):

- The PI and/or department is responsible for paying the review fees,
- If the HRPP/IRB review fees are included in the budget, the department can invoice the sponsor to recoup the money. Yale Center for Clinical Investigation (YCCI) provides billing services to departments who wish to use their service for study related invoicing.
- For studies that are reviewed by an external IRB, the department or the sponsor is responsible for payment of the external IRB review fees.

28.3 IRB Fees Schedule

Activities on protocols are charged review fee based on the fees schedule. Current HRPP/IRB schedule is posted on [the HRPP website](#). They fees are subject to change based upon the approval of the Yale University Office of Research Administration (ORA) Institutional Official (IO).

28.4 Exclusions

HRPP/IRB submissions for research studies that are fully funded by the following sources are not subject to assessments of review fees:

- Federal, State and Local Government (in whole or in part) except for multi-site studies where Yale serves as the sIRB of record for other sites (only review of other sites is billable),

- Internal grants,
- Department, internal discretionary fund, or other University funds sponsored research,
- Grants or subcontracts from other academic institutions.

In addition, the following types of research studies are excluded from the assessment of review fees:

- Emergency Use/Single Subject INDs protocols,
- Investigator initiated studies with no external support.

28.5 Fees Waiver Request

A waiver of HRPP/IRB review fees will be considered when funding is limited and when the fee will impede the conduct of the clinical research study. The waiver request will be approved or disapproved by the HRPP on a case-by-case basis for extenuating circumstances. Instructions on how to request waivers of review fees are available in the Investigator Manual.

29 Select State Statutes Related to Human Subjects Research

The General Statutes of Connecticut (CGS) are available on the [CT official state website](#). [Office of Legislative Research](#) issues reports summarizing CT legislature. They are searchable by topic on the [CT website](#).

CGS § 1-56r Decision Making Designations

This section allows an individual to designate another person to act on their behalf in certain contexts. In particular, this section allows health care decisions to be made by a personal representative as described in 19a-576.

CGS § 17a-101 et seq. Child Abuse Reporting

Connecticut General Statutes describe who is mandated to report child abuse as well as the content of such reports. Additional information is available on [the Department of Children and Families \(DCF\) website](#).

CGS § 17a-412 and 17b-451 et seq. Elder Abuse Reporting

Connecticut mandates that certain individuals report suspected elder abuse as described in this section. Additional information is available at [the CT Social Work Services resource website](#).

CGS § 19a-583 et seq. Confidentiality of AIDS-Related Information

AIDS-related information is subject to mandated reporting requirements and its disclosure is protected such that patient authorization is required in cases other than those mandated under state law.

CGS § 52-146 et seq. Confidential Communications

Connecticut limits disclosure of certain communications including doctor-patient, psychiatrist-patient, etc. as described in Chapter 899.

CGS § -42-297 Sweepstakes Requirements

Connecticut state law regarding gaming allows “sweepstakes” to be conducted without a license or permit but requires certain information to be disclosed in any advertising, including word of mouth advertising. In particular, such advertisements must include 1) the value of the prize, 2) odds of winning, 3) any restrictions on winning, and 4) name of sweepstakes sponsor. Note that “raffles” and “lotteries” require a permit under state law. Additional information is available on [the CT Department of Consumer Protection website](#).

CGS §46b-150b et seq, Emancipation Statutes

Any minor who has reached his/her sixteenth birthday and is residing in this state, or any parent or guardian of such minor, may petition the superior court for juvenile matters or the probate court for the district in which either the minor or the parents or guardian of such minor resides for a determination that the minor named in the petition be emancipated. These

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statutes set forth the requirements for a minor to be granted an order of emancipation, describe the effect of emancipation, and allow for emancipation under common law. Additional information can be found at the [CT Judicial Branch website](#).

CGS §17a-238 Rights of persons under supervision of Commissioner of Developmental Services

Connecticut state law requires that each person placed or treated under the direction of the Commissioner of Developmental Services in any public or private facility be protected from harm and receive humane and dignified treatment which is adequate for such person's needs and for the development of such person's full potential at all times, with full respect for such person's personal dignity and right to privacy consistent with such person's treatment plan as determined by the commissioner. The involvement of state-protected individuals in human subjects research requires the Commissioner's oversight and monitoring prior to its being undertaken. Additional information is available on the [CT Department of Developmental Services website](#) and [the Office of the Commissioner IRB website](#).

CGS §19a-36-A1 et seq. Reportable disease and laboratory findings

Diseases and results of laboratory tests that are mandated to be reported under state law are described herein. More information is available on the [CT Department of Public Health website](#).

30 ICH-GCP E6

To facilitate the acceptance of data for regulatory review in participating countries, clinical trials subject to ICH-GCP should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and applicable regulatory requirements. Among other ICH-GCP guidelines, ICH-GCP E6 outlines guidelines for investigators, IRBs, sponsors, and others on how to do so.

The Yale University Institutional Review Boards (IRBs) comply with ICH GCP guidance (E6(R2)) only to the extent that it is compatible with FDA and DHHS regulations. However, for industry-sponsored studies with contract requirements for institutional adherence to ICH GCP guidance (E6(R2)), the Yale University IRB will comply with all of the GCP statements outlined in the ICH-GCP (E6(R2)) guidance, provided that: a) The Principal Investigator (PI) indicates in the Institutional Review Board (IRB) application(s) that the sponsor requires the IRB review process to comply with ICH standards, and b) the Office of Sponsored Projects Office confirms it is a contractual requirement. Studies involving only behavioral interventions are not covered by this policy.

When Yale commits to comply with ICH-GCP E6 as a term of a grant or contract, investigators and the IRB take on additional responsibilities. Investigators are responsible for clearly indicating within their IRB application materials that proposed research is subject to ICH-GCP E6 and for attesting to compliance with ICH-GCP E6 guidelines. The Yale IRB will evaluate compliance with the aid of a worksheet and by consulting the current [ICH-GCP E6 guidance](#) posted by the FDA on its website.

30.1 IRB Responsibilities

In general, Yale University apply ICH-GCP guidelines only to the extent that they are compatible with FDA and DHHS regulations. When a sponsor requires institutional ICH-GCP compliance, the IRB will conduct a review in accord with ICH-GCP requirements. In addition to the IRB responsibilities, functions, and procedures outlined elsewhere in this manual, ICH-GCP E6 specifically requires that:

1. An IRB should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects;
2. The IRB/IEC should obtain the following documents:
 - a. Trial protocol(s)/amendment(s);
 - b. Written informed consent form(s) and consent form updates that the investigator proposes for use in the trial;
 - c. Subject recruitment procedures (e.g., advertisements);
 - d. Written information to be provided to subjects;
 - e. Investigator's Brochure (IB) and available safety information;

- f. Information about payments and compensation available to subjects;
 - g. The investigator's current curriculum vitae and/or other documentation evidencing qualifications; and
 - h. Any other documents that the IRB/IEC may need to fulfil its responsibilities.
3. The IRB should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates that actions were taken;
4. The IRB should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB requests;
5. The IRB should evaluate whether the available nonclinical and clinical information on an investigational product is adequate to support the proposed clinical trial;
6. The IRB should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year;
7. The IRB may request more information than is required by regulation or the ICH-GCP E6 guidance be given to subjects when, in the judgment of the IRB, the additional information would add meaningfully to the protection of the rights, safety, and/or well-being of the subjects;
8. When a nontherapeutic trial is to be carried out with the consent of the subject's LAR, the IRB should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials;
9. Where the protocol indicates that prior consent of the trial subject or the subject's LAR is not possible, the IRB should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations);
10. The IRB should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject; and
11. The IRB should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

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30.2 Investigator Responsibilities

In addition to the investigator responsibilities outlined elsewhere in this manual, ICH-GCP E6 specifically requires that:

1. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authorities;
2. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor;
3. The investigator should be aware of, and should comply with GCP and applicable regulatory requirements;
4. The investigator should permit monitoring and auditing by the sponsor, and inspection by appropriate regulatory authorities;
5. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties;
6. The investigator must have adequate resources to conduct the trial, including:
 - a. Being able to demonstrate (e.g., based on retrospective data) the potential for recruiting the required number of subjects within the agreed upon recruitment period;
 - b. Sufficient time to properly conduct and complete the trial within the agreed trial period;
 - c. Adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely; and
 - d. Ensuring that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions;
7. The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site;
8. If the investigator retains the services of any individual or party to perform trial-related duties and functions, the investigator should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to

ensure the integrity of the trial-related duties and functions performed and any data generated;

9. A qualified physician (or dentist, when appropriate), who is an investigator or sub-investigator on the trial, should be responsible for all trial-related medical (or dental) decisions;
10. During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided for any adverse events, including clinically significant laboratory values, related to the trial. The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware;
11. The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and agrees to the primary physician being informed;
12. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights;
13. Before initiating a trial, the investigator must have written and dated approval/favorable opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects;
14. As part of the investigator's application to the IRB, the investigator should provide the IRB with a current copy of the Investigator's Brochure (IB). If the IB is updated during the trial, the investigator should supply a copy of the updated IB to the IRB;
15. During the trial, the investigator should provide to the IRB all documents subject to review;
16. The investigator should sign the protocol, or an alternative contract, to confirm their agreement to comply with the approved protocol;
17. The investigator may not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to trial subjects;
18. In addition to reporting to the IRB, when the investigator implements a deviation from or change in the protocol to eliminate an immediate hazard(s) to subject(s) without prior approval, this must be reported as soon as possible to the sponsor;
19. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol;

20. The investigator is ultimately responsible for investigational product accountability and for all of the responsibilities for investigational product outlined in section 4.6 of ICH-GCP E6;
21. The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor (and IRB) any premature unblinding;
22. Additional requirements for Informed Consent -
 - a. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB's approval in advance of use. The subject or the subject's LAR should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented;
 - b. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's LAR;
 - c. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's LAR ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's LAR;
 - d. Neither the investigator, nor the trial staff, may coerce or unduly influence a subject to participate or to continue to participate in a trial;
 - e. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's LAR, and by the person who conducted the informed consent discussion;
 - f. Prior to participation in the trial, the subject or the subject's LAR should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's LAR should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects;
 - g. If a subject is unable to read or if a LAR is unable to read, an impartial witness should be present during the entire informed consent discussion. After the

written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's LAR, and after the subject or the subject's LAR has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's LAR and that informed consent was freely given by the subject or the subject's LAR.

- h. Consent for non-therapeutic trials (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) must be obtained from subjects who personally give consent and who sign and date the written informed consent form unless the IRB has expressly approved, in writing, that consent from a LAR is permitted;
- i. The consent discussion and written informed consent form should include the following additional elements:
 - i. An explanation of the trial treatment(s) and the probability for random assignment to each treatment;
 - ii. An explanation of the subject's responsibilities (avoiding any language that appears to restrict subject's rights);
 - iii. An explanation that the monitor(s), auditor(s), the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or LAR is authorizing such access;
 - iv. An explanation of the anticipated prorated payment, if any, to the subject for participating in the trial;
 - v. An explanation of the reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant;
 - vi. When there is no intended clinical benefit to the subject, the subject should be made aware of this;
 - vii. An explanation that, to the extent permitted by applicable laws or regulations, records identifying the subject will not be made publicly available, and, if the results of the trial are published, the subject's identity will remain confidential; and

- viii. A statement that the trial has the approval of the IRB.
23. Investigators must comply with the requirements for records and reports outlined in section 4.9 and 8 of ICH-GCP E6;
24. Investigators must comply with the requirements for safety reporting outlined in Sections 3.3.8 and 4.11 of ICH-GCP E6 (to the extent required by FDA regulations and the IRB of record) including the redaction of personally identifying information; and
25. Investigators must comply with the requirements for premature termination or suspension of a trial outlined in section 4.12 of ICH-GCP E6 including the requirements for sponsor and IRB reporting.

31 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 types 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.

31.1 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 Yale that includes the use of coded private information or specimens may be submitted for a “Human Subjects Research Determination” (See Section 4) or IRB review if the repository holder requires official determination or IRB approval.

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.

31.2 Research Repositories

Research repositories involve three distinct activities:

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

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3. Distribution of data/specimens.

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

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

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 have access to or be provided with the key or other means to re-identify; and
- Agreements with recipient investigators specifying the terms of use.

31.2.1 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. IRB review is not required 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. Research under the auspices of Yale that includes the use of coded private information or specimens may be submitted for a “Human Subjects Research Determination” (See Section 4) or IRB review if the repository holder requires official determination or IRB approval.

32 Research Involving or Generating Genetic Information

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

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

1. Is the testing intrinsic to the study? If not, has participation in the genetic testing component been provided as an opt-in?
2. Will test results be given? Is there an appropriate plan for return of results?
3. Will the subject or family member be provided the option to receive or not receive results? How will this decision be recorded?
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. Are there any practical limitations 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)? If so, what are they?
12. How will the information and/or biological materials be protected and who will have access?

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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 35)
15. Will the specimens, cell lines, or genetic information be stored and/or made available for future research? Is this provided as an opt-in when not intrinsic to the study?

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

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

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).

32.1 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;

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- If health insurance companies and health plans do receive such genetic information, they may not use it to make decisions regarding coverage, rates, or preexisting conditions; and
- Employers with 15 or more employees generally may not use genetic information for hiring, firing, promotion, or other decisions regarding terms of employment.

GINA’s protections do not extend to life insurance, disability insurance, or long-term care insurance.

GINA defines genetic information as information about:

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

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

The Yale 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 the Consent Glossary available in the Library section of the HRPP electronic system, which is a compilation of preferred research related terms for consent forms.

32.2 Genetics and State Law

Investigators must ensure that the research they conduct conforms with applicable law. When developing and conducting research involving genetic information in Connecticut, the following should be considered:

Connecticut statutes define genetic information broadly, as “information about genes, gene products or inherited characteristics that may derive from an individual or family member” (Connecticut General Statute [CGS] 38a-816, CGS 46a-60). Neither the term ‘family member’ nor ‘genetic testing’ is defined in the statutes.

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Connecticut statutes put restrictions on the use of genetic information for provision of insurance or employment purposes. Specifically, health insurers are prohibited from determining eligibility and risk classification based on genetic information. Like GINA, Connecticut statutes prohibit use of genetic information in hiring, firing, job assignments, compensation, and promotions and prohibits employers from requesting, requiring, or purchasing genetic information about an employee or family member. While GINA only applies to employers with 15 or more employees, Connecticut statutes apply to employers with three or more employees (CGS 46a-60).

When conducting research in other jurisdictions, investigators must ensure that the research conforms with applicable law in that jurisdiction. Investigators should be prepared to provide information on relevant law and their plans to ensure compliance to the IRB of record for the study, whether it is Yale IRB or another. Investigators may consult with the HRPP office as needed.

33 Incidental Findings with Possible Health and Safety Significance for Research Participants

Research protocols under purview of Yale must make adequate provision for monitoring the data collected to ensure the safety of participants. In the course of study monitoring, information may be identified that may impact the safety and/or wellbeing of the participants. When a finding is obtained with possible health or safety impact, the researcher should consider the relevant data and determine when it may be in the best interest of promoting the health or safety of the participants to contact, or re-contact the research participants to relate the relevant findings.

Whenever possible, the potential for findings with possible health or safety significance should be anticipated in the design of the research plan. The investigator should inform the participants regarding whether or not research results will be shared with them, and the plan for this should be in the protocol. In some cases, these anticipated communications would be limited to incidental findings that fall above a pre-defined threshold or test score.

Studies that have a reasonable possibility of generating clinically meaningful findings should retain the ability to re-contact participants while the test result is being analyzed so that communication with the participant is practicable. The necessary information to retain may include contact information and be kept linked to the tests until the results are known, after which time the link to contact information can be destroyed as appropriate. For instance, studies that involve administering validated, diagnostic psychological assessments that may require follow-up intervention or studies that involve brain scans that may uncover suspicious lesions should retain a means to contact participants until the outcome of the test is reasonably known.

In a study where communication of test results to study participants is anticipated, the communication plan must be described in the protocol and approved by the IRB. If the approved protocol does not include description of the communication plan to relate findings with potential to impact the health or safety of research participants, the communication requires further IRB approval prior to sharing the result with the participants.

When the potential need to share study findings with a research participant has arisen unexpectedly, the PI must submit a request for communicating the results to the participant to the IRB for its review. The IRB will consider the plan on either a study-wide or on a case-by-case basis, as appropriate, and generally will approve the disclosure of results with possible impact on participant health or safety when:

- The research test or evaluation is standard-of-care, is tested by a CLIA-certified (or equivalent) laboratory, and is performed consistent with good clinical practice by a qualified, certified clinician, or

- The research test is investigational in some aspect or is not performed by a clinician trained to interpret the clinical significance of the results, but extenuating circumstances warrant contacting the participant about the results. Such extenuating circumstances include when the findings are scientifically valid and confirmed (or confirmable), have significant implications for the participant's health, safety, or welfare, and a course of action to ameliorate or treat the participant's concerns is available, or
- The information was not anticipated to be obtained but suggests an imminent risk of harm to the participant or others which has the potential to be ameliorated through re-contacting the participant.

Disclosure of clinically meaningful findings should be conducted by a licensed physician (or psychologist, genetic counselor, or other professional as appropriate) whenever possible. If non-professional study personnel are responsible for conveying test results, they must be trained and supervised by professional/clinical study personnel. A description of the appropriately trained study personnel responsible for disclosing the participant findings must be included in the research plan when the plan for disclosure is submitted to the IRB for approval.

34 NIH Data Management and Sharing

Yale complies with the [NIH Data Management and Sharing Policy](#), to promote the sharing of scientific data via submission of said data into an NIH-supported Scientific Data Repository. The intent of NIH's policy is to accelerate biomedical research discovery, in part, by enabling validation of research results, providing accessibility to high-value datasets, and promoting data reuse for future research studies.

Research Covered by 2003 NIH Data Sharing Policy

NIH's 2003 Data Sharing Policy applies to research that fulfills all of the following conditions:

- The research is supported by NIH through grants, cooperative agreements, intramural research, contracts, or other funding agreements.
- The applicant sought \$500,000 or more in direct costs in any year of the proposed project periods.
- The application was submitted on or after October 1, 2003, but before January 25, 2023.

NIH's 2003 Data Sharing Policy applies to the sharing of **final research data**. Note that if an applicant seeks NIH support to transform or link datasets (as opposed to generating a new set of data), NIH's 2003 Data Sharing Policy still applies.

Final research data is recorded factual material commonly accepted in the scientific community as necessary to document and support research findings. For many scientific areas, final research data includes both raw data and analyses conducted on the data. For example, final research data for a clinical study would include a dataset that was used in the published study, but not the clinical documents (for example, medical records) that the dataset was derived from.

For details, see [Research Covered by 2003 NIH Data Sharing Policy](#).

Research Covered by the 2023 Data Management & Sharing Policy

The NIH Data Management & Sharing (DMS) Policy, effective January 25, 2023, applies to all research, funded or conducted in whole or in part by NIH, that results in the generation of **scientific data**.

Scientific Data is defined as data commonly accepted in the scientific community as of sufficient quality to validate and replicate research findings, regardless of whether the data are used to support scholarly publications.

- Scientific data **includes** any data needed to validate and replicate research findings.
- Scientific data **does not include** laboratory notebooks, preliminary analyses, completed case report forms, drafts of scientific papers, plans for future research, peer reviews, communications with colleagues, or physical objects such as laboratory specimens.

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For details, see [Research Covered by the 2023 Data Management & Sharing Policy](#).

34.1 IRB Submissions and DMS Plans

Sample language and points to consider when developing informed consent documents for data sharing is available in the NIH resource [Informed Consent for Secondary Research with Data and Biospecimens](#) (May 2022) and Consent Glossary available in IRES IRB. There may be limits on data sharing based on content of the informed consent process.

At the time of the institutional review of the initial protocol submissions for compliance with local requirements and during review of modifications to add new federal funding to approved research studies, the Yale HRPP will review the grant proposal for the following information about the proposed data sharing and management plan, as applicable:

- The name of the [NIH data repository/database](#) that data will be submitted to;
- Whether the data will be restricted through controlled access;
- Whether there are any data use limitations;
- The plan for informed consent and the proposed consent language (when informed consent requirements are not waived by the IRB); and
- A copy of the DMS Plan approved by NIH.

The HRPP will communicate to the reviewing IRB should any discrepancies between the research protocol and grant proposal be identified. The IRB will review the proposal for data management and sharing as described in the research protocol in accordance with the criteria for approval of research. The IRB may request revisions to a DMS Plan. NIH approval is needed for any DSM Plan revisions. For more information, see [Revising Data Management and Sharing Plans](#).

Investigator considerations when developing a Plan to share data from human subjects are outlined in NIH guidance:

- Research Covered by 2003 NIH Data Sharing Policy
 - [Sharing Data from Human Research Participants](#)
- Research Covered by the 2023 Data Management & Sharing Policy
 - [Protecting Privacy When Sharing Data from Human Participants](#)
 - [Responsible Management and Sharing of American Indian/Alaska Native Participant Data](#)

Investigators must follow all applicable federal, Tribal, state, and local laws, regulations, statutes, guidance, and institutional policies that govern research involving human participants and the sharing and use of scientific data derived from human participants. NIH also respects Tribal sovereignty, even in the absence of written Tribal laws or policies.

NIH Guide Notices:

- NOT-OD-22-214: [Supplemental Information to the NIH Policy for Data Management and Sharing: Responsible Management and Sharing of American Indian/Alaska Native Participant Data](#)
- NOT-OD-22-213: [Supplemental Information to the NIH Policy for Data Management and Sharing: Protecting Privacy When Sharing Human Research Participant Data](#)
- NOT-OD-22-198: [Implementation Changes for Genomic Data Sharing Plans Included with Applications Due on or after January 25, 2023](#)
- NOT-OD-22-189: [Implementation Details for the NIH Data Management and Sharing Policy](#)
- NOT-OD-21-016: [Selecting a Repository for Data Resulting from NIH-Supported Research](#)
- NOT-OD-21-015: [Allowable Costs for Data Management and Sharing](#)
- NOT-OD-21-014: [Supplemental Information on Elements of an NIH Data Management and Sharing Plan](#)
- NOT-OD-21-013: [Final NIH Policy for Data Management and Sharing](#)
- NOT-OD-14-124: [NIH Genomic Data Sharing Policy](#)
- NOT-OD-04-042: [NIH Policy on Sharing of Model Organisms for Biomedical Research](#)
- NOT-OD-03-032: [Final NIH Statement on Sharing Research Data](#)

35 Genomic Data Sharing (GDS)

Yale 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.

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 35.

35.1 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.

35.2 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, including GSR. **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 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/IRB 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 Yale 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 or should be classified as restricted access or unrestricted access;
- Whether the data is or should be classified as sensitive (e.g., studies involving populations from isolated geographic regions or with rare traits, studies that include data on potentially stigmatizing traits, etc.);
- Whether there are any data use limitations or modifiers (e.g., use limited to a specific disease, restricted to not-for-profit organizations, IRB approval requirement, etc.);
- The plan for informed consent and the proposed consent language; and

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- A copy of the genomic data sharing plan, if not already included in the grant application. For NIH studies subject to the 2023 Data Management and Sharing Policy, the genomic data sharing plan is encompassed in the DMS plan (see Section 34 above).

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 Yale 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.

36 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 are summarized below.

CoC's are obtained as follows:

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

Additional information about CoCs and the application process for research not covered by the NIH policy is available on the [NIH CoC Website](#). Information about discretionary CoC's issued by FDA is available in the FDA guidance document: [Certificates of Confidentiality](#).

36.1 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.

36.2 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 individual to whom the information pertains, be admissible as evidence or used in any action, suit, or other judicial, legislative, or administrative proceeding.

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

Nothing in the rule ([42 U.S.C. 241\(d\)](#)) may be construed to limit the access of a subject to information about themselves collected during the research.

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

36.3 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 expand 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

36.4 FDA

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

Investigators and institutions are responsible for determining when research with FDA support is covered by a CoC and for ensuring compliance with the requirements of 42 U.S.C. 241(d). Awardees are expected to ensure that any investigator or institution not funded by FDA who

receives a copy of identifiable, sensitive information protected by these requirements, understand they are also subject to the requirements of 42 U.S.C. 241(d). Awardees are also responsible for ensuring that any subrecipient that receives funds to carry out part of the FDA award involving a copy of identifiable, sensitive information protected by these requirements understand they are also subject to subsection 42 U.S.C. 241(d).

When research is not funded by the FDA but involves “the use or study of a product subject to FDA’s jurisdiction and subject to FDA’s regulatory authority” (e.g., a clinical investigation of a drug, device, or biologic), the sponsor or sponsor-investigator can [request a discretionary CoC from the FDA](#). Information about discretionary CoC’s issued by FDA is available in the FDA guidance document: [Certificates of Confidentiality](#).

36.5 NIH, CDC, and FDA CoC Determination

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

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

36.6 Application Procedures for Research Not Automatically Issued a CoC

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

When a researcher is conducting a 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](#)). 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.

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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 is not needed because the Privacy Certificate makes identifiable data immune from any legal action.

When research is not funded by the FDA but involves “the use or study of a product subject to FDA’s jurisdiction and subject to FDA’s regulatory authority” (e.g., a clinical investigation of a drug, device, or biologic), the sponsor or sponsor-investigator can [request a discretionary CoC from the FDA](#). When FDA funds or conducts research, a CoC is automatically issued.

CoCs may also be issued by other Federal agencies and departments, such as [SAMHSA](#) and [HRSA](#).

For more information, see the [NIH CoC Website](#).

36.7 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 or is pending. 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 or CDC requirements.

When reviewing research under a CoC, the Yale IRB will evaluate whether the research plan is consistent with the obligations to protect information and specimens under a CoC and, when consent will be obtained, whether the proposed consent language or other form of notification properly discloses the CoC and appropriately describes the associated protections and limitations. Sample consent language is available on the [NIH CoC Website](#) and the Consent Glossary in the IRB electronic system.

When 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.

37 Self-Experimentation

Self-experimentation refers to research in which the experimenter conducts the experiment on themselves. It can be in the form of a single-subject study where the experimenter is the only participant in the research or is one of the participants in research that involves multiple subjects.

The regulations do not regard research on oneself as different than research on others. When self-experimentation meets the definition of human subject research, review and approval by the IRB is required. Similarly, members of the research staff who wish to act as participants in their own research protocols should consider themselves human subjects. IRB approval is required prior to commencing any research activity that involves self-experimentation.

The IRB will review each protocol (or an amendment to add self-experimentation) and determine the appropriateness of the research. The IRB will consider as part of its review the level of self-experimentation and the potential risks and benefits to the investigator as a research subject. A main concern for the IRB when reviewing a protocol that involves self-experimentation is that investigator's bias when generating new knowledge may outweigh the investigator's concern for his/her own welfare. For this reason, the IRB may institute additional safeguards for the research project such as an addition of an independent research monitor. In addition, when members of the research team enroll in the study, the IRB will review the research in accordance with policy on enrollment of Yale employees.

The informed consent regulations are important to consider when an investigator proposes to participate as a research subject in their own protocol. A standard consent form must be developed and include all of the required elements. In addition, the IRB may ask that the consent form (or consent addendum) include an additional attestation from the investigator indicating that they intend to voluntarily conduct the procedures as described in the approved protocol and consent form on themselves and is aware that the procedures are considered research on human subjects.

38 Student Research

38.1 Human Subject Research and Course Projects

Learning how to conduct ethical human subject research is an important part of a student's educational experience. Research activities that are designed as part of a course requirement for purposes of learning experience only and are **not** "designed to develop or contribute to generalizable knowledge" **may** not require IRB review and approval if all of the following conditions are true:

1. Results of the research are viewed only by the course instructor for teaching purposes and discussed within the classroom for teaching and learning purposes;
2. Results of the research are not made public through presentation (outside of the classroom) and are not published in paper or electronic format (e.g., cannot be made available on the internet, cannot be published in a journal, etc.);
3. Research procedures are no more than minimal risk;
4. Permissions are obtained from any facilities or organizations where research activities, including recruitment, will take place;
5. Vulnerable populations are not targeted (e.g., children under age 18, prisoners, persons who are cognitively impaired, etc.);
6. Data collected are recorded in such a manner that the subjects are not identifiable (images in videotapes and photographs and voices on audiotape are identifiable); and
7. When appropriate, an informed consent process is in place.

38.1.1 Responsibility of the Course Instructor:

The course instructor is responsible for ensuring the protection of human subjects (including a process for obtaining voluntary informed consent from research subjects when appropriate), and for monitoring the students' progress.

When designing a project, students should be instructed on the ethical conduct of research and on the preparation of the IRB application when such is required. In particular, instructors and students should:

1. Understand the principles of the Belmont Report and their application;
2. Develop appropriate consent documents and an appropriate consent process;
3. Plan appropriate strategies for recruitment;
4. Identify and minimize potential risks to subjects or others;
5. Assess the risk-benefit ratio for the project;

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6. Establish and maintain strict guidelines for protecting privacy and confidentiality; and
7. Allow sufficient time for IRB review, if applicable, and completion of the project.

In making a determination of whether or not a class research project requires IRB review, the instructor is encouraged to contact the HRPP/IRB office for assistance or to submit a for a determination following the procedures outlined in Section 4.

38.2 Individual Research Projects Conducted by Students

When students conduct, or participate as a research team member, in human subjects research other than class work as described above, they must follow the standard procedures for research described throughout this manual, as applicable to the research. Students may only serve as PI on human subjects research conducted under the auspices of Yale under the supervision of a Yale Faculty Advisor who meets Faculty Handbook requirements to serve as a PI. Students may serve as a sub-investigator or member of the research team. When students of Yale conduct, or participate as a research team member, in research at or with another organization, they must contact the Yale HRPP/IRB office to determine if review by the Yale IRB is required, or if a reliance agreement is needed, prior to engaging in the activity. It is important to keep in mind that any human subject research activity that will ultimately contribute to part or all of a thesis, dissertation, or other type of publication or presentation must go through the IRB review process prior to enrolling subjects and collecting data. IRB review/approval cannot occur after a study has begun.

Students and advisors should contact the IRB Office with any questions.

39 Community Based Research

Community based research (CBR) is research that is based in a community and conducted in collaboration with members of that community. *Community* is often self-defined, but general categories of community include geographic community, a community of individuals with a common problem or issue, or a community of individuals with a common interest or goal.

Where research is being conducted in communities, investigators are encouraged to involve members of the community in the research process, including the design and implementation of research and the dissemination of results when appropriate.

The most significant community involvement is in a subset of CBR called Community Based Participatory Research (CBPR) where there is an equal partnership between the academic investigators and members of a community, with the latter actively participating in all phases of the research process including the design and implementation of research and the dissemination of results when appropriate.

Questions to be considered as CBR studies are developed, and issues that the IRB will consider when reviewing CBR, are as follows:

- How was the community involved or consulted in defining the need for the proposed research (i.e., getting the community's agreement to conduct the research)?
- How was the community involved or consulted in generating the study research plan?
- How will the research procedures, including recruitment strategies and consent processes be assessed to ensure sensitivity and appropriateness to various communities (e.g., literacy issues, language barriers, cultural sensitivities, etc.)?
- How will the community be involved in the conduct of the proposed research?
- How will community members who participate in the implementation of the research be trained and supervised?
- How have "power" relationships between investigators and community members on the research team, and in subject recruitment strategies been considered to minimize coercion and undue influence?
- What are the risks and benefits of the research for the community as a whole?
- How will boundaries between multiple roles (e.g., investigator, counselor, peer) be maintained, i.e., what happens when the investigator/research staff is the friend, peer, service provider, doctor, nurse, social worker, educator, funder, etc.)
- How will the research outcomes be disseminated to the community?
- Is there a partnership agreement or memorandum of understanding to be signed by the investigator and community partners that describes how they will work together?

Investigators conducting community-based research are encouraged to work with the [Cultural Ambassadors Program](#) at Yale, which is available to:

- Participate in projects, community engagement activities and community events designed to promote and increase participation in clinical trials.
- Assist in the development of recruitment plans for specific trials.
- Assist in the development of protocols for specific trials.
- Provide translation services for informed consents and other materials into Spanish.

40 Transnational Research

The Yale 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.

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 an 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 Yale 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, Yale 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. When appropriate, the IRB communicates and coordinates with the local institutions or ethics committees.

In settings where there are no IRBs/ECs, Yale 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 Yale 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 Yale IRB with recommendations based on his or her expertise.

40.1 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 approvals and permissions to conduct the proposed research (e.g., institutional, governmental or ministerial, IRB, local, or tribal);
7. When applicable, whether the investigator has provided an appropriate plan, and any necessary supporting documentation, to comply with the requirements of country law for investigational articles; and
8. Mechanisms for communicating with the investigators and research staff when they are conducting the research in other countries.

40.2 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 approvals and permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local, or tribal);
4. Complying with the requirements of country law; including, when applicable, requirements for research involving investigational articles and requirements for data management and privacy such as [EU GDPR](#);
5. 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

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to be able to communicate with subjects throughout the study (e.g., to ask and answer questions);

6. Ensuring that the following activities will occur:
 - a. Initial review, continuing review (when required), and review of modifications;
 - b. Post-approval monitoring of the conduct of the research in accordance with the plan approved by the IRB; and
 - c. Management and reporting of complaints, noncompliance, unanticipated problems involving risk to subjects or others, and other issues that arise in accordance with the research plan, the requirements of the IRB, and the requirements of the locale where the research takes place;
 - d. Not relying upon an IRB or EC that does not have policies and procedures for the activities listed above;
 - e. 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
 - f. Ensuring that there are mechanisms for communicating with the IRB when they are conducting the research in other countries.

40.3 Consent Documents

The informed consent documents must be appropriate for and in a language understandable to the proposed subjects. The IRB will review the proposed document in English. Translated versions of the consent documents must be submitted to the IRB for approval. IRB may ask for a back translation /of the exact content contained in the foreign language informed consent document, with the credentials of the translator detailed in the IRB application or Modification Request form. All documents, including verification of the back translation when applicable, are maintained in the IRB file.

40.4 Monitoring of Approved Transnational 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 may require documentation of regular correspondence between the Yale investigator and the foreign institution or site and may require verification from sources other than the Yale investigator that there have been no changes made to the research since its last review. Yale investigators receive annual reminders on the anniversary date of the IRB approval about a

requirement to submit reportable events and modification requests prior to their implementation to the IRB for review and approval.

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41 Lead Investigator/Coordinating Center

When Yale IRB is serving as the IRB of record for a PI or site who is serving as the lead investigator or lead/coordinating center of a multi-site or collaborative research project, the PI must describe within the protocol and IRB Submission Form how the research will be overseen and how issues relevant to the protection of human subjects (e.g., IRB initial and continuing approvals, study modifications, reports of unanticipated problems, interim results, data-safety monitoring, etc.) will be coordinated and communicated among participating sites and investigators. For FDA-regulated clinical trials, the plan should address the plan for study monitoring and for the reporting and evaluation of adverse events, significant new risk information, and any other reports mandated by regulation or policy.

The lead PI or lead/coordinating center is responsible for serving as the liaison with other participating sites and investigators and for ensuring that all participating investigators obtain IRB review and approval prior to initiating the research, maintain approval, and obtain IRB approval for modifications to the research. The Yale IRB will evaluate whether the plan for research oversight and management of information that is relevant to the protection of human subjects is adequate.

42 Research Involving the VA Connecticut Healthcare System

Yale University and the VA Connecticut Healthcare System in West Haven, CT (the VA) are separate entities and each maintains its own Federal Wide Assurance and institutional review board (IRB). As such, any non-exempt human subjects research conducted by Yale faculty at both Yale and the VA requires the approval of both a Yale IRB and the VA IRB.

42.1 Review of Studies Conducted at Yale and the VA

For any non-exempt studies that will be conducted both at Yale and the VA, the Principal Investigator (PI) must complete both Yale and VA forms and all required attachments for new applications, renewals, and amendments. No such research can begin, continue, or be modified until the PI receives approval from both the Yale IRB and the VA IRB.

42.2 Review of Studies Conducted at the VA Only

All studies that Yale faculty conduct at the VA and not at Yale must be approved by the VA's IRB.

For all new studies that take place entirely at the VA, the PI must complete only the VA IRB forms and all required attachments. No Yale forms are required to be completed and submitted to either the VA or Yale IRB.

When Yale faculty conduct studies **entirely** at the VA, Yale University is deemed to be not engaged in the research, if all of the following are true:

- The human subjects research does not take place at Yale facilities, in whole or in part;
- The human subjects research is not funded with Yale funds, including sponsored awards from an external sponsor administered by Yale;
- The human subjects research uses only Connecticut VA Health System resources or non-Yale resources; and
- Any Yale employees involved in the human subjects research are working in other than their capacity as a Yale employee.

The VA IRB Request to Review Research Project (Initial Review Application) will include items requiring Principal Investigators to state whether each of the above conditions has been satisfied and thus enable them to determine whether Yale is engaged in the research. If Yale is not engaged in the research, the Principal Investigator is not required to submit the study to the Yale IRB for its review and approval.

When Yale is not engaged in the research (e.g., not prime, not involved in the design, conduct, or analysis of the research – see Section 1.8 for more information) the study is reviewed by the VA per local requirements.

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When Yale is engaged in the research, the study must be submitted to the Yale IRB and the VA IRB. The VA IRB is responsible for reviewing compliance with VA requirements. When Yale is engaged and conducting research at Yale all institutional requirements apply. If the research activities are not occurring at Yale but Yale is engaged, then Yale IRB will review the study but only apply relevant institutional requirements depending on the nature of the engagement.

NOTE: Federally funded studies engaging Yale and VA will also require review by both IRBs. The VHA DIRECTIVE 1200.05(2), Section 5 (f)(8)(c), specifically prohibits VA IRB to serve as the IRB of record for non-VA institutions. Upon receipt of the research submission, the local VA Human Research Protections Administrator will submit an exception request to the Office of Research and Development (ORD) who has the authority to grant exceptions from the use of a single IRB for VA Facilities participating in research subject to the cooperative research provisions. The approval of the exception is kept by the VA IRB.

43 Department of Defense

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

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

Investigators conducting DoD supported research must complete and submit the Yale IRB DoD Application Supplement in addition to the protocol materials submitted to the IRB for initial review. The supplement application, entitled 'Human Research Protocol Application Supplement For Research Funded by the Department of Defense (DoD) or Army, Office of Naval Research, Air Force or Marine Corps Components' can be found in the Library section of the IRB electronic system. This supplement aids the investigator and the IRB in ensuring compliance with unique DoD requirements.

In addition to requirements set by the funding agency, investigators conducting human research supported by the DoD or its components (Army, Navy, Air Force Marine Corps) must comply with contracting requirements and processes required of [Yale's Office of Sponsored Projects](#).

Yale IRB will review DoD research in accordance with the Common Rule (at [32 CFR 219](#)) and applicable DoD requirements, including:

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

It is the responsibility of the PI to ensure compliance with DoD requirements for human subject research. HRPP staff, chairs and members will use these policies and procedures, DoDD 3216.02, the HRP-318 Additional Federal Criteria worksheet, and any relevant DoD Component-specific instructions or materials to guide the IRB review and oversight of DoD research.

43.1 Activities Not Considered Human Subjects Research ('excluded activities')

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

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

43.2 Single (sIRB) Mandate

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

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

When a DoD institution is engaged in a DoD-covered research study and is relying upon the Yale IRB, each of the following conditions must be met:

- Each institution engaged in non-exempt human subjects research must have a current FWA.
- The Yale IRB must be registered in accordance with 45 CFR 46 Subpart E.
- The DoD institution must review the protocol to ensure that all applicable local and DoD requirements are addressed.
- The DoD institution and Yale have a written reliance agreement defining the responsibilities and authorities of each institution in complying with all legal requirements, including that the IRB will apply the DoD requirements outlined in DoDI 3216.02, including the institutional responsibilities outlined in Section 3.6(b).
- If the research is classified, the Component OHRP must approve the agreement to rely on Yale's IRB.

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

43.3 Education and Training

All personnel involved in the conduct of DoD research must complete initial and continuing education in the protection of human subjects as described in this manual (see Section 3). Personnel must also familiarize themselves with DoD's specific requirements by reviewing these policies and procedures, [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.

43.4 Selection of Subjects

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

43.5 Evaluating Risk

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

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

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

43.6 Informed Consent/HIPAA Authorization

43.6.1 Additional Consent/Authorization Elements

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

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

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

When a DoD component will acquire data under a pledge of confidentiality for exclusively statistical purposes, the data may not be disclosed in identifiable form for any other purpose unless consent is obtained.

43.6.2 Limitation of Waivers and Alterations of Informed Consent

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

Per [DoDI 3216.02](#), research involving a human being as an experimental subject is defined as:

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

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

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

The requirement for advanced informed consent may be waived (e.g., for planned emergency research) by the DoD Office for Human Research Protections ([DOHRP](#)) or its delegate if the following conditions are met:

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

Investigators are responsible for ensuring that all DoD requirements are met before initiating the research. Investigators who wish to seek a waiver of the requirement for advanced informed consent should consult with the relevant DoD component’s Human Research Protections Office. Documentation of DoD approval for the waiver should be provided to the IRB.

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

43.6.3 Posting of Clinical Trial Informed Consent Forms

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

43.7 Additional Protections for Human Subjects

43.7.1 Pregnant Women, Fetuses, or Neonates as Subjects

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

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

Explicit written approval is required from the DOHRP before the research begins for research that would not otherwise be approvable under Subpart B but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

43.7.2 Prisoners as Subjects

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

- In addition to the four allowable categories of research involving prisoners in Subpart C, two additional categories are allowable:
 - Certain epidemiological research in accordance with the HHS waiver published in [Federal Register, Volume 68 pages 36929-36931](#) that meets the requirements of [45 CFR 46 Subpart C](#), [DoDD 3216.02](#), and other applicable requirements.
 - Research that would meet the criteria for exemption described at [32 CFR 219.104](#), but such research must first be approved by an IRB and meet the

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requirements of [45 CFR 46 Subpart C](#), [DoDD 3216.02](#), and other applicable requirements.

- When a previously enrolled human subject becomes a prisoner, and the research was not previously approved for the inclusion of prisoners:
 - The PI must promptly notify the IRB, and
 - Yale must notify the HRPO and other federal agencies (if required).
 - The HRPO must concur with the IRB before the subject can continue to participate while a prisoner.

43.7.3 Children as Subjects

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

Detainees or Prisoners of War

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

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

43.7.4 DoD-Affiliated Personnel as Subjects

The recruitment and inclusion of DoD-affiliated personnel (i.e., Service members, Reserve Service members, National Guard members, DoD civilians, and DoD contractors) in research must be approached with care and in accordance with the requirements of DoDI 3216.02 and any applicable DoD-component requirements. DoD considers DoD-affiliated personnel to be vulnerable to coercion and undue influence due to the nature of the command structure of defense organizations.

Investigators who intend to recruit DoD-affiliated personnel are advised to seek collaboration with a military investigator familiar with DoD and service-specific requirements. A letter of support from Commanders of military facilities or units in which recruitment will occur or the study will be conducted may be required by the Component HRPO and the IRB. Some military sites may also require that personnel seek written permission from their supervisor prior to participation in research.

When the research includes surveys of DoD personnel, investigators are responsible for ensuring that the survey(s) are submitted to and approved by the DoD Information

Management Control Officer (IMCO) prior to implementation but after the research is approved by the IRB. When a survey crosses DoD components, investigators are responsible for ensuring that any additional DoD-required reviews and approvals take place before implementing the survey.

Specific requirements of [DoDI 3216.02](#) include the following:

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

information provided about the research is consistent with the IRB-approved script and materials, including digitally provided materials.

- Should be available to address DoD-affiliated personnel's concerns about participation.
- Compensation, including non-monetary compensation, to DoD-affiliated personnel for participation in research while on duty is prohibited other than compensation for blood draws (maximum of \$50 per blood draw) in accordance with [24 U.S.C. 30](#). Personnel may be compensated for participation in research when not on duty (e.g., off-hours) in reasonable amounts consistent with local standards and the nature of the research. Plans to compensate subjects must be approved by the IRB.

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

43.8.1 LSGD Definition

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

43.8.2 Requirements for LSGD Research

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

- The disclosure of DoD-affiliated personnel's genomic data may pose a risk to national security; accordingly, such research requires administrative, technical, and physical safeguards commensurate with risk, including the secondary use or sharing of de-identified data or specimens.
- All research involving LSGD collected from DoD-affiliated personnel must be covered by a Certificate of Confidentiality (CoC). Exceptions to the CoC must be listed in the informed consent form. For more information on CoC's see Section 35 of this manual.
- Research involving LSGD collected from DoD-affiliated personnel is subject to DoD Component security review to ensure the adequacy of the proposed administrative, technical, and physical safeguards, including the secondary use or sharing of de-identified data or specimens.

43.9 Classified Research

Yale does not currently conduct Classified Research. Investigators who seek to engage in such research must seek special permission from Yale's IO who will engage other appropriate organizational leaders in the decision-making process.

43.10 Chemical or Biological Agents

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

Yale does not intend to engage in DoD conducted or supported research involving the above-noted exceptions. Investigators who seek to engage in such research must seek special permission from Yale's IO who will engage other appropriate organizational leaders in the decision-making process.

43.11 International Research

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

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

43.12 DoD HRPO Approval for Human Subjects Research

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

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

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Investigators are responsible for ensuring that all DoD-required reviews and approvals take place before the research commences.

43.12.1 Non-Exempt Human Subjects Research (HSR)

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

- Documentation that the DoD-supported HSR has been reviewed and approved by an IRB, including scientific merit, amendments, and additional reviews.
 - The IRB may rely on outside experts to provide an evaluation of scientific merit.
- Documentation of key investigators' human research protection training.
- IRB-approved protocol documents.
- Current FWA and IRB registration numbers.
- Any other information required by the Component. The required information would be listed in the DoD Extramural Submission Instruction for the relevant Component, which must be submitted to the IRB with all other study documentation for IRB review.

43.12.2 NHSR and Exempt Human Subjects Research

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

43.12.3 Component-Level Administrative Review

Certain categories of non-exempt human subject research require Component-level administrative review (CLAR) and approval in addition to IRB and CHRPO approval. These categories include:

- Research that will be conducted in a foreign country unless the research will be conducted by a DoD overseas institution, or the research only involves DoD-affiliated personnel who are U.S. citizens.
- The involvement of DoD personnel in the conduct of the research is secondary to that of the non-DoD institution.
- Research involving a human being as an experimental subject that requires a waiver of informed consent under [10 U.S.C. 980\(b\)](#).
- The research involves any fetal or fetal tissue research subject to [42 U.S.C. 289g-289g-2](#).

- The research involves the collection of LSGD from DoD-affiliated personnel. Such research must also undergo DoD Component security review before the research can begin.
- Classified research.
- Research that requires approval by the DoD Office for Human Research Protections (DOHRP).

CLAR also includes review of IRB reliance agreements, when applicable.

Investigators are responsible for ensuring that all DoD-required reviews and approvals take place before the research commences.

43.13 Reporting Requirements

Yale HRPP/IRB or Yale PI, as applicable, must promptly (i.e., no longer than within 30 days or as defined by the DoD Component) notify the Component Office of Human Research Protections (COHRP) of the following:

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

Note: Investigators should be aware that the DoD Component HRPO may require HRPO approval of IRB-approved changes to research before the changes are implemented.

- Transfer of IRB oversight to a different IRB.
- Notification by any federal body, State agency, official governing body of a Native American or Alaskan native tribe, other entity, or foreign government that the non-DoD institution's DoD-supported human subjects research is being audited or is under for cause investigation, and the subsequent report.
- Any unanticipated problems involving risks to subjects or others, suspension or termination of IRB approval, or any serious or continuing noncompliance pertaining to DoD-supported research, and the actions taken as a result. Note: Substantiated allegations related to classified research must be reported immediately.
- The results of the IRB's continuing review, when continuing review is required.
- Change in status when a previously enrolled human subject becomes pregnant, or when the researcher learns that a previously enrolled human subject is pregnant, and the

protocol was not reviewed and approved by the IRB in accordance with Subpart B of 45 CFR 46.

- Change in status when a previously enrolled human subject becomes a prisoner, and the protocol was not reviewed and approved by the IRB in accordance with Subpart C of 32 CFR 219.
- A DoD-supported study's closure.

43.14 Addressing and Reporting Allegations of Noncompliance

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

43.15 Addressing and Reporting Allegations of Research Misconduct

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

43.16 Recordkeeping Requirements

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

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

44 Department of Justice

The U.S. Department of Justice (DOJ) is not currently a signatory to the revised Common Rule. DOJ's regulations for the protection of human subjects at [28 CFR 46](#) are consistent with the pre-2018 Common Rule requirements (when DOJ was a signatory). DOJ has not adopted Subparts B, C and D. The National Institute of Justice (NIJ) and the Office of Justice Programs (OJP) conduct and fund DOJ research. Confidentiality regulations for DOJ research are described at [28 CFR 22](#). Research conducted within the Federal Bureau of Prisons is subject to the requirements described at [28 CFR Part 512](#).

This section summarizes additional requirements for the conduct and IRB review of human subjects research conducted or supported by DOJ/NIJ/OJP (including funding through grants, subgrants, contracts, subcontracts, cooperative agreements, and interagency agreements) and human subjects research conducted in the Federal Bureau of Prisons.

44.1 Principal Investigator Responsibilities

In addition to complying with the pre-2018 Common Rule requirements outlined by DOJ at [28 CFR 46](#), PIs conducting research supported by DOJ/NIJ/OJP have the following responsibilities. PIs must:

1. Submit a Privacy Certificate to NIJ to document understanding of investigator's obligations under the confidentiality regulations found in [28 CFR 22](#). NIJ provides guidelines for the certificate on its [website](#). [A model Privacy Certificate can be found here: <https://www.justice.gov/atr/file/705856/download>](#);
2. Comply with the requirements of the Privacy Certificate, including the requirement to obtain [separate written consent](#) for the reporting of domestic, child, or elder abuse;
3. Inform subjects (in the confidentiality section of the consent form) that private, identifiable information will be kept confidential and will only be used for research and statistical purposes. If, due to sample size or some unique feature, the identity of the individual cannot be maintained, the subjects need to be explicitly notified. If the investigator intends to disclose any information, the subject needs to be explicitly informed what information would be disclosed, under what circumstances, and to whom. The subject must be informed of any potential risks which may result from this disclosure and must explicitly provide prior written consent;
4. When applicable, disclose in the consent form that the research is funded by DOJ/NIJ/OJP;
5. Submit a copy of the IRB approval as well as supporting documentation of the IRB's institutional affiliation, assurance, etc. to the NIJ prior to initiation of any research activities that are not exempt from the requirements of 28 CFR 46; or

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Submit supporting documentation of the IRB’s determination that the research qualifies for exemption under 28 CFR 46.101(b);

6. Comply with [NIJ’s policy](#) for the protection of the privacy and well-being of participants in NIJ research studies through the statutory protection provided to private information under the authority of [42 U.S.C. § 3789g](#) and the other DOJ regulations on the Confidentiality of Identifiable Research and Statistical Information found in [28 CFR 22](#);
7. Sign and maintain an Employee Confidentiality Statement for themselves and their research staff. A model employee confidentiality statement can be found at <https://www.nij.gov/funding/humansubjects/employee-confidentiality.htm>; and
8. Send a copy of all de-identified data, including copies of the informed consent document, data collection instruments, surveys and other relevant research materials to the [National Archive of Criminal Justice Data](#).

44.2 Bureau of Prisons

Additional requirements for research conducted research [within the Bureau](#) are described at [28 CFR Part 512](#) and in [Program Statement 1070.07](#). Although some research may be exempt from 28 CFR part 46 under 46.101(b)(5), as determined by the Office of Research and Evaluation (ORE) of the Bureau, no research is exempt from 28 CFR Part 512. However, ORE may determine that certain activities are not research (e.g., implementation of Bureau initiatives through a pilot project).

IRB approval must be obtained by Yale IRB (first) and the BOP IRB. Sufficient time must be allotted for review by both IRBs; per the information currently provided on [BOP’s website](#), BOP approval for a proposal that qualifies for expedited review typically takes 12 weeks. The content that must be included in the BOP proposal are outlined in [Program Statement 1070.07](#), all information and materials submitted to the BOP must also be submitted to the Yale IRB.

The following principles and requirements for research conducted within BOP are in addition to those outlined in 28 CFR 46 and will be evaluated during the IRB review.

Requirements for Approval:

1. The PI must have academic preparation or experience in the area of study;
2. The PI must assume responsibility for actions of other research team members;
3. PI’s who are not employees of BOP must sign a [statement of compliance](#);
4. The rights, health, and human dignity of subjects must be respected;
5. The project must have an adequate research design and contribute to the advancement of knowledge about corrections;

6. The research design must be compatible with both the operation of prison facilities and the protection of human subjects. Researchers must observe the rules of the institution or office where the research is conducted;
7. The project may not involve medical experimentation, cosmetic research, or pharmaceutical testing;
8. The project must minimize risk to subjects and risks to subjects must be reasonable in relation to anticipated benefits;
9. Selection of subjects within any one institution must be equitable;
10. Incentives may not be offered to inmate subjects to help persuade inmate subjects to participate. However:
 - a. Soft drinks and snacks to be consumed at the test setting may be offered;
 - b. Reasonable accommodations such as nominal monetary compensation (i.e., do not exceed twice the minimum wage for each hour of the subject's expected participation in the research activity) for time and effort may be offered to non-inmate subjects who are both:
 - i. No longer in BOP custody; and
 - ii. Participating in authorized research conducted by Bureau employees or contractors.

Access to BOP Records:

1. Employees, including consultants, of the BOP who are conducting authorized research projects may be provided access to those records relating to the subject which are necessary to the purpose of the research project without having to obtain the subject's consent (with a waiver of consent approved by the IRB);
2. Except as described below, non-employees of the BOP are limited in access to information to that information available under the Freedom of Information Act (FOIA);
3. A non-employee of the BOP may receive records that are not individually identifiable when advance written assurance that the record(s) will be as a statistical research or reporting record is provided to the agency. [[28 CFR 512.15](#)]

Informed Consent Requirements:

1. Informed consent must be sought, when applicable (See [28 CFR 512.15](#) and [512.16](#)) and follow the requirements outlined in [BP-S606](#);
2. Additional required consent elements for research conducted within the BOP:
 - a. Identification of the researchers;
 - b. Anticipated uses of the results of the research;

- c. A statement that participation is completely voluntary and that the participant may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable);
 - d. A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, a researcher may not guarantee confidentiality when the participant indicates intent to commit future criminal conduct or harm themselves or someone else, or, if the participant is an inmate, indicates intent to leave the facility without authorization; and
 - e. A statement that participation in the research project will have no effect on the inmate participant's release date or parole eligibility.
3. Documentation of consent –
- a. Researchers (not employed by the BOP) must obtain the subject's signature on the statement of informed consent prior to initiating the research activity. The researcher may not be required to obtain the signature if the researcher can demonstrate that the only link to the subject's identity is the signed statement of informed consent or that there is significantly more risk to the subject if the statement is signed. The signed statement must be submitted to the Chairperson of the appropriate BOP IRB. See [Program Statement 1070.07](#) for requirements that apply when consent is obtained by an employee or contractor of BOP;
 - b. The original of any signed consent form must be placed in the specific research project's file at the institution where the research is conducted. A copy of any signed consent form which grants a researcher access to an Inmate's Central File must be placed in the non-disclosable portion of the Inmate Central File and a copy must be offered to the inmate.

Post-Approval Requirements:

1. Except as noted in the informed consent form, researchers may not provide identifiable research information to any person without the subject's prior written consent to release the information (e.g., identifiable research information cannot be admitted as evidence or used for any purpose in any action, suit, or other judicial, administrative, or legislative proceeding without written consent);
2. Except for computerized data records maintained at an official Department of Justice site, records that contain non-disclosable information directly traceable to a specific person may not be stored in, or introduced into, an electronic retrieval system;
3. If the researcher is conducting a study of special interest to the Office of Research and Evaluation (ORE) but the study is not a joint project involving ORE, the researcher may

be asked to provide ORE with the computerized research data, not identifiable to individual participants, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the project.

4. At least once a year, the PI must provide the Chief, Office of Research and Evaluation, with a report on the progress of the research.
5. At least 12 working days before any report of findings is to be released, the PI must distribute one copy of the report to each of the following: the Chair of the Bureau Research Review Board, the Regional Director, and the Warden of each institution that provided data or assistance. The PI must include an abstract in the report of findings.
6. Prior to submitting for publication the results of a research project conducted under this subpart, the researcher shall provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons;
7. In any publication of results, the PI must acknowledge the Bureau's participation in the research project; and
8. The PI must expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.

45 Department of Energy

The U.S. Department of Energy (DOE) is a signatory to the Common Rule with regulations equivalent to 45 CFR 46 published under [10 CFR 795](#). Research conducted or supported by DOE, or performed in DOE facilities, is subject to additional requirements for investigators and for reviewing IRBs. These requirements are outlined in this section.

[DOE Order 443.1C](#) establishes DOE-specific policy and principles for the protection of human subjects. When DOE research involves contractors, the contractor's responsibilities for protecting human subjects are included in the "Contractor Requirements Document" included in contracts. DOE provides [additional resources](#) on its website that investigators and IRBs may also find helpful.

All human subjects research conducted with DOE funding, at DOE institutions, or by DOE contractor personnel, whether domestic or international, must be conducted under a FWA or comparable assurance and be IRB-approved in accordance with 10 CFR 745.103.

Yale IRB will review DOE research in accordance with the Common Rule and applicable DOE-specific requirements.

45.1 Definitions

DOE expands upon the definitions provided in the Common Rule with the following additional or modified definitions:

Adverse Event. Any unfavorable medical 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, whether or not considered related to the subject's participation in the research.

A **significant adverse event** is an adverse event that is unexpected and substantively impacts the human subjects.

A **serious adverse event** is any adverse event temporally associated with the subject's participation in research that meets any of the following criteria: a) results in death; b) is life-threatening; c) requires inpatient hospitalization or prolongation of existing hospitalization; d) results in a persistent or significant disability/incapacity; e) results in a congenital anomaly/birth defect, or f) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Breach. An incident involving the loss of control, compromise, unauthorized disclosure, unauthorized acquisition, or any similar occurrence where:

- A person other than an authorized user accesses or potentially accesses PII; or

- An authorized user accesses or potentially accesses PII for other than the authorized purpose.

Breaches do not require evidence of harm to an individual, or of unauthorized modification, deletion, exfiltration, or access to information. PII can be breached in any format, including physical (paper), electronic, and verbal/oral.

Classified Human Subjects Research. Research involving human subjects that is classified, in whole or in part, in accordance with the Federal sponsor and/or DOE criteria.

De-identified Data. Records that have had enough personally identifiable data removed or obscured such that the remaining information does not identify an individual and there is no reasonable basis to believe that the information can be used to identify an individual.

Generalizable. Information/research findings that are intended to be applied to populations or situations beyond that studied/will have meaning and impact outside of the single immediate activity itself.

Modification of the Human Environment. Research: (1) in which people have their environment intentionally changed or manipulated for the purposes of the research, with or without their knowledge; and/or (2) that cannot be validly conducted without people present (other than those conducting the research), regardless of whether identifiable private information is collected about them.

Personally Identifiable Information (PII). Information that can be used to distinguish or trace an individual's identity, either alone or when combined with other information that is linked or linkable to a specific individual. PII can include unique individual identifiers or combinations of identifiers, such as an individual's name, Social Security number, date and place of birth, mother's maiden name, biometric data, etc.

Research. A systematic investigation, including research development, testing and evaluation, designed to contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, 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.

Unanticipated Problem. In general, to be classified as an unanticipated problem, any incident, experience, or outcome should meet all three of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied

2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
3. Likely to place subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

45.2 Human Subjects Research Determinations

DOE requires that the following research is submitted to the IRB for determination of whether the research is human subjects research as defined by the Common Rule. Investigators may not make independent determinations in these circumstances. The potential risks to individuals must be considered by the IRB before such research may begin.

1. Research that uses social media data.
2. Research that involves the study of humans in a systematically modified environment.

45.3 Human Subjects Research

DOE requires that the following activities are managed as Human Subjects Research and require IRB review:

1. Generalizable studies in human environments (e.g., occupied homes and offices, classrooms, and transit centers like subway systems and airports) that use tracer chemicals, particles, and/or other materials, such as perfluorocarbons, to characterize airflow;
2. Generalizable studies in occupied homes and/or offices that:
 - a. Manipulate the environment to achieve research aims (e.g., increasing humidity and/or reducing influx of outside air through new energy-saving ventilation systems);
 - b. Test new materials (e.g., sequentially changing the filter materials in the HVAC system while monitoring the effects on air quality and energy use); or
 - c. Collect information on occupants' views of appliances, materials, or devices installed in their homes or their energy saving behaviors through surveys and focus groups. Some surveys may be online surveys administered through providers such as Amazon Mechanical Turk and Survey Monkey;
3. Human Terrain Mapping (HTM) – HTM is defined by DOE as research and data gathering activities primarily conducted for military or intelligence purposes to understand the “human terrain,”—the social, ethnographic, cultural, and political elements of the people among whom the U.S. Armed Forces are operating and/or in countries prone to political instability. This work includes observations, questionnaires, and interviews of

groups of individuals, as well as modeling and analysis of collected data, and may become the basis for U.S. military actions in such locations. In addition to HTM, such activities are often referred to as human social culture behavior (HSCB) studies.

Yale does not routinely engage in DOE HTM. Investigators who seek to engage in such research must seek special permission from Yale's IO who will engage other appropriate organizational leaders in the decision-making process.

45.4 Strategic Intelligence Partnership Program (SIPP)

Research that is funded through the SIPP must be reviewed and approved by the Central DOE IRB-Classified, regardless of whether the research is classified or unclassified.

45.5 DOE Advance Notification

The DOE Human Subjects Protection (HSP) Program Manager, and when a National Nuclear Security Administration (NNSA) element is involved, the NNSA HSP Program Manager, must be notified in writing prior to the initiation of human subjects research activities, including exempt human subjects research, when the research involves:

1. An institution without an established IRB.
2. A foreign country.
3. A potential for significant controversy (e.g., negative press or reaction from stakeholder or oversight groups).
4. Research subjects in a protected class (i.e., prisoners, children, individuals with impaired decision-making capacity, or DOE/NNSA federal or contractor employees as human subjects who may be more vulnerable to coercion and undue influence to participate) that is outside of the reviewing IRB's typical range/scope.
5. The generation or use of classified information

45.6 DOE IRB Reliance

Research that involves more than one DOE site (e.g., research team members, data, or human subjects are from more than one DOE site) must be reviewed and approved by one of the DOE central IRBs unless review by another IRB is authorized by the DOE and/or NNSA HSP Program Manager. Likewise, research that involves DOE Federal and/or contractor employees must be reviewed and approved by the appropriate DOE IRB unless the DOE site or DOE Headquarters determine that review by another IRB would be appropriate. In all cases, whenever DOE serves as the reviewing IRB or relying organization for human subjects research, a written agreement (e.g., an IRB reliance agreement, a Memorandum of Understanding) must be in place.

45.7 Protection of Data

DOE-regulated research involving the collection and/or use of Personally Identifiable Information (PII) must comply with [DOE Order 206.1 Department of Energy Privacy Program](#). Protocols for research involving PII or PHI must address DOE's specific requirements for the protection of such information, these requirements are currently outlined on DOE's website "[Frequently Asked Questions for Researchers](#)." Additional information on DOE's requirements for the protection of research data is available on DOE's website "[DOE-Specific Requirements](#)".

The IRB will review the investigator's plan for the protection of data and may accept the plan as proposed or require changes to enhance protections and ensure compliance with DOE and other applicable requirements.

Loss, suspected loss, or suspected or confirmed breach of PII/PHI must be reported **immediately** upon discovery, (**as soon as aware of incident**), to the: DOE funding office Program Manager and the IRB(s) overseeing the research. If the DOE Program Manager and/or IRB is unreachable, the PI is responsible for immediately notifying the DOE Integrated Joint Cybersecurity Coordination Center (iJC3) at 1-866-941-2472.

Within 48 hours, the DOE or NNSA HSP Program Manager must also be notified of any corrective actions taken or to be taken and may modify the corrective actions as appropriate. Corrective actions must also be reported to the HRPP(s) and/or IRB(s) of record in accordance with their policies and procedures. The HRPP or IRB may enhance the plan as appropriate to ensure the protection of human subjects but may not remove or diminish any component of the plan that DOE has accepted or required.

Yale Investigators may consult with [Yale Information Security](#) for further guidance.

45.8 Classified Research

Yale does not conduct classified research. Investigators who seek to engage in such research must seek special permission from Yale's IO who will engage other appropriate organizational leaders in the decision-making process.

45.9 DOE Employees, Contractors, and Students

DOE considers DOE personnel (employees, contractors, and students) to be vulnerable to pressures to cooperate with research conducted by their managers and/or coworkers. Additionally, DOE discourages researchers from conducting research on themselves, unless clearly justified and approved by both the IRB and the researchers' management. When Yale IRB reviews involving DOE personnel, it will consider whether the proposed plan for the recruitment, consent, ongoing participation of subjects, and the protection of subject privacy and confidentiality adequately protects vulnerable populations as described in Section 15.3. Additionally, the IRB may make use of the Central DOE IRBs checklist for protecting employees

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who participate as research subjects (available on the [DOE Specific Requirements](#) webpage) and may consult with the DOE HSP to determine whether there are any additional DOE requirements or recommendations that should be taken into consideration.

45.10 Reporting Requirements

In addition to the reporting requirements outlined throughout this manual, investigators must report the following **within 48 hours** to the IRB and the DOE (or NNSA) HSP Program Manager when conducting DOE research:

1. Any significant adverse events, unanticipated problems, and complaints about the research;
2. Any non-compliance with applicable regulations, IRB requirements, DOE HSP (or NNSA) program procedures or other requirements; and
3. Any suspension or termination of IRB approval.

Investigators must **immediately (as soon as aware)** report:

1. Any serious adverse event.
2. Any finding of a suspected or a confirmed data breach involving PII as outlined in Section 44.7.

Reports should include a description of any corrective actions to be taken. The HSP (or NNSA) Program Manager and IRB will review the report and may accept or modify the corrective action plan and take any other actions necessary to ensure the protection of human subjects and the integrity of the research.

46 Environmental Protection Agency

The Environmental Protection Agency (EPA)) is a signatory to the Common Rule with regulations equivalent to 45 CFR 46 published under [40 CFR 26 \(Subpart A\)](#). EPA has outlined additional regulations that apply to EPA research in the following subparts:

[Subpart B](#) – Prohibition of Research Conducted or Supported by EPA Involving Intentional Exposure of Human Subjects who are Children or Pregnant or Nursing Women

[Subpart C](#) – Observational Research: Additional Protections for Pregnant Women and Fetuses Involved as Subjects in Observational Research Conducted or Supported by EPA

[Subpart D](#) – Observational Research: Additional Protections for Children Involved as Subjects in Observational Research Conducted or Supported by EPA

[Subpart K](#) – Basic Ethical Requirements for Third Party Human Research for Pesticides Involving Intentional Exposure of Non-Pregnant, Non-Nursing Adults

[Subpart L](#) – Prohibition of Third Party Research Involving Intentional Exposure to a Pesticide of Human Subjects who are Children or Pregnant or Nursing Women

[Subpart M](#) – Requirements for Submission of Information on the Ethical Conduct of Completed Human Research

[Subpart O](#) – Administrative Actions for Noncompliance

[Subpart P](#) – Review of Proposed and Completed Human Research

[Subpart Q](#) – Standards for Assessing Whether to Rely on the Results of Human Research in EPA Actions

Additional EPA requirements for human research are outlined in [EPA Order 1000.17A](#) “Policies and Procedures on Protection of Human Subjects in EPA Conducted or Supported Research” and [EPA Order 1000.17B](#) “Policy for Increasing Access to Results of EPA-Funded Extramural Scientific Research”.

EPA regulations and requirements for the protection of human subjects apply to research supported or conducted by the EPA **and** to research in which the intent is submission of data to the EPA or when the results of the research may be held for later inspection by the FDA.

Yale investigators must comply with all applicable EPA requirements in addition to other applicable regulations, policies, **and** the requirements of the IRB of record. Investigators are responsible for clearly indicating within their IRB application materials that proposed research is subject to EPA regulations and for providing information regarding compliance with EPA requirements. The Yale IRB will evaluate compliance with the aid of a worksheet and by consulting regulations and guidance.

The information provided in this section summarizes key EPA standards and requirements.

46.1 EPA Definitions:

Intentional Exposure - Research involving intentional exposure of a human subject means a study of a substance in which the exposure to the substance experienced by a human subject participating in the study would not have occurred but for the human subject's participation in the study.

Observational Research - Observational research means any human research that does not meet the definition of research involving intentional exposure of a human subject.

Observational Human Exposure Studies. As defined in [Scientific and Ethical Approaches for Observational Exposure Studies](#) (SEAOES), observational human exposure studies are studies that involve the collection of environmental samples, data, and information from study participants in their everyday environments as they go about their normal activities. They involve neither the deliberate exposure of participants nor the control of environmental conditions in a way that impacts the participants' naturally occurring exposures.

Pesticide - Pesticide means any substance or mixture of substances meeting the definition in 7 U.S.C. 136(u) (Federal Insecticide, Fungicide, and Rodenticide Act, section 2(u)).

Substance – A substance includes any chemical, biological organism, or physical property tracked or regulated by the EPA or identified in an environmental statute. The [Substance Registry Services \(SRS\)](#) is the EPA's central system for information about substances tracked or regulated by EPA.

Assent - Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

Child – A child is a person who has not attained the age of 18.

Guardian - Guardian means an individual who is authorized under applicable State, Tribal, or local law to consent on behalf of a child to general medical care.

Parent - Parent means a child's biological or adoptive parent.

Permission - Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research.

46.2 EPA Human Subjects Research Review Official (HSRRO) Approval

All human subjects research conducted or supported by EPA must either be approved or be acknowledged as exempt research by the EPA Human Subjects Research Review Official (HSRRO) before any work involving human subjects research can begin. Preliminary review by the HSRRO can be requested for any research project, contract, grant application, cooperative agreement, cooperative research and development agreement (CRADA), interagency

agreement or any formal agreement involving EPA support of such studies. However, preliminary review is not required for any project, and if provided does not substitute for approval following IRB review.

To obtain approval or a concurrence of exemption by the HSRRO, researchers must submit the IRB-approved research package or documentation of exemption, including evidence of IRB approval and any correspondence between the IRB and the researchers. Researchers must also provide evidence of a Federalwide Assurance (FWA) on file with the U.S. Department of Health and Human Services (HHS) or other agency that their institution or organization will comply with regulatory provisions in the Common Rule.

Information about HSRRO review can be found on the following EPA website:
<https://www.epa.gov/osa/basic-information-about-human-subjects-research-0>.

46.3 PI Reporting Requirements

After research is approved, PIs are responsible for notifying EPA and the HSRRO (and HSO where applicable) of IRB suspension or termination of the research, of Unanticipated Problems Involving Risk to Subjects or Others that the IRB deems reportable, and any event that is significant enough to result in the removal of a subject from the study. In addition, for grantees of EPA, the PI must notify his/her Project Officer promptly, according to the terms specified by the IRB of record for the project.

46.4 Intentional Exposure

EPA outlines requirements and restrictions applicable to research involving intentional exposure to substances or pesticides in the following subparts:

[Subpart B](#) prohibits research involving intentional exposure (see definition above) of pregnant women, nursing women, or children.

[Subpart L](#) explicitly extends the prohibition to include intentional exposure of pregnant women, nursing women, or children to a **pesticide**.

[Subpart K](#) describes the requirements for third-party research involving intentional exposure of non-nursing, non-pregnant adults to substances and pesticides.

Among other provisions, Subpart K requires that:

1. Informed consent is obtained from subjects (there is no provision for LARs or for waiver or alteration of consent);
2. Informed consent must be documented using a written consent form or short form method (there is no provision for waiver of documentation of consent);

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3. If the research involves intentional exposure to a pesticide, the prospective subject must be informed of the identity of the pesticide and the nature of its pesticidal function (as an element of consent); and
4. The proposed research must be submitted to the EPA for approval after approval by the IRB(s). The submission requirements are outlined in [§26.1125](#).

46.5 Observational Research

EPA outlines requirements and restrictions applicable to observational research involving in the following subparts:

[Subpart C](#) describes the rules that apply to observational research conducted or supported by EPA that involves pregnant women (and thus their fetuses). In summary, such research is subject to the Common Rule Subpart B requirements stipulated at [45 CFR 46.203](#) (Duties of IRBs), [45 CFR 46.204](#) (Research Involving Pregnant Women or Fetuses), and [45 CFR 46.206](#) (Research Involving, After Delivery, the Placenta, the Dead Fetus, or Fetal Material).

[Subpart D](#) describes the rules that apply to observational research conducted or supported by EPA that involves children. In summary, the subpart stipulates that IRBs may only approve (and that EPA will only fund or conduct) research that satisfies all applicable conditions outlined in the subpart, including that:

1. EPA will conduct or fund observational research in which the IRB finds that **no greater than minimal risk** to children is presented, **only** if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §26.406.
2. EPA **will not** conduct or fund observational research that **involves an intervention or procedure that involves greater than minimal risk** to children **unless** the IRB finds and documents that:
 - a. The intervention or procedure holds out the prospect of direct benefit to the individual subject or is likely to contribute to the subject's well-being;
 - b. The risk is justified by the anticipated benefit to the subjects;
 - c. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
 - d. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §26.406.
3. [§26.406](#) describes the requirements for permission from parents (or guardians) and for assent from children. The EPA requirements are consistent with the requirements outlined in [§46.408](#) of 45 CFR 46. For each of the allowable categories (above) of

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observational research involving children, the IRB may determine that the permission of one parent is sufficient.

46.6 Observational Human Exposure Studies

All human observational exposure studies conducted or supported by EPA will adhere to the principles set forth in [SEAOES](#). SEAOES addresses six major topic areas:

1. Identifying elements to be considered in study conceptualization;
2. Ensuring protection of vulnerable groups;
3. Addressing privacy and other concerns related to observational human exposure studies;
4. Creating an appropriate relationship between the participant and investigator;
5. Building and maintaining appropriate community and stakeholder relationships; and
6. Designing and implementing strategies for effective communication.

46.7 Other EPA Regulations

[Subpart M](#) describes the requirement for submission of information about the ethical review and conduct of research whenever a report containing the results of the research is submitted to the EPA for consideration for consideration in connection with actions that may be performed by EPA.

[Subpart O](#) describes the actions that EPA may take when they find that an IRB, institution, or investigator are not compliant with EPA's requirements.

[Subpart P](#) describes the requirements and procedures for EPA's and EPA's Human Studies Review Board review of proposed and completed human research under [§26.1125](#) and [§26.1701](#).

[Subpart Q](#) describes the standards EPA applies in deciding whether to rely upon the results of research involving intentional exposure to substances or pesticides in EPA actions.

47 Department of Education

The U.S. Department of Education (ED) is a signatory to the Common Rule with regulations equivalent to 45 CFR 46 published under [34 CFR 97](#). Research conducted or supported by ED is reviewed by the Yale IRB in accordance with the Common Rule as described throughout this manual with the following variations and additional requirements.

ED has not adopted Subpart B (Pregnant Women, Fetuses, or Neonates) or Subpart C (Prisoners) of the Common Rule.

ED requires reporting of **alleged** (1) unanticipated problems involving risks to subjects or others; and (2) serious or continuing noncompliance with the Common Rule or Subpart D (protection of children in research). Other mandated reports, as described in Section 21, are submitted to ED instead of OHRP when the research is funded or sponsored by ED. When applicable, Yale will follow the directions for incident reporting provided on [ED's Protection of Human Subjects in Research](#) website.

47.1 Family Educational Rights and Privacy Act (FERPA)

The [Family Educational Rights and Privacy Act](#) (FERPA) is a Federal law that protects the privacy of student education records at educational entities that receive funds from the ED. In general, schools must have written permission from the parent or eligible student to release any information from a student's education record. However, FERPA allows schools to disclose personally identifiable information from an education record of a student without consent if the disclosure is to organizations conducting studies for, or on behalf of, educational agencies or institutions to:

1. Develop, validate, or administer predictive tests;
2. Administer student aid programs; or
3. Improve instruction. [\[34 CFR 99.31\(a\)\(6\)\]](#)

A written agreement with the receiving organization is required, including:

1. The purpose, scope, and duration of the study(ies);
2. The information to be disclosed;
3. A requirement that the receiving organization uses the personally identifiable information from the educational records only for the purpose(s) of the study as stated in the agreement;
4. A requirement that the receiving organization conducts the study in a manner that does not permit personal identification of students and parents by anyone other than representatives of the organization with legitimate interests; and

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5. A requirement that the receiving organization destroys or returns all personally identifiable information when the information is no longer needed for the purposes for which the study was conducted and that specified the time period in which the information must be returned or destroyed.

Education records may be released without consent under FERPA if all personally identifiable information has been removed including:

1. Students' names and other direct identifiers, such as students' Social Security Numbers or student numbers;
2. Indirect identifiers, such as the name of students' parents or other family members, the students' or families addresses, and personal characteristics or other information that would make the students' identities easily traceable, and dates and places of birth and mothers' maiden names;
3. Biometric records, including measurable biological or behavioral characteristics that can be used for automated recognition of an individual, including fingerprints, retina and iris patterns, voiceprints, DNA sequence, facial characteristics, and handwriting; and
4. Other information that, alone, or in combination, is linked or linkable to a student that would allow a reasonable person in the school community, who does not have personal knowledge of the relevant circumstances, to identify to student with reasonable certainty.

At Yale when FERPA applies, investigators must provide the IRB with information describing how they will ensure compliance with the rule. A letter of support or other documentation from the school supporting the conduct of the research should be provided. The IRB will review the information provided to verify compliance, including verification that permission for the use of the records will be obtained or that it is not required under an allowed use or exception.

47.2 Protection of Pupil Rights Amendment (PPRA)

The [Protection of Pupil Rights Amendment](#) (PPRA) affords parents of elementary and secondary students certain rights regarding the conduct of survey, collection and use of information for marketing purposes, and certain physical exams. PPRA applies to the programs and activities of a state educational agency (SEA), local educational agency (LEA), and any other recipient of ED funds. These rights transfer from parents to students when they reach the age of 18 or are an emancipated minor. This section is not intended to comprehensively address PPRA as a whole, rather it addresses PPRA requirements as they most commonly relate to research.

47.2.1 Definitions:

Instructional Material means instructional content that is provided to a student, regardless of its format, including printed or representational materials, audio-visual materials, and materials

in electronic or digital formats (such as materials accessible through the Internet). The term does not include academic tests or academic assessments.

Invasive Physical Examination means any medical examination that involves the exposure of private body parts, or any act during such examination that includes incision, insertion, or injection into the body, but does not include a hearing, vision, or scoliosis screening.

Personal Information means individually identifiable information including: (1) a student's or parent's first and last name; (2) a home or other physical address (including a street name and the name of a city or town); (3) a telephone number; or (4) a Social Security Number.

Research or Experimentation Program or Project means any program or project in any program that is designed to explore or develop new or unproven teaching methods or techniques.

47.2.2 Rights under PPRA

When **research is funded by ED**, no student can be required to submit **without prior consent** to a survey that concerns one or more of the following protected areas:

1. Political affiliations or beliefs of the student or the student's parent;
2. Mental and psychological problems of the student or his or her family;
3. Sex behavior and attitudes;
4. Illegal, anti-social, self-incriminating, and demeaning behavior;
5. Critical appraisals of other individuals with whom the student has close family relationships;
6. Legally recognized privileged and analogous relationships, such as those of lawyers, physicians, and ministers;
7. Religious practices, affiliations, or beliefs of the student or student's parent; or
8. Income, other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under a program.

Parents have the right to **receive notice and an opportunity to opt a student out** of:

1. Any other survey that concerns any of the above protected areas, **regardless of funding**;
2. Any non-emergency, invasive physical exam or screening required as a condition of attendance, administered by the school or its agent, that is not necessary to protect the health and safety of a student, except for hearing, vision, or scoliosis screenings, or any physical exam or screening permitted or required under state law; and
3. Activities involving collection, disclosure, or use of personal information collected from students for marketing or to sell or otherwise distribute the information to others. (This

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does not apply to the collection, disclosure, or use of personal information collected from students for the exclusive purpose of developing, evaluating, or providing educational products or services for, or to, students or educational institutions.)

Parents also have the **right to inspect** upon request and before administration or use:

1. Surveys that concern any of the protected areas and surveys created by third parties;
2. Instruments used to collect personal information from students for any of the above marketing, sales, or other distribution purposes;
3. Any instructional material used as part of the educational curriculum for the student; and
4. Instructional material, including teachers' manuals, films, tapes, or other supplementary instructional material, which will be used in conjunction with any research or experimentation program or project.

47.2.3 Procedures

At Yale, when PPRA applies, investigators should review the school's PPRA policies and must provide the IRB with information describing how they will ensure compliance with the rule and the school's policies. A letter of support or other documentation from the school supporting the conduct of the research and its compliance with PPRA should be provided. The IRB will review the information provided to verify compliance.

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PART II

Standalone Policies, Procedures, and Guidelines

Part II of this manual contains links to additional standalone HRPP policies, procedures, and guidelines relevant to the conduct of human subjects research under the purview of the Yale HRPP (including research under the oversight of an external IRB). Additional relevant Yale policies, procedures, and guidelines under the authority of other University departments, offices, or programs reside elsewhere. Links to key policies, procedures, and guidelines are below but this list is not exhaustive. Investigators, study personnel, students, and staff are responsible for compliance with all applicable policies, procedures, and guidelines.

A. Yale Human Research Protection Program Standalone Policies, Procedures, and Guidelines

- [HRPP Policy on Oversight of Yale Sponsor-Investigator held Investigational New Drug \(IND\) Applications, Investigational Device Exemptions \(IDE\) or Emergency Use or Emergency Use Authorizations \(EUA\)](#)

The purpose of this policy is to establish oversight and reporting requirements for Yale Sponsors and Sponsor-Investigators of INDs, IDEs or EUAs.

- [HRPP Policy on Institutional Conflicts of Interest In Human Research](#)

This policy describes the University statement of principles regarding institutional conflicts of interest that may affect the protection of participants in human subjects research conducted at Yale.

- [Research Recruitment at Yale and Yale New Haven Hospital](#)

The purpose of this document is to provide investigators conducting research under the purview of the Yale designated IRB (Yale IRB or an external IRB authorized by the Yale Human Research Protection program (HRPP) to provide review of Yale research on behalf of Yale), with an overview of the requirements regarding the recruitment of patients or use of data from patients who have received care at Yale University affiliated clinics, including research centers, or any hospital, clinic, or care center from the Yale New Haven Hospital System (YNHHS) and its affiliates.

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- **[Guidance on Committee Reviews Required for Human Subjects Research Protocols Using Radiation](#)**

This guidance outlines the roles, review and oversight responsibilities, and governing documents for each Yale University or Yale New Haven Hospital committee that must review human subjects research involving ionizing radiation. This guidance also provides guidance regarding investigator responsibilities when using ionizing radiation in research involving human subjects and applicable reporting requirements.

- **[Clinical Trial Registration and Reporting Requirements](#)**

This policy describes Yale's responsibilities related to registration and disclosure requirements for Yale conducted clinical trials to ensure compliance with applicable FDA requirements, NIH policy, the International Committee of Medical Journal Editors (ICMJE) policy, and the Medicare National Coverage Determination (NCD) Manual as it relates to the Centers for Medicare and Medicaid Services (CMS) clinical trial identifier requirement for all billing claims related to clinical trials.

- **[Guideline - Quality Improvement Projects](#)**

The purpose of this document is to provide guidance regarding how to determine whether a proposed project meets the definition of Quality Improvement (QI)/Quality Assurance (QA) or Research.

- **[Yale Human Research Protection Program Business Continuity Plan](#)**

This document describes the actions to be taken in case of a business interruption, emergency, or disaster that is, or soon will be, disrupting HRPP operations. It describes and outlines the activities to be undertaken within the HRPP components for a broad set of possible emergency scenarios that could occur that would impede the operations of the HRPP.

**B. Yale University and Other University Schools, Departments, Offices, or Programs
Standalone Policies, Procedures, and Guidelines**

- [University Policy 1360, Human Research Protection](#)
- [University Policies & Procedures](#)
- [Researchers: Policy guidelines for Yale Faculty, Students, and Staff governing Research at Yale](#)
- [Research Administration University-Wide Policy Documents](#)
- [Yale Research Support](#)
- [Yale Faculty Handbook](#)
- [Yale University Policy on Conflict of Interest](#)