



Yale University
Human Research Protection Program (HRPP)

Investigator Manual
Version Date: July 24, 2023

Table of Contents

- 1. Overview of Human Research Protection Program.....6
- 1.1. Scope6
- 1.2. Purpose of this manual6
- 1.3. Human Research Protection Program.....6
- 2. Human Subject Research.....6
- 2.1. Different regulatory classifications that research activities may fall under.....7
- 2.2. IRB’s determinations when reviewing proposed research.....7
- 2.3. IRB approval criteria for Human Subjects Research.....8
- 2.4. Quality Improvement/Quality Assurance and IRB review8
- 2.5. Determining whether a project is Quality Improvement/Quality Assurance.....8
- 3. University Requirements related to human subjects research.....9
- 3.1. Who can serve as the Principal Investigator on the research protocol.....9
- 3.2. Training.....9
- 3.3. Disclosures of Significant Financial and Non-Financial Interests 10
- 3.4. Ancillary Committees..... 10
- 3.5. Investigator Obligations..... 11
- 3.6. Management Plan for Research at Satellite Locations 12
- 3.7. Record Retention..... 14
- 3.8. Use of Joint Data Analytics Team (JDAT) for Data Requests 14
- 4. State and Other Regulatory Requirements and Guidance Related to Human Subjects Research... 14
- 4.1. State Requirements..... 14
- 4.2. ICH GCP Compliance 15
- 5. Submissions to Yale IRB 15
- 5.1. Overview of documents for submission to IRB 15
- 5.1.1. Research Protocol 17
- 5.1.2. Consent document..... 18
- 5.1.3. IRB Submission Form..... 19
- 5.2. Initial Study Submission..... 19
- 5.2.1. Listing Research Team Members in the IRB Electronic System 19
- 5.3. Study Modifications 21
- 5.4. Continuing Reviews 21
- 5.5. Study Closures 22
- 5.6. Review Process..... 23
- 5.7. IRB review outcomes 23
- 6. Informed Consent Considerations 24
- 6.1. Overview of Consent Documentation..... 24

6.2. E-Consent.....	25
6.3. Documentation of consent using short form.....	26
6.4. Alternative methods of obtaining consent from participants when consent process cannot be conducted in person.....	28
6.5. Assent.....	29
6.6. Consent process.....	29
6.7. Reconsent process.....	30
7. Study Recruitment and Payment for Study Participation.....	33
7.1. Recruitment of subjects.....	33
7.2. Payments to study participants for participation.....	35
7.3. Eligibility exceptions.....	36
8. Confidentiality.....	36
8.1. Research Data.....	36
8.2. Certificates of Confidentiality.....	36
8.3. Sharing data after completion of the study.....	38
8.4. Genomic Data Sharing.....	42
9. Submission of Reportable Items to Yale IRB.....	43
9.1. Reporting protocol deviations and noncompliance to the IRB.....	43
9.2. Reporting adverse events and/or unanticipated problems to the IRB.....	43
10. Conducting Research Outside of Yale or with Non-Yale Investigators.....	45
10.1. Engagement in research at non-Yale institution.....	45
10.2. Conducting research at Yale New Haven Health System entities.....	45
10.3. Conducting research at the VA.....	45
10.4. Adding unaffiliated investigators to the protocol.....	46
11. Special Topics.....	48
11.1. School based research for K-12 students.....	48
Limits to Confidentiality.....	49
School Concerns.....	49
Schools as Research Partners.....	52
Reporting Issues Arising in the Course of the Research.....	52
11.2. Deception in research.....	52
11.3. Oral history and humanities projects.....	53
12. Special Considerations for Drug/Device Research.....	54
12.1. Emergency use of an unapproved drug, biologic, or device.....	54
13. Using External IRBs for Review of Research.....	54
13.1. Initial Submission.....	55
13.2. Ongoing Responsibilities.....	56

13.3. Transfer of studies approved by Yale IRB.....	57
13.4. Studies under NCI CIRB purview	57
14. Requesting Use of Yale IRB as sIRB	58
14.1. HRPP agreement to serve as the sIRB for external sites	58
14.2. Investigator’s responsibilities when serving as the overall PI	58
14.3. Relying Investigator Responsibilities and Guidance	60
14.4. Initial IRB Approval.....	62
Preparing documents for multi-site research.....	63
Submitting the multi-site protocol for IRB review.....	64
Working with the sites to obtain site-specific information.....	65
Submitting site information for approval	65
Distributing the approval documentation to the sites	67
14.5. Modification Request Process	69
Submitting modification to protocol and Yale site.....	69
Submitting materials for site modifications.....	69
Distributing approval materials to sites.....	71
14.6. Continuing Review Submission Process	72
Obtaining information from sites for continuing review report	72
Submitting continuing review report	73
Distributing approval materials to sites.....	75
14.7. Reportable New Information Submission Process	76
Distributing IRB determination to sites	76
14.8. sIRB Questionnaire.....	77
15. Appendices	78
Appendix A-1 Additional Requirements for DHHS-Regulated Research	78
Appendix A-2 Additional Requirements for FDA-Regulated Research	80
Appendix A-3 Additional Requirements for Clinical Trials (ICH-GCP-E6 (R2)).....	86
Appendix A-4 Additional Requirements for Department of Defense (DOD) research.....	94
Appendix A-5 Additional Requirements for Department of Energy (DOE) Research	96
Appendix A-6 Additional Requirements for Department of Justice (DOJ) Research	98
Appendix A-7 Additional Requirements for Department of Education (ED) Research	102
Appendix A-8 Additional Requirements for Environmental Protection Agency (EPA) Research.....	103
Appendix A-9 Additional Requirements for Veterans Administration (VA) Research	104
Appendix A-10 Additional Requirements for Research Subject to EU General Data Protection Regulations (GDPR).....	118
Appendix B Emergency/Disaster Preparedness Considerations for Investigators Conducting Human Research	119
Appendix C Ancillary Committees	120

	<p>Human Research Protection Program Investigator Manual</p>	<p>Version 2.1 07/24/2023</p>
---	--	-----------------------------------

Appendix D Guide to Obtaining IRB Approvals to Conduct Research within the Yale New Haven Health System 128

Appendix E Reports of New Information (RNI) versus Modifications (MOD) 133

Revision History 137

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

1. Overview of Human Research Protection Program

1.1. Scope

Throughout this document “organization” refers to Yale University.

1.2. Purpose of this manual

This document, Investigator’s Manual, is designed to guide you through policies and procedures related to the conduct of Human Research that are specific to this organization. For detailed information on federal, state, and Yale policies related to the conduct of Human Research, please review the Yale Human Research Protection Program Policy (HRPP) and Standard Operating Procedure Manual.

General information regarding Human Research protections and relevant federal regulations and guidance is incorporated into the required human protections training. For additional information see [section 3.2](#) below on required training.

1.3. Human Research Protection Program

The Yale University HRPP Policy and Standard Operating Procedure Manual describes this organization’s overall plan to protect subjects in Human Research that includes:

- The mission of the Human Research Protection Program,
- The ethical principles that the organization follows governing the conduct of Human Research,
- The applicable laws that govern Human Research,
- When the organization becomes “engaged in Human Research” and when someone is acting as an agent of the organization conducting Human Research,
- The types of Human Research that may not be conducted, and
- The roles and responsibilities of individuals within the organization.

2. Human Subject Research

The Yale University HRPP Policy and Standard Operating Procedure Manual” defines the activities that this organization considers to be “Human Research.” An algorithm for determining whether or not an activity is Human Research can be found in the “WORKSHEET: Human Research (HRP-310),” located in the Library space in IRES IRB. Use this document for assistance in determining whether an activity meets either the Department of Health and Human Services (DHHS) or Food and Drug Administration (FDA) definition of Human Research, keeping in mind that the IRB makes the ultimate determination in questionable cases as to whether or not an activity constitutes Human Research subject to IRB oversight.

You must not conduct Human Research without prior IRB review and approval (or an organizational review and approval of exempt Human Research). If you have questions about whether an activity is Human Research or not, contact the [HRPP Office](#) who will provide you with a determination. If you wish to have a written determination, provide a request to the IRB Office in IRES IRB.

2.1. Different regulatory classifications that research activities may fall under

Submitted activities may fall under one of the following four regulatory classifications:

- Not "Human Subjects Research": Activities must meet the organizational definition of "Human Research" to fall under IRB oversight. Activities that do not meet this definition are not subject to IRB oversight or review. Review the IRB Office's "WORKSHEET: Human Research (HRP-310)" for reference. Contact the IRB Office in cases where it is unclear whether or not an activity is Human Research.
- Exempt: Certain categories of Human Research may be exempt from regulation but require either a determination of exemption or a limited IRB review. It is the responsibility of the organization, not the investigator, to determine whether Human Research is exempt from IRB review, including exempt protocols which require a limited IRB review. Review the IRB Office's "WORKSHEET: Exemption (HRP-312)" for reference on the categories of research that may be exempt.
- Review Using the Expedited Procedure: Certain categories of non-exempt Human Research may qualify for review using the expedited procedure, meaning that the project may be approved by a single designated IRB reviewer, rather than the convened board. Review the IRB Administration's "WORKSHEET: Eligibility for Review Using the Expedited Procedure (HRP-313)" for reference on the categories of research that may be reviewed using the expedited procedure.
- Review by the Convened IRB: Non-Exempt Human Research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB.

2.2. IRB's determinations when reviewing proposed research

The IRB may approve research, require modifications to the research to secure approval, table research, defer decision, or disapprove research:

- Approval: Made when all criteria for approval are met. See "How does the IRB decide whether to approve Human Research?" below.
- Modifications Required to Secure Approval: Made when IRB members require specific modifications to the research before approval can be finalized.
- Deferred: Made when the IRB determines that the board is unable to approve research and the IRB suggests modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB in person or in writing.
- Disapproval: Made when the IRB determines that it is unable to approve research and the IRB cannot describe modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision and gives the investigator an opportunity to respond to the IRB in person or in writing.

2.3. IRB approval criteria for Human Subjects Research

The criteria for IRB approval can be found in the “WORKSHEET: Exemption (HRP-312)” for exempt Human Research, “WORKSHEET: Criteria for Approval (HRP-314)” for non-exempt Human Research, and the Initial IRB Member Review Worksheet. The latter worksheet references other checklists that might be relevant.

These checklists are used for initial review, continuing review, and review of modifications to previously approved Human Research.

You are encouraged to use the checklists to write your Investigator Protocol in a way that addresses the criteria for approval.

2.4. Quality Improvement/Quality Assurance and IRB review

The majority of quality improvement (QI) projects do not require review by the IRB, but rather fall under the purview of the relevant academic or clinical department where the project is to take place. There are, however, cases where the project would fall under the purview of the IRB. Projects which qualify as “research” and which involve “human subjects,” as defined in the federal regulations at 45 CFR 46.102(e) and (f) and further explained below, would require IRB review under Yale policy. The most common reason for QI projects to require IRB review is that they are projects involving systematic investigations intended to develop generalizable knowledge.

If the proposed project will involve collecting identifiable information about a living individual AND will be used to inform broad policy or generalize findings, then the project must be submitted to the IRB for review.

The following may be indicators that IRB review is required:

- The study is funded by an agency or sponsor which seeks to support projects designed to create generalizable knowledge such as U.S. Department of Health and Human Services, National Institutes of Health, National Science Foundation, Agency for Healthcare Research and Quality (AHRQ), pharmaceutical sponsor, etc.
- The study involves multiple individuals’ perspectives on the issue of interest AND these perspectives are analyzed to reach generalized conclusions.

The following examples are projects which would not require IRB review:

- The goal of the project is to document a specific issue or event, or the experience of individuals, e.g., conducting a root-cause analysis of a medical error.
- The project compares and contrasts policies, procedures or events to identify general commonalities or inform policy decisions without the collection of information about identified individuals.

2.5. Determining whether a project is Quality Improvement/Quality Assurance

Quality Improvement (QI) and Quality Assurance (QA) projects involve systematic, data-guided initiatives or processes designed to improve clinical care, patient safety, health care operations, services and programs

	<p>Human Research Protection Program Investigator Manual</p>	<p>Version 2.1 07/24/2023</p>
---	--	-----------------------------------

or for developing new programs or services (e.g. teaching evaluations, patient/employee service surveys). QI/QA is intended to use experience to identify effective methods, implement the methods broadly, and evaluate the immediate impact or effect of the implemented changes.

A QI/QA project may involve implementing a practice, for example, to improve the quality of patient care, and collecting and immediately assessing data regarding the degree to which implementation of the practice was successful for clinical, practical, or administrative purposes. Process-based QI/QA activities strive to overcome barriers to dissemination and implementation of best practices.

Results of a QI/QA project could and should be shared with others, either via presentations or publications.

In general, QI/QA activities would NOT be considered human subjects research and therefore NOT need to be submitted to the IRB if the following applies:

1. The individuals are not randomized to different intervention groups.
2. The project goal is to implement existing/known knowledge to improve or enhance health/clinical care or educational processes.
3. The project does not have a fixed goal, methodology, population and time period; rather, based on data collection that is immediately evaluated and assessed, practices or behaviors are modified quickly.
4. The project does not delay feedback of the data from monitoring to the implementation of the change.

For additional information, see Special Topics in the HRPP Policy and Standard Operating Procedure Manual.

3. University Requirements related to human subjects research

3.1. Who can serve as the Principal Investigator on the research protocol

The Yale IRB has adopted a policy from the Faculty Handbook pertaining to who may serve as a Principal Investigator (PI) on a research protocol, which applies to all research studies requiring approval by an IRB at Yale. Faculty with status of associate research scientist, instructor, lecturer, part-time faculty, adjunct faculty, former faculty, clinical faculty, visiting faculty require special permission to serve as the Principal Investigator.

Students and trainees cannot serve as the PI on the research project. They require a Faculty Advisor who meets the eligibility criteria to serve as the PI and who agrees to serve in that role.

The request to serve as the PI should be uploaded in the Local Site Documents page in IRES IRB.

3.2. Training

This section describes the training requirements imposed by the Yale. You may have additional training imposed by other federal, state, or organizational policies.

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

Human Subjects Protection Training

All investigators and staff conducting research must complete human subjects protection training with continuing education modules every three years. Members of the research team who have not completed human research protections training may not take part in aspects of the research that involve human subjects. Visit the [HRPP website](#) for a list of the acceptable human subjects protection training modules.

Good Clinical Practice

Individuals engaged in the conduct of a clinical trial (per the NIH definition) must complete a Good Clinical Practice (GCP) training. The training must be refreshed every three years. Visit the [HRPP website](#) for a list of the acceptable GCP training modules.

HIPAA Training

Investigators engaged in human subject research conducted at HIPAA covered entities that involves collection or interaction with PHI, must also complete HIPAA training. Visit [Yale HIPAA website](#) to learn about the available training modules.

3.3. Disclosures of Significant Financial and Non-Financial Interests

Individuals involved in the design, conduct, or reporting of research, research consultation, teaching, professional practice, institutional committee memberships, and service on panels such as Institutional Review Boards or Data and Safety Monitoring Boards are considered to have an institutional responsibility.

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: <http://www.yale.edu/coi/>

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.

Additional information can be found in the Yale HRPP Policy and Standard Operating Procedure Manual, section on Disclosures and Management of Personal Interests in Human Research.

3.4. Ancillary Committees

There are other groups at Yale and Yale New Haven Health that may need to review research proposals prior to the initiation of research. Depending on the ancillary committee's requirements, certain approvals must be obtained by the investigator prior to the IRB review. The requirements apply to research conducted

by Yale/YNHH investigators regardless of which IRB serves as the IRB of record for the study. A current list of the ancillary committees along with the description of when their reviews apply and instructions on how to obtain the approval is available in [Appendix C](#).

3.5. Investigator Obligations

- Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.
- 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.
- If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution 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.
- Ensure that Research Staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties assigned to them during the study.
- Update the IRB office with any changes to the list of study personnel.
- Personally conduct or supervise the Human Research. Recognize that the investigator is accountable for the failures of any study team member.
 - a) Conduct the Human Research in accordance with the relevant current protocol as approved by the IRB, and in accordance with applicable federal regulations and local laws.
 - b) When required by the IRB, ensure that consent or permission is obtained in accordance with the relevant current protocol as approved by the IRB.
 - c) Do not modify the Human Research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to subjects.
 - d) Protect the rights, safety, and welfare of subjects involved in the research.
- Submit to the IRB:
 - Proposed modifications as described in this manual.
 - A continuing review application as requested in the approval letter.
 - A continuing review application when the Human Research is closed.
- Do not start Human Research activities until you have the final IRB approval letter.
- Do not start Human Research activities until you have obtained all other required institutional approvals, including approvals of departments or divisions that require approval prior to commencing research that involves their resources.

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

- Report any applicable Unanticipated Problems involving Risks to Subjects or Others (UPIRSOs) and incidents of noncompliance per HRPP Policies.
- Submit an updated disclosure of financial interests within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest. Follow this link to the COI Office Website to complete the form: <http://www.yale.edu/coi/>
- Do not accept or provide payments to professionals in exchange for referrals of potential subjects (“finder’s fees.”)
- Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment (“bonus payments.”)
- See additional requirements of various federal agencies in Appendix A. These represent additional requirements and do not override the baseline requirements of this section.
- Apply ICH E6 (R2) and Good Clinical Practice as applicable to the Research.

3.6. Management Plan for Research at Satellite Locations

Yale and Yale New Haven Hospital (YNHH) include multiple locations where research can be conducted. These locations are driven by patient care needs– they make access to healthcare easier for individuals living in different parts of the state and outside of the state. For example, Yale Smilow Cancer Center has multiple (over a dozen) different care centers where patients are seen. For research purposes, the additional locations operating under the umbrella of Yale or YNHHS will be referred to as satellite sites or satellite locations and the Principal Investigator’s primary location as the primary site. Satellite locations will not communicate directly with the IRB and there are no assigned local/site PIs. Instead, the PI should appoint a sub-investigator at each satellite location to serve as the primary contact for research teams. Delegations of responsibilities to sub-investigators from satellite locations must be accounted for in the delegation of authority log.

Consistent with applicable regulations and guidelines (e.g., FDA requirements, GCP, etc.), the PI maintains the same responsibilities for research at satellite locations as with the primary site. However, research at satellite sites requires additional considerations. If the Principal Investigator is not familiar with the satellite locations, a visit to understand the infrastructure is encouraged. An individual study plan for managing satellite locations should be put in place to address the following aspects of research oversight:

- **Research system start-up procedures**

The PI must ensure that research support teams that build OnCore calendars for accurate billing and patient management include the satellite locations. Yale’s OnCore and EPIC have been integrated allowing for a seamless transfer of information. If the satellite site’s instance of EPIC is not compatible with OnCore, the PI must provide the satellite site with an alternative plan for billing and the data management.

- **Training of staff**

Initial training for study team: The Principal Investigator or his/her designee (Study Coordinator, Research Nurse) must train all study team members at satellite locations on proper execution of the protocol, subject recruitment, inclusion/exclusion criteria, adverse event definitions and reporting, etc. In addition, the PI must ensure that all research team members at satellite locations must have valid Human Subjects Protection training and Good Clinical Practice training (completed within the previous 3 years), and HIPAA training. Training should be documented in the investigator site files.

Training for study team who did not attend initial training: The Principal Investigator or his/her designee must ensure that members joining the research team after the initial training receive the same level of training as other study team members. Training should be documented in the investigator site files.

Ongoing training: The Principal Investigator or his/her designee must ensure that study teams at satellite locations are notified and trained on amendments to the protocol, new significant information that would require reconsent, etc. Training should be documented in the investigator site files.

- **Communication Plan**

Correspondence related to research from the primary site – All relevant communication received from the IRB, sponsors, or others related to the research must be promptly communicated to the satellite locations (generally no later than 5 business days of receipt). In some cases, there may be additional training required (see above). The research staff at satellite locations must understand the communications standards. For example, if email will be used to distribute the information, the naming convention for emails must be consistent and clear.

Communication from the satellite locations – Research teams at satellite locations must be provided with the communication requirements regarding reporting adverse events and any other relevant information that requires immediate reporting to the PI, Sponsor, IRB, or other applicable regulatory bodies.

Ongoing communication – Regular meetings (e.g., weekly, monthly, or another predetermined frequency) should be scheduled with all satellite locations and the primary site to discuss the progress of the study, review screening and enrollment logs, provide updates on monitoring reports, review any new information, etc.

- **Shipment of the investigational products**

Whenever possible, study investigational products should be shipped directly from the sponsor to the satellite locations. If it is not allowed by the sponsor or not otherwise feasible, the Principal Investigator must work with the Investigational Drug Services (IDS) Pharmacy to ensure that the investigational products can be transported to the correct locations, per GCP requirements, sponsor's instructions, and IDS policies and procedures.

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

- **Research Records Management**

Review of Research Data/CRFs – The PI must review accuracy of the CRFs at predetermined frequency by participating in meetings with study monitors.

Investigator Site File and Participant Source Documentation– The Investigator Site File (ISF) should be kept at the primary location. Study binders with participant source documentation may be maintained at each satellite location, and may be made available for on-site monitoring at the primary site, upon request.

3.7. Record Retention

In order to comply with the requirements of OHRP and FDA, IRB records for research not subject to HIPAA must be 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) must be maintained for 6 years from the completion of research or the exemption determination. IRB records for research cancelled without participant enrollment must be retained for at least three (3) years after closure. If your Human Research is sponsored, contact the sponsor before disposing of Human Research records.

For more information on record retention, see the Yale HRPP Policy and Standard Operating Procedure Manual.

3.8. Use of Joint Data Analytics Team (JDAT) for Data Requests

Researchers conducting research that involves collecting information from EPIC must use services of Joint Data Analytics Team (JDAT). Requests for information from EPIC must be submitted to JDAT after the IRB determination (with applicable HIPAA waiver) is obtained. Investigators are not permitted to pull information from medical records for research purposes without JDAT’s specific authorization.

Data from medical records will include data only from individuals who did not opt-out of research. Investigators who received permission to review medical records without JDAT services must ensure that no data from individuals who specifically opted-out is included in the research data. For more information see [JDAT website](#).

4. State and Other Regulatory Requirements and Guidance Related to Human Subjects Research

4.1. State Requirements

There are several Connecticut (CT) state laws that investigators should be aware of that may relate to the conduct of human subjects research, including laws that impact informed consent procedures, child and

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

elder abuse reporting, confidentiality related to certain medical conditions, raffle/lottery requirements, etc. Depending on the type of research being conducted and/or the type of data/specimens being collected, investigators may need to tailor their consent forms to address certain state requirements or may need to report certain information in accordance with state law. For detailed information on CT state laws that may affect human subjects research, please review the “Special Topics” section of the Yale HRPP Policy and Standard Operating Procedure Manual.

Investigators are advised to seek additional information when conducting research outside Connecticut, as there are likely to be state or international laws which would apply to the conduct of human subjects research in those territories.

4.2. ICH GCP Compliance

The Yale IRBs comply with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidance (E6(R2)) 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, the Yale IRBs will comply with all of the GCP statements outlined in the ICH GCP guidance, provided that: a) The PI indicates in IRB application that the sponsor requires the IRB review process to comply with ICH standards, and b) the Office of Sponsored Projects confirms it is a contractual requirement.

For studies subject to ICH GCP, Investigators are responsible for:

- Clearly indicating within their IRB application materials that proposed research is subject to ICH GCP and for attesting to compliance with ICH-GCP (E6) guidelines. The Yale IRB will evaluate compliance with the aid of a worksheet (HRP-314, Worksheet: Criteria for Approval or Initial IRB Member Review Worksheet) and by consulting the current [ICH GCP \(E6\) guidance](#) posted by the FDA on its website.

If the investigator does not plan to follow ICH GCP guidelines, then adherence to ICH GCP should not be mentioned in the study protocol, consent document(s), or any other study documents. Additional information on ICH GCP (E6) can be found in the “Special Topics” section of the Yale HRPP Policy and Standard Operating Procedure Manual and [Appendix A-3](#) of this manual.

5. Submissions to Yale IRB

5.1. Overview of documents for submission to IRB

You will need to prepare several different documents for submission to the IRB. If your research requires review and approval by an ancillary committee and it uses the IRES IRB system for submission of its documents, upload them in the Local Site Documents page.

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

See the table below for descriptions of the basic documents that may be required for submission to Yale IRB. Additional documents not listed in the table that are created for purposes of research such as survey questions, interview guides, assessments, etc. should be uploaded in the Local Site Documents page.

Name of the Document	IRES IRB Location	Purpose
Overall protocol documents and documents related to Yale's site		
Protocol	Basic Information Page	Describes the purpose of the research, rationale of why it is important to conduct the research, describes research procedures, statistical analysis. This document can be written by the investigator or provided by the sponsor of the research;
IRB Submission Form	Local Site Documents	Describes how the research will be conducted at Yale e.g., differences between the protocol and what will happen at Yale, specifies recruitment at Yale, includes requests for waivers of consent and HIPAA Authorization; The IRB Submission Form is not required for requests for exempt research, Not Human Subject Research determinations, or Emergency Use Requests.
Consent Template	Study Documents	Provided by the sponsor for multi-site studies; if Yale investigator serves as the overall PI for multi-site research, consent template may be prepared as a basis for consent documents to be used at other sites; consent templates must meet regulatory requirements for consent, but they will not include Yale specific information.
Consent Documents	Local Site Documents	Consent document prepared for use at Yale site or by Yale investigators; they must meet regulatory requirements for consent and will include Yale specific information and locally required language.
Drug Attachments	Drugs	Studies that involve administration of drugs will either include an Investigator's Brochure or FDA Package Insert with prescribing information and patient labeling (for FDA approved drugs); FDA correspondence related to the status of the drug (e.g., letter showing IND #) or the trial (Clinical Hold letters) may also be included.

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

Device Attachments	Device	Studies investigating safety or effectiveness of a medical device should include device manuals; FDA correspondence related to the status of the device (e.g., FDA letter if exemption from IDE requirements) or the trial (Clinical Hold letters) may also be included.
Recruitment Materials	Local Site Documents	Materials proposed for recruiting participants, which may include posters, flyers, phone scripts, script for audio or video recordings, screenshots of website.
Additional documents for studies where Yale serves as the IRB of record for other sites		
Local Context Questionnaire	Local Site Documents, Site workspace	Describes how the research will be conducted at the site under purview of investigator from another institution for which Yale IRB serves as the IRB, includes information about the local (state or institutional) requirements related to the research, includes requests for waivers of consent and HIPAA Authorization;
Consent Documents	Local Site Documents, Site workspace	Consent documents developed for the site, should be based on the IRB approved template;
Recruitment Materials	Local Site Documents, Site workspace	Recruitment materials that were specifically designed to be used by the site in addition to the recruitment materials developed for the protocol;
HIPAA RAF	Local Site Documents, Site workspace	If a site's institution does not allow use of the HIPAA Authorization in the consent form (compound authorization) but the research collects or uses PHI, then there will be a stand-alone HIPAA Research Authorization Form developed by the site;

5.1.1. Research Protocol

For externally sponsored research, the sponsor will provide the protocol document. For investigator-initiated studies, Yale IRB does not require a specific protocol template to be used. Investigators may choose to use the [Protocol Builder](#) program to create a research protocol, or utilize TransCelerate or other programs/templates to create the study protocol. Yale IRB also offers multiple protocol templates to be used as a starting point for drafting a new Investigator Protocol. These templates include instructional text that clearly outline the information the IRB looks for when reviewing research. Protocol templates can be located on the HRPP website and the Library space in IRES IRB.

Here are some key points to remember when developing an Investigator Protocol:

- The instructional text serves as guidance to investigators when developing an Investigator Protocol for submission to the IRB. All italicized comments are meant to be deleted prior to submission.
- For any items described in the sponsor's protocol or other documents submitted with the application, investigators may simply reference the page numbers of these documents within the Investigator Protocol rather than repeat information.
- When writing an Investigator Protocol, always keep an electronic copy. You will need to modify this copy when making changes to the Investigator Protocol.
- If you believe your activity may not be Human Research, contact the IRB Office prior to developing your Investigator Protocol.
- Note that, depending on the nature of your research, certain sections of the template may not be applicable to your Investigator Protocol. Indicate this as appropriate.
- You may not involve any individuals who are members of the following populations as subjects in your research unless you indicate this in your inclusion criteria as the inclusion of subjects in these populations has regulatory implications:
 - Adults unable to provide legally effective consent
 - Individuals who are not yet adults (infants, children, teenagers)
 - Pregnant women
 - Prisoners

5.1.2. Consent document

Yale IRB provides several templates to be used as a starting point in drafting a consent document for investigator-initiated studies. The available templates include compound authorization form, parental permission, consent, adolescent and child assent forms as well as consent documents used for collection of data/specimens for repositories and information sheets for verbal consent.

Consent documents (including summaries for short form consent documents) must contain all of the required and all additional appropriate elements of informed consent. Review the "Long Form of Consent Documentation" section in the IRB's "WORKSHEET: Criteria for Approval (HRP-314)," to ensure that these elements are appropriately addressed.

For externally sponsored research, the sponsor will often provide a consent template. There is no need to transfer the information from the sponsor consent template to Yale versions. Instead, review the documents provided by the sponsor and revise the document to reflect how the study will be conducted at Yale or YNHH. Refer to the Consent Glossary available in the IRES IRB system for required and suggested consent language for certain sections of the consent form e.g., subject injury provision language that was preapproved by the sponsor for use in research consent forms at Yale.

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

5.1.3. IRB Submission Form

Most human subject research submissions will require an IRB Submission Form, in addition to a protocol. While the protocol should include a general information about the study, the IRB Submission Form details how the study is conducted at Yale. If the IRB Submission Form asks for information that is already contained in the protocol, simply refer to the section of the protocol. It is not necessary to copy information from the protocol.

5.2. Initial Study Submission

Submissions of initial studies must be made in IRES IRB. Only the Principal Investigator or assigned PI Proxy can submit the action in IRES IRB. Refer to IRES IRB System Manual in the [IRES IRB Help Center](#) for instructions on creating and submitting study for initial review.

5.2.1. Listing Research Team Members in the IRB Electronic System

The research record in the IRB electronic system, IRES IRB, must include the names of the following team members engaged in human subjects research under Yale IRB or HRPP purview:

- Principal Investigator (PI),
- PI Proxy, if one is identified for the study,
- Investigators,
- Individuals external to Yale who require a reliance agreement OR Unaffiliated Investigator Agreement, *and*
- Other members of the research team who report financial interests related to the research.

Team members who do not meet these criteria do not need to be listed in IRES IRB.

Principal Investigator conducting a clinical trial must maintain a [Delegation of Authority and Responsibility log](#), which documents delegation of specific tasks related to conduct of the research to other research staff. The log is not part of the submission to the IRB and may include individuals who are not required to be listed in the IRES IRB. The log should be maintained in the study regulatory binder and be updated with addition or removal of the research team members or when the nature of the delegated tasks change.

If the Principal Investigator wishes to list all of the members of the research team in IRES IRB, the study team members page in the system includes a selection of available roles to further describe research roles of each individual.

Investigators

For purposes of this procedure¹, an investigator is considered an individual who, as part of the research team, will assist the Principal Investigator by making a direct and significant contribution to the data and

¹ The criteria for investigators to be listed in IRES IRB may differ from the FDA definition of a sub-investigator or NIH definition of key personnel. The assessment of who should be listed on FDA Form 1572 or who should be included in the grant application to NIH must be made independently of this procedure.

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

the execution of a project in a substantive and measurable way. The contributions of the investigators are not easily replaced in that the investigator's absence from the project would be expected to negatively impact the approved scope of the project or research progress.

Individuals who meet that definition must be listed in IRES IRB if they are also engaged in the portion of the research that involves human subjects. For example, if an individual makes an intellectual contribution to the scientific development of the project and also performs research procedure required by the study protocol, this individual must be listed as an investigator in IRES IRB.

Investigators who are NOT engaged in the human subjects research should not be listed in IRES IRB.

PI Proxies

PI Proxy is a role designated in the IRES IRB system. It provides the ability to submit research documents to the HRPP/Yale IRB and respond to the IRB's or HRPP's requests for revisions on behalf of the Principal Investigator. The designation of the PI Proxy is not a delegation of responsibility for the study to another person. It is only giving an individual an ability to submit documents in the IRES IRB system. The PI gets notified via system generated email when the PI Proxy makes a submission on his/her behalf.

The Principal Investigator should establish an internal procedure related to working with PI Proxies that will allow for proper sign-off on any documentation prior to submitting them in the electronic system.

The role of a PI Proxy is protocol specific. In order to designate a PI Proxy on a study, the individual must be listed on a study team member list. For an ongoing study, a modification must be submitted to the protocol to add the person to the list. Once included on the study team member list, the PI can assign PI Proxy in the main study workspace in IRES IRB.

External Investigators

Individuals engaged in human subjects research who are not formally affiliated with Yale or with an institution that relies on Yale IRB for review of research studies via a reliance agreement (e.g., Yale New Haven Hospital, Haskins Labs) must be listed in IRES IRB. Often, individuals who do not have Yale NetID or who have been assigned a Yale NetID as a Sponsored Identity will be considered external to Yale. They will require additional agreements in place such as Unaffiliated Investigator Agreement or a reliance agreement if the external individual is acting as an agent of an institution with a Federalwide Assurance.

Individuals who do not have Yale NetIDs can be listed on an External Research Team Members log, which must be uploaded into the Study Team Members page along with the documentation of required training. Names of external individuals who have received Yale NetID will be available for selection in the Study Team Members page. Completion of training documented in Training Management System will show in IRES IRB.

Research Staff with Reported Significant Financial Interest Related to the Research

It is the PI's responsibility to verify with each member of the research team whether he/she has any financial interest related to the study. If there is a financial interest related to the study, the research team member must be listed in the Study Team Members page with the indication of a financial interest. Such individual

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

should also complete a Conflict of Interest disclosure form (<https://your.yale.edu/research-support/conflict-interest-office>) to the Conflict of Interest Office.

5.3. Study Modifications

All modifications to the study must be submitted for IRB review and approval in IRES IRB. IRB approval is required prior to implementation of the modification, except where necessary to eliminate apparent immediate hazards to human subjects. If changes are made to eliminate immediate hazards, the IRB must be promptly notified via Report of New Information.

Changes in research include but are not limited to:

- Amendments and modifications to research documents such as the protocol, consent form, investigator's brochure, and other study documentation;
- Changes in research locations, which require revisions to the pages in IRES IRB;
- New risk information regarding the study drug or device, etc.

When submitting modifications to any study-related document that requires IRB review, a summary of changes and a rationale must be included in the Modification Summary. Revisions to documents must be tracked using 'track changes' function. Highlights or using a different color font will not be accepted. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Only the Principal Investigator or assigned PI Proxy can submit the action in IRES IRB. Refer to IRES IRB System Manual in the [IRES IRB Help Center](#) for instructions on creating and submitting study modifications.

5.4. Continuing Reviews

As a standard HRPP practice, reminder notices are sent via email through the IRES IRB system to investigators in advance of a protocol's expiration. However, it is the responsibility of the principal investigator to ensure that research studies are reapproved in a timely manner.

Research that is approved for a specified approval period cannot proceed past the expiration date. To extend the approval period, create and submit a continuing review request in IRES IRB 60 days prior to the study's expiration to ensure adequate time for IRB review. If the continuing review also involves modifications to previously approved research, create a combined continuing review/modification submission. Only the Principal Investigator or assigned PI Proxy can submit the action in IRES IRB. Refer to IRES IRB System Manual in the [IRES IRB Help Center](#) for instructions on creating and submitting continuing review requests.

The dates for the second and all subsequent continuing reviews of research will be based on the date the continuing review is approved (with or without modifications) by the IRB. If the approval of a Human Research protocol expires, the protocol will be administratively closed with no grace period after the expiration date. All Human Research procedures related to the protocol must cease, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection or analysis of private identifiable information. Continuing Human Research procedures without current IRB approval is a

violation of federal regulations and Yale University institutional policy. On the expiration date all research and fund expenditures also must stop. Stopping fund expenditures means that no funds may be drawn down from the payment system and no obligations may be made against Federal funds for research involving human subjects at Yale sites engaged in such research for any period not covered by IRB approval.

If current subjects will be harmed by stopping Human Research procedures that are available outside the Human Research context, provide these on a clinical basis as needed to protect current subjects. If current subjects will be harmed by stopping Human Research procedures that are not available outside the Human Research context, immediately contact the IRB chair and provide a written list of the currently enrolled subjects and why they will be harmed by stopping Human Research procedures. Interventions and/or interactions with current subjects may only continue upon appeal by the principal investigator to the IRB, and only if the IRB finds an overriding safety concern or ethical issue which makes continuation of the subject in the research to be in the best interest of the currently enrolled subject. In no case may new subjects be enrolled prior to re-approval of the project by the IRB.

Failing to have protocols reapproved prior to the lapse date could be considered non-compliance or continuing noncompliance per HRPP Policy.

Reminders to help complete your protocol submission:

- Confirm the funding source(s) in the electronic protocol record. All current funding sources must be listed in order to allow for a congruency review and to ensure funding of the study is not held up. If there are changes to the Funding information, a modification must also be submitted.
- Confirm all active study personnel and remove or add personnel as appropriate via modification. Please also be advised that human subject protection training is required at least once every three years for all study staff. If the PI training is not complete, the submission will not be accepted by the IRB.

5.5. Study Closures

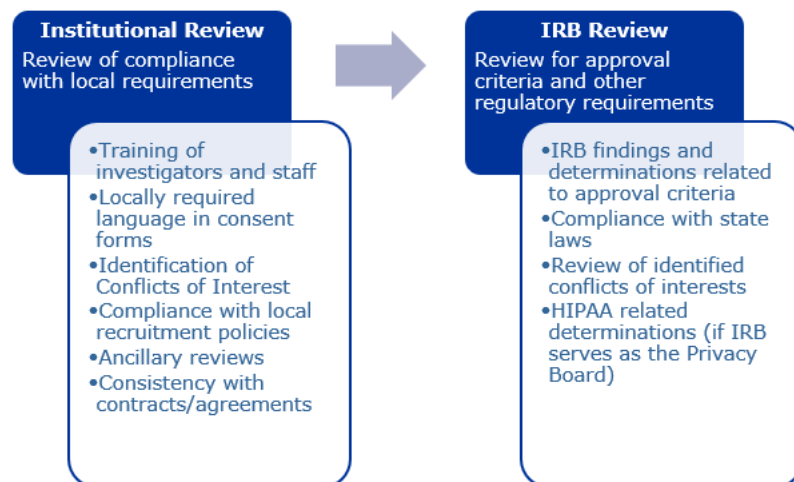
Non-exempt research studies can be closed if all of the following criteria apply:

- The study is permanently closed to enrollment or was never open for enrollment,
- All subjects have completed all study-related interventions, including follow-up procedures (if any),
- Collection of private identifiable information is complete (if any), and
- Analysis of private identifiable information is complete (if any).

Create a Continuing Review/Closure submission, attach all requested supplements, and submit electronically to the IRB. Only the Principal Investigator or assigned PI Proxy can submit the action in IRES IRB. If the continuing review application for closing out a Human Research study is not received by its expiration date, the protocol will be administratively closed with no grace period after the expiration date.

5.6. Review Process

Submissions received in IRES IRB will first undergo review by the Institutional Review team for compliance with institutional requirements (see section # 3 on [University Requirements related to human subjects research](#)). Investigators may receive request for clarifications if there are questions about completeness of the submission or compliance with institutional requirements. Once the submission is deemed complete, it is triaged to undergo IRB review. Submissions meeting criteria for expedited review are assigned to an expedited review queue. Submissions requiring full board review, are assigned to the agenda for the next available IRB meeting.



5.7. IRB review outcomes

The IRB will provide you with a written decision indicating that the IRB has approved the Human Research, requires modifications to secure approval, has deferred approval or has disapproved the Human Research.

- If the IRB has approved the Human Research: The Human Research may commence once all other organizational approvals have been met. IRB approval may be effective for a limited period of time, which is noted in the approval letter. Unless held by the IRB, documents may receive approval watermarks according to the following practice:

Initial approval

The following watermarks are applied to headers and footers of the documents:

- Consent and assent forms and the research protocol receive approval watermark stating *'Approved by the Yale University IRB MM-DD-YY'*;
- Documents uploaded in the Recruitment Materials section of IRES IRB, as well as the Drugs and Device attachments receive acknowledgment watermark stating *'Acknowledged by the Yale IRB MM/DD/YY'*;

	<p>Human Research Protection Program Investigator Manual</p>	<p>Version 2.1 07/24/2023</p>
---	--	-----------------------------------

- Documents uploaded as Local Study Documents (e.g., IRB Submission Form, Unaffiliated Investigator Agreements, Special Permission to Serve as the PI, etc.) do not receive any watermarks.

Continuing Review Approval

No documents receive approval/acknowledgment watermarks.

Modification approval

Documents that are revised or new documents added to the protocol as a result of the modification will receive approval/acknowledgment watermarks. Refer to Initial approval section for the exact wording of the watermarks that will be applied to documents.

Continuing Review with a Modification approval

Only documents that are revised or added to the protocol as a result of the modification will receive approval/acknowledgment watermarks. Refer to the Initial approval section above for the exact wording of the watermarks. Documents not affected by the modification will not receive any watermarks.

- If the IRB requires modifications to secure approval: Make the requested modifications and submit them to the IRB. If all requested modifications are made, the IRB will issue a final approval. Research cannot commence until this final approval is received unless specified otherwise in the approval letter. If you do not accept the modifications, write up your response and submit it to the IRB.
- If the IRB defers the Human Research: The IRB will provide a statement of the reasons for deferral and suggestions to make the study approvable and give you an opportunity to respond in writing. In most cases if the IRB’s reasons for the deferral are addressed, the Human Research can be approved.
- If the IRB disapproves the Human Research: The IRB will provide a statement of the reasons for disapproval and give you an opportunity to respond in writing.

In all cases, you have the right to address your concerns to the IRB directly at an IRB meeting.

6. Informed Consent Considerations

6.1. Overview of Consent Documentation

In order to involve human subjects in research, an investigator must first obtain the legally effective informed consent of the subject. Consent should be documented in writing by use of the IRB approved consent form.

Under certain circumstances, the IRB can grant a waiver of the documentation of consent (per 45 CFR 46.117), in which case, consent from subjects can be obtained verbally or via electronic means, such as clicking “Agree” prior to beginning an online survey (this should not be confused with formal eConsent).

	<p>Human Research Protection Program Investigator Manual</p>	<p>Version 2.1 07/24/2023</p>
---	--	-----------------------------------

The IRB may still require an information sheet to be provided to the study participants. This form needs to be submitted to and reviewed by the IRB. To determine whether your study would qualify for a waiver of documentation of consent, review HRP CHECKLIST 411 'Waiver of Written Documentation of Consent'.

It is possible, that a study may meet criteria for a waiver of consent, in which case, there will be no need for the consent form. To determine whether your study meets the requirements for a waiver of informed consent, refer to HRP CHECKLIST 410 'Waiver or Alteration of Consent Process'.

Use the consent document and signature block approved by the IRB. Complete all items in the signature block, including dates and applicable checklists.

The following are the requirements for long form consent documents:

- The subject or representative signs (or makes their mark) and dates the consent document.
- The individual obtaining consent signs and dates the consent document.
- Whenever the IRB or the sponsor require a witness to the oral presentation, the witness signs and dates the consent document.
- For subjects who cannot read, or whenever required by the IRB or the sponsor, a witness to the oral presentation signs and dates the consent document.
- A copy of the signed and dated consent document is to be provided to the subject.

For greater than minimal risk studies it is important to document the **process** of consent. The documentation of the process should be kept in the subject's research records and at a minimum should include the following information:

- Individuals present during the consent discussions;
- Questions asked by the study subjects and answers provided; and
- The subject's decision.

6.2. E-Consent

Electronic consent, or e-Consent, is the use of electronic or digital means, whether in person or remotely, that utilize electronic media to convey information relating to a research study and to document informed consent of subjects who wish to participate in such study. The e-Consent mechanism must contain all of the elements of informed consent required by 45 CFR 46, and, if applicable, FDA Regulations (21 CFR 50), unless the IRB has appropriately waived one or more of the elements.

e-Consent for FDA Regulated Research

If a research study involves an FDA-regulated product and is subject to FDA regulations, compliance with the requirements of 21 CFR 11 is required and other applicable regulatory requirements. In addition to meeting applicable regulatory requirements, all systems may first need to be certified by Yale IT before it can be used for e-Consent. At the present time, the only systems at Yale University that have been certified to be HIPAA and 21 CFR 11 compliant for utilization of e-Consent is through Yale New Haven Hospital's Epic or YCCI managed RedCap. Therefore, these are the only systems that can be used to obtain e-Consent

	<p>Human Research Protection Program Investigator Manual</p>	<p>Version 2.1 07/24/2023</p>
---	--	-----------------------------------

for FDA regulated research at this time. For information regarding the Epic eConsent functionality, please contact: Clinicalresearchresources@yale.edu; for YCCI managed RedCap, see <https://medicine.yale.edu/ycci/researchservices/systems/redcap/>.

e-Consent for Non- FDA Regulated Research

For non-FDA regulated clinical studies in which Epic builds are not completed or non-clinical studies, the Yale-licensed version of REDCap may be used to obtain e-Consent when a signed consent is required. If the study is eligible for a waiver of written documentation of consent in accordance with 45 CFR 46.117(c), then you may obtain consent via other media, such as the Yale-licensed version of Qualtrics.

Discussions with subjects, including during the consent process, can occur by telephone or via teleconference systems such as the Yale approved version of ZOOM.

6.3. Documentation of consent using short form

A short form is used for obtaining consent from individuals who do not speak English in situations where there is not sufficient time to translate the consent document into his/her language. There are specific requirements regarding using short forms for obtaining consent:

- The investigator obtaining informed consent, with the assistance of an interpreter if needed, provides orally to the participant the elements of informed consent and any additional information included in the IRB-approved English version of the long form.
- This presentation may be an oral translation of the IRB-approved English version of the long form. The oral presentation must be in language understandable to the participant.
- The investigator, with the assistance of an interpreter if needed, answers any questions from the prospective subject.
- There must be a witness to the oral presentation who must not be the person obtaining informed consent. Furthermore, the witness should be fluent in the language of the oral presentation.
- The participant is given the IRB-approved translated short form and a copy of the IRB-approved English version of the long form, which serves as the written summary.
- The documents are signed and dated.

The regulations do not specify who can serve as a witness. The FDA and OHRP guidance provide explanation that an interpreter can serve as a witness and that the individual obtaining consent, cannot. Both FDA guidance and GCP guidance include a statement about ‘impartial’ witness². [E6\(R2\) Good Clinical Practice: Integrated Addendum to ICH E6\(R1\)](#) defined the term ‘impartial witness’ as ‘A person, who's independent of this trial, that can't be unfairly influenced by people associated in this trial, who attends the informed consent process if the subject or the subject's legally acceptable representative can't read, and who reads the informed consent form and any other written information provided to the topic.’

² [FDA Guidance](#): ‘FDA recommends that an impartial third party, not otherwise connected with the clinical investigation (for example, clinical staff not involved in the research or a patient advocate), serve as the witness.’

A role of the witness is to attest that the consent process was adequate (e.g., that the elements in the short form were discussed, questions were answered, etc.) and that the participant gave a voluntary consent. A family member may be able to independently assess that, regardless of their own opinions. In its discussion on FDA guidance on consent³, the Secretary's Advisory Committee on Human Research Protections' (SACHRP) stated that '[...] an adult family member can serve as a witness in this role, where there is no reasonable concern that the proposed witness is not acting in the best interest of the individual.'

Whenever possible, investigator should identify somebody who speaks both languages and is independent of the participant and the study team. However, if that is not possible and based on the interactions with the family member, the investigator believes that the family member acts in the best interests of the participant, the family member can serve in the role of the witness. If researchers observe that the family member is pressuring the participant to sign consent documents or persuading the participant not to ask questions, or observe any other behavior of concern, the family member may not be an appropriate choice for a witness. It may be appropriate to allocate additional time for discussions and considerations, arrange for another witness, or make a point of checking in with the participant at another time with another witness as part of the ongoing consent process.

For FDA regulated research, there are additional expectations⁴ regarding obtaining long version of consent:

'For FDA-regulated research, the investigator must promptly obtain a translated copy of the IRB-approved English version of the long form, which served as the written summary. The investigator promptly submits it to the IRB for review and approval. Once the translated long form/written summary is approved by the IRB, the investigator provides it to the subject as soon as possible. FDA considers this step essential to the requirement that informed consent be documented by the use of a written consent document and that the subject be provided a copy (21 CFR 50.27). Many of the clinical investigations regulated by FDA involve ongoing interventions and may involve long-term follow-up. FDA believes that translation of the long form is critically important as a means of providing subjects an ongoing source of information understandable to them.'

Yale IRB preapproved several translated versions of the short form, which are available in the IRES IRB library. These forms do NOT require additional approvals and should be used as published. Note, these forms do not contain HIPAA language necessary to obtain subjects' authorization to use their PHI for research. As such, the use of translated HIPAA Research Authorization forms or a waiver of documentation of HIPAA authorization will be required. Translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu).

³ [SACHRP Commentary on the FDA Draft Guidance Entitled, "Informed Consent Information Sheet; Guidance for IRBs, Clinical Investigators and Sponsors," released July 15, 2014, docket number FDA-2006-D-0031](#)

⁴ [FDA Guidance, Section B, 2. Informed Consent Procedures when Enrollment of Subjects who do not Understand English is Unexpected, Step 3 – Take Additional Actions Following Subject Enrollment](#)

6.4. Alternative methods of obtaining consent from participants when consent process cannot be conducted in person

When the consent process cannot be conducted in person at the clinical trial site, an alternative method may be used. 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 will 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 will 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 will sign and date the consent document and return the signed consent to the study team as a scanned document via email or fax, delivered in-person or via mail.
- If utilizing e-consent, signature will be obtained using one of the Yale ITS validated and approved eConsent platforms that are 21 CFR Part 11 compliant.
- Once the research team receives the signed informed consent document from the participant, the investigator who conducted the consent process will sign and date the document using the current date. Under the signature line, the investigator will document that consent was obtained over the telephone or video conferencing, and will include 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 will be appended to the participant's research record (and medical record when applicable) and a copy will be then provided to the participant.
- No research activities may occur until the proof of signed consent form is received by the investigator.

	<p>Human Research Protection Program Investigator Manual</p>	<p>Version 2.1 07/24/2023</p>
---	--	-----------------------------------

*If the participant cannot print the consent form provided electronically, a witness, who is not otherwise connected with the clinical investigation, will be present during the discussion. After the discussion, the participant will 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.

6.5. Assent

Depending on the assessment of the maturity and cognitive abilities of the children to be enrolled, assent may be written or verbal. Children capable of reading and writing should be provided an assent form written in language appropriate for their cognitive level. The assent process as well as any forms must be approved by the IRB. In general, the following standards will be applied:

Infants and Young Children: If the child is under the age of 7, or found intellectually unable to provide assent, only a parental permission form is required.

Children: If the subject's intellectual capabilities fall within the range of a normal 7-12 year-old, an assent form is required in addition to the parental permission form.

Adolescents: If the subject is 13-17 years of age, and has age-appropriate cognition and understanding, an adolescent assent form is required in addition to a parental permission form.

6.6. Consent process

Consent is a process that contains three crucial elements: providing information relevant to the study, confirming a potential subject's comprehension, and seeking the subject's voluntary participation.

A few points to remember:

- Do not just read the consent document to the subject and then ask him/her to sign it. The process should include a dialogue between the researcher and the potential subject based on the information included in the consent form.
- If possible, include different modes of presenting information (e.g., recorded video, slides with key points, charts or tables with study visits, etc.).
- Ensure that there is sufficient time available to the potential subject to think about participation in the study. Would it be appropriate to invite the individual's family member to be part of the

discussion? Would it benefit the subject to take the consent document home to have additional time to think about if they'd like to participate in the study or not, prior to providing an answer to the researcher?

- Ensure that consent is obtained in situations free of undue influence or coercion. Do not act in a threatening way and do not overpromise the benefits of the study.
- Ensure that subjects understand the nature of the study (along with risks and benefits) and what they are being asked to do. Ask open ended questions to ensure understanding (e.g., 'Tell me about the risks of the study' and not 'Is fatigue a risk of the study medication?')

6.7. Reconsent process

Subjects need to be informed of any significant new information that emerges during the course of the study that may affect subjects' willingness to continue to participate. Subjects should be informed in a timely manner about issues that affect their health and well-being.

The following questions and considerations will aid you in the determination of notification and re-obtaining consent from subjects.

Questions	Considerations
<p>Who must be notified or have consent re-obtained?⁵</p> <ul style="list-style-type: none"> • All subjects ever enrolled in the study regardless of their current status • Only subjects active on study intervention or another subset of subjects 	<p>Does the change affect different groups of subjects differently?</p> <p>If so, which groups of subjects are affected? Does it depend on the subject's status (active, previously enrolled), arm of the study, or gender or age groups?</p> <p>Will the impact of the change affect subjects after the study is complete?</p>
<p>What exactly is the change that requires communication?</p> <ul style="list-style-type: none"> • New risks • New inconveniences 	<p>Could the information affect a subject's willingness to continue participation?</p>

⁵ Note – FDA does not require re-consenting of subjects that have completed their active participation in the study, or of subjects who are still actively participating when the change will not affect their participation; for example, when the change will be implemented only for subsequently enrolled subjects. (See Institutional Review Boards Frequently Asked Questions – Information Worksheet at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126420.html>)

<ul style="list-style-type: none"> • New procedures • New treatment alternatives • New costs • Other significant findings 	Will the change require a different level of commitment from the subject; e.g., additional procedures?
---	--

Below are examples of changes that could affect study participants based on their study status.

Active Study Participants	
New Information Likely to Affect Participants	Information Not Likely to Affect Participants
<ul style="list-style-type: none"> • New or increased risks of the study intervention/study procedures • Additional study procedures required by the study; e.g., additional Lumbar Puncture or MRI • Changes in doses or frequency of the study drug • Modifications to the study design; e.g., timeline of their study visits • Changes to payments or cost for participation; e.g., previously provided drug now being charged to participant's insurance, changes to remuneration • New FDA approval of drugs involved in the study or those that create new alternative treatment 	<ul style="list-style-type: none"> • Administrative changes such as the date or version number of the consent form • Modifications to the arm of the study that does not apply to all participants; e.g., changes for non-smokers while the subject is enrolled in the arm for smokers • Addition of procedures that the subject will not be asked to undergo; e.g., baseline MRI • Minor editorial changes in the consent/protocol for clarity

Previously Enrolled Study Participants Who Concluded Their Participation	
Information Likely to Affect Participants	Information Not Likely to Affect Participants
<ul style="list-style-type: none"> • Newly discovered long term side effects of the study drug • New adverse events associated with the implanted study device 	<ul style="list-style-type: none"> • New short term side effects of the study drug/procedure • Changes to the study design • Any information that would not affect currently enrolled subjects

The choice of the appropriate method of subject notification depends on many factors including the urgency of the information, a requirement set by the sponsor or the IRB, and a necessity for the action on part of the participant; e.g., agreement to the new study procedure or continuation in the study given the new information. Rely on your professional judgment to determine how quickly the new information must be communicated to the participants. The following questions and considerations will aid in the determinations regarding methods and timeline for re-consenting and notification.

Questions	Considerations
<p>When must notification or re-consent occur to protect subject safety and rights (regardless of logistics)?</p> <ul style="list-style-type: none"> • Immediately (as soon as possible) • Before next study visit • Before specific study procedures • Within specified time period • Dependent on affected participant subset 	<p>Are subjects coming in for study visits or are remaining study procedures done at home or over the phone?</p> <p>Are subjects impacted now or in the future?</p> <p>Are subjects who have completed study procedures/visits impacted?</p>
<p>Where and How should notification be implemented?</p> <ul style="list-style-type: none"> • In-person visit • Letter with phone follow-up • Revised consent form/addendum 	<p>Consider:</p> <ul style="list-style-type: none"> • Complexity and need for interactive explanation and discussion • Need for physical demonstration or other presentation of information best done in person • Timeline for next subject visit • If the participant is decisionally impaired or a minor, need for legal guardian or parent to be involved and re-consented

Examples of methods for subject notification/re-consenting:

	Affected Participants
<p>Research participant’s decision needed regarding their continued participation</p>	<ul style="list-style-type: none"> • <u>Consent addendum</u> – allows for emphasis on the new information with the understanding that information presented in the main consent may still apply; e.g., new risks are discussed in the consent addendum but protections of confidentiality do not change. • <u>Full Revised Consent Form</u> – should be used when changes to the consent form are extensive. Can be used with a memo/cover letter that

	<p>highlights the changes, which would also be addressed during the re-consenting discussions.</p>
<ul style="list-style-type: none"> • Notification needed only OR • Only verbal consent required 	<ul style="list-style-type: none"> • <u>Documented phone call</u> – participants may be informed via phone call when their participation has concluded and they do not need to provide continued consent. The IRB can also determine that research participant’s verbal agreement to continue to participate in the study is sufficient e.g., addition of a questionnaire that would be conducted over the phone. • <u>Informational Letter</u> – participants are informed via written communication. Receipt should be acknowledged and documented in the study file, can be followed by a phone call.
<p>Immediate notification needed</p>	<ul style="list-style-type: none"> • <u>Phone Call</u> – when the study participants are at immediate risk and an action is needed (e.g., stopping the study medication), a phone call should be placed as soon as the new information emerges, prior to the approval of the notification documents by the IRB. The phone call should be documented and followed by written notification/re-consenting.

Follow this process:

- Make an initial determination whether new information should be communicated to current and/or previously enrolled study participants and decide on the most appropriate form of communication.
- Submit a modification to the consent form and the protocol in IRES IRB.
- Include your proposed plan for notification of the participants or rationale for why the new information does not need to be communicated to participants.
- Once IRB approval is obtained and if re-consent is required, ensure that participants should provide their consent prior to their involvement in the procedural change.

The IRB will review your plan for subject notification and determine whether any additional actions are needed. The determination will be included in the approval letter of the modification. Review the finding in the letter to communicate to your research team members. You need to comply with the IRB’s decision as not doing so may constitute noncompliance.

7. Study Recruitment and Payment for Study Participation

7.1. Recruitment of subjects

Recruitment methods used to solicit volunteers into human research must be equitable and free of bias, undue influence and coercion and must respect the privacy of potential research participants. The IRB must

review and approve the methods, materials, procedures, and tools used to recruit potential research participants before they are implemented.

Examples of the types of recruitment materials that have to be reviewed and approved by the IRB include:

- Print advertisements: flyers, brochures, posters, newspaper ads
- Internet advertisements: web pages, postings on social media
- Press releases is the intent is to recruit participants
- Radio and Television advertisements
- Telephone and email screen scripts
- Recruitment letters
- Bulletin boards or billboards
- Study newsletters that are created with the intent to recruit subjects

What does not require IRB review:

- Clinical trial listings, such as those seen on clinicaltrials.gov,
- General study newsletters that are not distributed as recruitment materials do not require individual review. The intent to use and the expected content of the newsletters need to be described in the protocol application and approved by the IRB, but continuing IRB review and approval of issued newsletters is not required if their purpose is informational only.
- Press releases as long as the information contained in the document does not include the following:
 - Name of the specific study
 - Eligibility – inclusion and exclusion criteria
 - Investigator or specific research study personnel
 - Sponsor of the study
 - Payment information (compensation/reimbursement) for participation
 - Specific contact information (name, telephone number, etc.)
- Changes to the existing and approved recruitment materials if they only apply to the contact information.

Generally, recruitment materials should be limited to the information a prospective research participant needs to determine their eligibility and interest in the research, such as:

- The name and address of the investigator,
- The IRB protocol number,
- A statement about purpose of the research,
- Participants eligibility criteria,
- May include a brief list of study participation benefits, if any, and the risks for participating in a research study,

- The amount of time or other commitment required of the subjects in the study,
- The location of the research site and the name of the person or office a potential participant can call to obtain additional information.

Considerations for drafting advertisements:

- No claims should be made, either explicitly or implicitly that the drug or device is safe or effective for the purposes under investigation, or that the test article is known to be comparable or superior to any other drug or device.
- Advertisements for studies using investigational drugs or devices must also not use terms such as “new treatment,” “new medication,” or “new drug” without explaining that the test article is investigational.
- Advertisements must not promise “free medical treatment” when the intent is only to say subjects will not be charged for taking part in the study.
- Advertisements should not be coercive or use exculpatory language.
- Advertisement should not be emphasizing the payment or the amount to be paid by such means as larger or in bold font.
- Advertisement should not promise or imply a certainty of cure, favorable outcome, or other benefit beyond what is included in the IRB-approved protocol and/or consent form.

Yale and Yale New Haven Hospital have specific policies in place regarding allowable methods of recruitment including using medical records to identify potential participants. For more information, see Special Topics section of the HRPP Policy and Standard Operating Procedure Manual.

7.2. Payments to study participants for participation

Participants can be offered payments for their participation in research. They have to be described in the protocol or IRB submission form and the consent forms. There are two types of payments that can be offered:

Stipends are paid to the study subject at a flat rate by procedure or study without regard to any actual out-of-pocket costs and are taxable. Stipends can be paid using a bank card or by cash/check⁶. The Consent Glossary provides specific language for use of bank cards. Refer to HRP WORKSHEET 316 ‘Payments’ for important considerations regarding how the payments should be designed (including timing) not to create undue influence and follow the available agency guidance⁷.

⁶ For additional information on remuneration methods at Yale, see [3417 PR.01 Human Research Study Participant Remuneration](#)

⁷ [See FDA Guidance on Payment and Reimbursement to Research Subjects.](#)

Expense Reimbursements are costs reimbursed to the study subject based on their actual costs incurred and not as a flat rate payment. Generally, there are specific sponsor criteria associated with such expense reimbursements such as minimal travel distance, maximum amounts for hotel, meals, etc. There may also be specific pre-approval requirements. Receipts are normally required to be submitted to the sponsor. These costs are invoiced to the Sponsor and not paid automatically. Expense reimbursements are not taxable. If such costs are allowed by the Sponsor, expense reimbursement terms must be clearly explained in the consent form. It is important not to confuse the stipends (taxable) with reimbursements (non-taxable). For information about e-payments for stipends and expense reimbursements see 'Subject or Participant Payments' on [the YCCI website](#).

7.3. Eligibility exceptions

All changes to the study, including enrolling ineligible subjects, must be reviewed and approved by the IRB prior to implementation of the change, except where the changes are necessary to eliminate apparent immediate hazards to human subjects. Changes must be submitted via a modification in IRES IRB system. If there is no associated change to revise the inclusion/exclusion criteria in the protocol, sponsor approval to enroll a participant who does not meet the criteria must be included with the submission.

8. Confidentiality

8.1. Research Data

Yale classifies data collected or maintained by Yale users and systems that support the data into three categories:

- High Risk Data
- Medium Risk Data
- Low Risk Data

Most identifiable research data falls into the High Risk Data category. Risk classification determines the appropriate security requirements for a Yale IT System. These security requirements are known as Yale's Minimum Security Standards (MSS). Certain systems are approved at Yale to be used with High Risk Data. When deciding what applications or systems to use for collection, storage, or sharing of your data, you should consult this guide listing the systems that are approved for use with High Risk Data: <https://cybersecurity.yale.edu/service-classification>. If the proposed service is not included in the list and a third party vendor operating the service has access to Yale PHI, a Business Associate Agreement (BAA) is needed. The HRPP may coordinate with Yale Privacy Office to verify whether the BAA is in place and refer you to the Yale IT Services for consultation regarding the system compliance with Yale's Minimum Security Standards requirements.

8.2. Certificates of Confidentiality

A Certificate of Confidentiality (CoC) protects an investigator from certain disclosures (compulsory legal demands, such as court orders and subpoenas) of private information about participants. All biomedical,

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

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 will be issued an automatic CoC by NIH as part of the award itself. Principal Investigators of studies not funded by NIH can voluntarily apply to NIH for CoC. The IRB can require that one be obtained. Read more about Certificates of Confidentiality on the [NIH website](#) and [FAQ website](#).

When a CoC has been issued for a study, either automatically through a funding mechanism or by request from investigator, study consent documents must include information about the protections and limitations of the Certificate of the Confidentiality. You can find recommended language in the Consent Glossary document, located in the Library section of IRES IRB.

If the CoC is a requirement of the IRB, your study may not be approved until the CoC is in place. Requests to NIH for CoC for non-NIH funded studies are made in [an online request system](#). You have to complete the submission in one session as you cannot save unanswered sections and return to them later. Have the following prepared:

1) Project details:

- a) Research title,
- b) Start and end dates,
- c) Written description of the aims and research procedures,

2) Institutional and performance sites details:

- a) Name and the address of the institution,
- b) Performance site(s) names and addresses,
- c) Contact for the Institutional official (Pamela Caudill, email: pamela.caudill@yale.edu, phone: 203-785-2518)

3) Principal Investigator and Key Personnel details:

- a) PI's name, phone, email, degree and position at Yale
- b) Key Personnel's names, degrees, and current positions

4) If your research involves administration of drugs:

- a) Name of drugs that will be administered,
- b) Route of administration,
- c) Dosage.

The Yale Institutional Official will receive an email asking for institutional assurances. Yale HRPP will work with the Institutional Official to confirm that the request for the Certificate of Confidentiality is valid, and that the IRB is aware of the request and reviewed the consent forms for the required language. You will receive an email with the CoC when it is issued. Provide the CoC to the IRB either in response to Modifications Required requesting the CoC or via a modification to add the document to the Local Site Documents page.

Several non-NIH HHS agencies including **CDC, FDA, HRSA, SAMHSA, IHS** and other agencies, including Agency for Healthcare Research & Quality or Department of Justice, issue Certificates of Confidentiality or similar Privacy Certificates. Locate the appropriate funding agency on [the Certificate of Confidentiality website](#) and follow the instructions for the submission process.

8.3. Sharing data after completion of the study

Investigators are encouraged to share their research data with other researchers. Data Sharing Plan may also be a requirement of the funder:

- [NIH Policy for Data Management and Sharing](#), effective January 25, 2023 requires a plan at the time of the grant application⁸
- Other agencies may already have policies in place ([The Agency for Healthcare Research and Quality Data Management Plan Policy](#))

When deciding whether and how to share research data, the following issues must be considered:

- Issues of participant’ personal privacy (the more identifiable the data, the higher the risk to personal privacy, see the table below with the degree of identifiability of data)
- Potential for inappropriate use, even with restrictions on access and purpose of reuse
- Costs associated with making the data usable by others
- Administrative resources required for agreements and licenses
- Different cultural norms and data protection policies
- National security and public safety
- Proprietary rights (private sector funding)
- Funder and institutionally driven data sharing expectations e.g., which data must be shared, relevant standards, donation to a specific repository within specified timelines, etc.

Type of Data	Degree of identifiability
Identifiable data	Data that can be associated with the specific person as it contains direct and indirect identifiers.
Coded	Data where identifiers were replaced with a code, a link to the identifiers exist, but identity of the individual cannot be reasonably ascertained by an individual not engaged in the data collection.
Anonymized	Previously identifiable data that have been de-identified and for which a code or other link no longer exists, there is NO means for linking anonymized data back to a specific individual.
Anonymous	Data that was collected without identifiers and that were never linked to an individual.

⁸ For more information see [NIH FAQ section on 2023 Data Management & Sharing Policy](#)

Aggregate	Statistical data that does not contain individual-level entries, large numbers of individuals renders the individual attributes not identifiable.
-----------	---

You should take the following elements into consideration when creating **Data Sharing Plans**⁹ for grant submissions:

- Document the type of data that will be produced,
- Decide on which data will be shared (e.g., raw video vs. transcripts) and restrictions on sharing and reuse of the data based on the sensitivity of the data,
- List the standards to make the data FAIR and CARE principles (see the description of the principles below),
- Identify the technology tools for sharing during the project and after the project (research and name specific TRUSTworthy Repositories and Data Sharing Platforms required or appropriate for the data and timelines for sharing, see the description of the principle below),
- Document all procedures and any relevant policies or legal requirements (e.g., HIPAA, GDPR; see [Yale Privacy Office website](#) for more information on contractual agreements),
- If possible at this stage, describe and delegate data management roles and responsibilities to the team members.

Data Sharing Principles

- FAIR¹⁰

F	A	I	R
Findable	Accessible	Interoperable	Reusable
Data and metadata should be easy to find by both, humans and computer systems.	Data and metadata should be stored for the long term such that they can be easily accessed and downloaded or locally used by machines and humans using standard communication protocols.	Data should be ready to be exchanged, interpreted and combined in a (semi)automated way with other data sets by humans as well as computer systems.	Data and metadata are sufficiently well-described to allow data to be reused in future research, allowing for integration with other compatible data sources. Proper citation must be facilitated, and the conditions under which the data can be used should be clear to machines and humans.

⁹ See 25 elements of the Agency for Healthcare Research and Quality Data Management Plan Policy, <https://grants.nih.gov/grants/guide/notice-files/NOT-HS-20-011.html>

¹⁰ Wilkinson, M., Dumontier, M., Aalbersberg, I. et al. The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* 3, 160018 (2016). <https://doi.org/10.1038/sdata.2016.18>

- **CARE Principles for Indigenous Data Governance¹¹**

C Collective Benefit	A Authority to Control	R Responsibility	E Ethics
Data ecosystems shall be designed and function in ways that enable Indigenous Peoples to derive benefit from the data.	Indigenous Peoples' rights and interests in Indigenous data must be recognized and their authority to control such data be empowered.	Those working with Indigenous data have a responsibility to share how those data are used to support Indigenous Peoples' self-determination and collective benefit.	Indigenous Peoples' rights and wellbeing should be the primary concern at all stages of the data life cycle and across the data ecosystem.

- **The TRUST Principles for digital repositories¹²**

T Transparency	R Responsibility	U User focus	S Sustainability	T Technology
Repositories must provide transparent, honest, and verifiable evidence of their practice	Take responsibility for the stewardship of their data holdings and for serving their user community (adhere to community's metadata standards, manage intellectual property, etc.)	Needs to focus on serving its target user community	Ensuring sustainability of a TRUSTworthy repository is necessary to ensure uninterrupted access to its valuable data holdings for current and future user communities	Demonstrate fitness of its technological capabilities by: <ul style="list-style-type: none"> • Implementing relevant and appropriate standards, tools, and technologies for data management and curation. • Having plans and mechanisms in place to prevent, detect, and respond to cyber or physical security threats.

¹¹ Global Indigenous Data Alliance, GIDA, <https://www.gida-global.org/care>

¹² Lin, D., Crabtree, J., Dillo, I. et al. The TRUST Principles for digital repositories. *Sci Data* 7, 144 (2020). <https://doi.org/10.1038/s41597-020-0486-7>

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

Budget Considerations

- Understand existing resources in your department at the University (See IT and [Library pages](#))
- Verify the allowable costs e.g., NIH distinguishes between institutional overhead costs (e.g., infrastructure) and costs of conducting research (access to data) and allowable direct costs¹³
- Think costs related to **personnel** and **infrastructure**:
 - National Academies of Sciences, Engineering, and Medicine, (2020) [Life-Cycle Decisions for Biomedical Data The Challenge of Forecasting Costs](#)

Ensure that the following are budgeted for appropriately:

- Curating data and developing supporting documentation
 - Formatting (FAIR data principles, standards used in the discipline)
 - Anonymizing (HIPAA de-identification methods, aggregating)
 - Preparing usable metadata sets (supporting documentation such as data dictionaries)
- Local data storage considerations
 - Local IT infrastructure
- Preserving and sharing data
 - Deposit fees to repositories
 - Long-term storage.

When deciding on who and how others can access the data, consider the following:

Restricted access:

- How it can be accessed (sandbox, API, etc.,)
- What reason it can be used for (consistent with the consent form signed by the individual)
- Additional approvals may be required (approvals from local IRBs to ensure secure IT systems, Data Use Agreements, Data Governance Committee Approvals)

Open access:

- Access to data is open to users and can be reused without restrictions
- License may be attached to ensure proper citations of the data origins

Even with open access data, information about the following should travel with the data:

- Responsibilities of the users (data protections, no reidentification efforts)
- Specific recommendations regarding data citation for publications and presentations

¹³ See [Supplemental Information to the NIH Policy for Data Management and Sharing: Allowable Costs for Data Management and Sharing](#)

If data sharing is required as part of the grant application or if you plan on sharing the data voluntarily, consent must appropriately describe future sharing¹⁴. At a minimum, the following should be included:

- Information about future storage and sharing of the data with individuals outside of the research team (including around the world) will have access to the data,
- Explanation that future research may focus on variety of areas, not only what the study is about,
- Description of the level of the identifiability of the information that will be shared,
- Risk of future individual identification,
- If known, the name of the repository or another data sharing platform and who control the access,
- Distinction between Voluntary vs. Mandatory sharing (if participants do not agree to sharing, they cannot participate in research),
- Explanation whether it is possible to withdraw from the future sharing.

Examples of language describing future data sharing is available in the Consent Glossary posted in the IRES IRB website. For additional information, see the Provost website on Data Sharing and Management.

As with all federally funded studies, when you submit the research protocol in IRES IRB either for IRB review or with a request to use an external IRB, the HRPP will review the grant and compare it to the protocol documents. This review will include elements of your data sharing plan as described in the grant. If the grant application involves donating the data to a specific repository, the HRPP will ensure that the reviewing IRB, whether internal Yale IRB or an IRB external to Yale, has access to pertinent details of your data sharing plan and the consent forms include the name of the repository and a meaningful description of how the participant's data will be shared.

8.4. Genomic Data Sharing

Requesting IRB GDS Assurance

Per the NIH Genomic Data Sharing (GDS) Policy, when large-scale human or non-human genomic data is generated from NIH funded research it must be submitted to NIH (see [NIH Genomic Data Sharing Policy](#)).

If your proposed project involves a genomic data sharing plan for the generation of human genomic data, investigators must submit an Institutional Certification, or, in some cases, a Provisional Institutional Certification to the National Institutes of Health (NIH). The Extramural Institutional Certification can be found at <https://sharing.nih.gov/genomic-data-sharing-policy/institutional-certifications/completing-an-institutional-certification-form#step-0>.

¹⁴ See NIH 'Points to Consider and Sample Language for Future Use and/or Sharing', <https://osp.od.nih.gov/wp-content/uploads/Informed-Consent-Resource-for-Secondary-Research-with-Data-and-Biospecimens.pdf>

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

Before the Institutional Certification can be signed by the Yale University Institutional Official (IO), you will be required to complete a [Qualtrics survey for requesting IRB assurance](#). The Qualtrics survey will provide the IRB with the information necessary to perform the IRB Assurance and confirm that the information between the genomic data sharing plan provided in the Data Resource sharing section of the grant proposal and the language in the protocol and consent form(s) are consistent. Please note: There are specific requirements related to information that must be included in the consent forms for studies subject to this policy. Examples of applicable language are included in the Consent Glossary, available in the Consent Forms tab of the Library in IRES IRB.

Once the assurance review is complete, the IRB will generate an IRB assurance letter. The letter will be emailed to you and your OSP proposal manager so that it can be sent to the NIH along with the signed Institutional Certification.

For questions regarding the IRB GDS Assurance request, please email HRPP@yale.edu or call 203-785-4688.

Helpful links:

[Qualtrics survey for requesting IRB assurance](#)

[NIH Guidance on elements of consent under GDS Policy](#)

[NIH genomic data sharing FAQ](#)

9. Submission of Reportable Items to Yale IRB

Review [Appendix E](#) on the types of events that must be submitted to Yale IRB as Reportable New Information (RNI) in IRES IRB. Some events may require a submission of a modification in addition to the RNI.

9.1. Reporting protocol deviations and noncompliance to the IRB

Reports and allegations of serious and/or continuing noncompliance must be reported to the IRB office within five (5) business days of becoming aware of the incident/issue via a Reportable New Information (RNI) mechanism in IRES IRB. Refer to the Yale HRPP Policy and Standard Operating Procedure Manual for more information on serious and potentially continuing noncompliance.

9.2. Reporting adverse events and/or unanticipated problems to the IRB

The Yale IRB requires the following Reportable Events to be reported to both the IRB and any appropriate funding and regulatory agencies:

- Events that are serious or life-threatening and unanticipated [or anticipated but occurring with a greater frequency than expected] and are possibly, probably, or definitely related to study procedures; or

- Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) that may require a temporary or permanent interruption of study activities .

The following events may represent UPIRSOs that should be promptly reported:

- Adverse device effects that are unanticipated;
- Adverse events or injuries that are serious, unexpected, *and* related;
- Breaches of confidentiality involving risks;
- Data and Safety Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports altering the risk/benefit profile by identification of increased risks;
- Revisions to safety information, such as Investigational New Drug (IND) Safety Reports and MedWatch Reports, that meet the definition of a UPIRSO;
- New information indicating an unexpected increase in risks or decrease in potential benefits (e.g., literature/scientific reports or other published findings);
- Protocol deviations, violations, or other accidental or unintentional changes to the protocol or procedures involving risks or with the potential to recur;
- Unapproved changes made to the research to eliminate an apparent immediate hazard to a subject;
- Other problem or finding (e.g., loss of study data or forms) that an investigator or research staff member believes could influence the safe conduct of the research.

Events Not Requiring Prompt Reporting

Potential risks and adverse events that may be reasonably anticipated (i.e., “expected”) should be described in the informed consent process/form and do not require prompt reporting to the IRB by PIs. The following are examples of events that do not require prompt reporting:

- Adverse device effects that are non-serious, anticipated, *or* unrelated;
- Adverse events or injuries that are non-serious, expected, *or* unrelated;
- Deaths not attributed to the research (e.g., from “natural causes,” accidents, or underlying disease when the Principal Investigator has ruled out any connection between the study procedures and the subject’s death);
- DSMB reports; interim analyses; or other reports, findings, or new information not altering the risk/benefit profile;
- Protocol deviations or violations unlikely to recur or not involving risks to subjects;
- Subject complaints that were resolved or complaints not involving risks;
- Problems or findings not involving risk (unless the PI believes the information could affect subjects’ willingness to continue in the research).

External events that do not meet the reporting requirements (e.g., not related or not involving risk) and that are not relevant to the protection of Yale research subjects or others should NOT be reported to the IRB.

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

10. Conducting Research Outside of Yale or with Non-Yale Investigators

10.1. Engagement in research at non-Yale institution

Projects engaging Yale or YNHH in human subjects research require Yale IRB review. Yale can enter into agreements that allow Yale to cede IRB review to another institution or an independent IRB. Federally funded non-exempt collaborative and multi-center research engaging multiple domestic sites also require review by a single IRB (with certain exceptions). In cases where IRB review is ceded to another organization, the research proposal must be submitted to Yale HRPP for review of compliance with local requirements. See [section 13](#) on Using External IRBs for details.

10.2. Conducting research at Yale New Haven Health System entities

Although it is a separate institution functioning under its own FWA, Yale IRB serves as the IRB of Record for Yale New Haven Hospital. Other hospitals within the Yale New Haven Health System (YNHH) use Bridgeport IRB as their IRB of Record. As such, Yale and Yale New Haven Hospital researchers conducting research activities at other YNHH hospitals must also submit the protocol application to Bridgeport IRB for review or for review of compliance with institutional requirements if Yale IRB is requested to serve as the IRB of record for the other YNHH sites. See [Appendix D](#) for instructions on how to submit research request engaging YNHH entities.

10.3. Conducting research at the VA

For any non-exempt studies that will be conducted both at Yale and the VA, you must submit the protocol to both Yale and VA IRBs for review and approval. Yale IRB will accept documents reviewed by VA IRB. In addition, Yale IRB Submission Form and consent form for Yale participants must be submitted for review in IRES IRB. No such research can begin, continue, or be modified until the PI receives approval from both the Yale IRB and the VA IRB.

When Yale faculty conduct studies entirely at the VA, Yale University is deemed to be not engaged in the research when 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.

If Yale is not engaged, then 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

	<p>Human Research Protection Program Investigator Manual</p>	<p>Version 2.1 07/24/2023</p>
---	--	-----------------------------------

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.

For all new studies that take place entirely at the VA and when Yale is deemed engaged, then you must submit the protocol to both Yale and VA IRBs for review and approval. Reliance agreements to allow for use of only one IRB to review such studies are not possible. Yale IRB will accept documents reviewed by VA IRB so that there are no additional forms that have to be completed for Yale IRB, with the exception of IRES IRB electronic submission. No such research can begin, continue, or be modified until the PI receives approval from both the Yale IRB and the VA IRB. Most of the time, VA IRB approval must be obtained first.

For additional requirements related to VA research, see [Appendix A](#). If there are any inconsistencies between Yale policies and the VA requirements, the VA requirements must take precedence for the VA regulated research.

10.4. Adding unaffiliated investigators to the protocol

Unaffiliated Investigator Agreements are a way for Yale University to extend the terms of its Federalwide Assurance (FWA) to external individuals from unassured¹⁵ institutions engaged in non-exempt human subjects research conducted by Yale investigators, regardless of which IRB serves as the IRB of Record. Any external individual affiliated with an assured institution and working on a Yale research protocol is required to have approval from his/her own Institutional Review Board (IRB). Alternatively, the institutions can enter into a reliance agreement allowing Yale IRB to serve as the IRB of record.

Answer the following questions to determine whether Unaffiliated Investigator Agreement is appropriate:

- 1) **Is the individual engaged in nonexempt human subjects research?** To determine whether the individual is engaged, use the Worksheet 311 (Engagement Determination), available in IRES IRB Library.
 - a. If NO, the individual is not engaged, or the research is exempt, Unaffiliated Investigator Agreement is not necessary.
 - b. If YES, proceed to question #2.

- 2) **Is the individual affiliated with an unassured institution or not affiliated with any institution?** To determine whether the institution has its own FWA, search for the name of the institution in the [OHRP database](#).
 - a. If NO, the institution has its own active FWA, Unaffiliated Investigator Agreement is not appropriate. An approval from the external investigator's IRB or a reliance agreement will be required.

¹⁵ Unassured Institution is an institution that does not have its own FWA. If an institution routinely engages in federally funded research, the institution should file an FWA.

	<p style="text-align: center;">Human Research Protection Program Investigator Manual</p>	<p style="text-align: right;">Version 2.1 07/24/2023</p>
---	--	--

- b. If YES, either because the external investigator's institution does not have its own FWA or the investigator does not have affiliation with any institution, Unaffiliated Investigator Agreement is appropriate.

Two levels of approvals are required to add an Unaffiliated Investigator to a study:

- 1) Approval of the Unaffiliated Investigator Agreement by the Institutional Official or the designee, and
- 2) Approval to add the individual to a study.

Both approvals are processed by HRPP via IRES IRB at the same time. The following materials are required to be submitted in IRES IRB with a personnel modification to add an unaffiliated investigator to each study:

- 1) A completed and signed **Request to Serve as a Yale University Unaffiliated Investigator** uploaded in the Supporting Documents page. The request is available in the IRES IRB Library. The Unaffiliated Investigator should indicate on the request whether he or she is seeking approval as an Individual or an Institutional Investigator. Proposed investigators who are not affiliated with any institution must complete the materials for Unaffiliated Individual Investigator. Proposed investigators who are affiliated with an institution, agency or practice that is not routinely engaged in research must complete the materials for Unaffiliated Institutional Investigator.
- 2) Copy of the Unaffiliated Investigator CV;
- 3) Copy of verification of Human Subjects Protection training completed within the last 3 years (unless Yale NetID was obtained, in which case the HRPP will verify the training status through Training Management System);
- 4) Copy of Good Clinical Practice training completed within the last 3 years if research meets the criteria for a clinical trial (unless Yale NetID was obtained, in which case the HRPP will verify the training status through Training Management System);
- 5) Copy of verification of HIPAA training, if applicable. Note: if the unaffiliated investigator must access Yale systems, a Sponsored Identity must be requested by the Yale PI's Business Office. HIPAA training must be completed online. Individuals who will not access Yale PHI and do not require access to Yale systems do not need a sponsored identity. Non-Yale HIPAA training certificate will be accepted.
- 6) For Unaffiliated Institutional Investigators - Letter of Institutional Support.

Note – individuals without Yale NetID must be listed on External Team members log uploaded in the Study Team Members along with all the necessary documentation. Acceptable training certificates are described on [the HRPP website](#).

Unaffiliated Investigators are required to be familiar with the following documents. These documents can be accessed by clicking on the links listed below.

- A. The Belmont Report <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>

	<p>Human Research Protection Program Investigator Manual</p>	<p>Version 2.1 07/24/2023</p>
---	--	-----------------------------------

- B. U.S. Dept of Health and Human Subjects (HHS) Regulations for the protection of human subjects at 45 CFR, part §46 and all subparts
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>
- C. The U.S. Food and Drug Administration (FDA) regulations for the protection of human subjects at 21 CFR part §50
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50> (for FDA regulated research)
- D. The specific terms of the Yale University FWA
<http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html>
- E. Relevant Yale University institutional and IRB policies and procedures for the protection of human subjects <https://your.yale.edu/research-support/human-research/policies-procedures-guidance-and-checklists>
- F. HIPAA at Yale, Researchers Guide to HIPAA <https://hipaa.yale.edu/training>

11. Special Topics

11.1. School based research for K-12 students

Research conducted in schools raises a distinct set of concerns with regard to protection of research participants. In addition to the usual requirements of IRB review, an investigator who intends to conduct research in a school needs to be aware of these issues when designing a research study. In particular, research involving K-12 students raises issues regarding appropriate consent methods, influence of peer pressure, confidentiality concerns and the desire of students to please teachers and parents.

Schools that receive funding from the US Department of Education are required to comply with the Family Educational Rights and Privacy Act (FERPA, 34 CFR Part 99) as well as the Protection of Pupil Rights Amendment (PPRA, 34 CFR Part 98). Under FERPA, schools are generally required to obtain authorization from the student (if over 18) or parent/guardian in order to release individually identified academic information other than directory information.

Consent and Assent

Participants in school-based studies are likely to be minors and thus may not be able to give legally effective consent. The minimum age at which an individual can consent to research participation varies from state to state and may be distinct from other consent statutes such as ability to consent to medical treatment. The laws of the state in which the study is conducted are the ones to be followed. In Connecticut, the age of majority is 18. Written parental permission is required for all participants under the age of 18 except in rare cases as determined by the IRB.

Despite their inability to legally consent, ethical standards require that the autonomy of minors be respected by requesting assent to participate. Assent is similar to consent although the information provided to gain assent must be tailored to the intellectual capacity of the children. For example, a form similar to the parental consent form may be appropriate for high school seniors whereas a less detailed

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

verbal description may be most appropriate with kindergartners. Most research should proceed only when both the parent and the child have agreed to take part in the study.

Limits to Confidentiality

Most studies conducted in schools promise confidentiality of the student's responses. When this promise is made, it is absolute and the only instances in which it can be breached involve state-mandated reporting requirements (e.g., reporting of abuse or some infectious diseases), prevention of harm to the participant or others, or subpoena. The promise of confidentiality is to the student and his/her parent or legally-authorized representative. Thus, in cases where there is a need to intervene, it is not considered a breach of confidentiality to contact the parents. The one exception would be circumstances in which it would be more damaging to the child for the parents to be informed, such as instances of child abuse. In such cases, it may be prudent to consult the child first. These limitations of confidentiality must be conveyed to the students, including under what circumstances their parents would be informed of their responses.

Providing information about an individual participant to anyone other than the student and parent/guardian is considered to be a breach of confidentiality. This includes providing individually identifiable information to the schools, whether or not it is in the student's best interest. Although the school is often thought of as a partner in the research, they are nonetheless not automatically privileged to see the individually identifiable data. The confidentiality promised to the students and their parents/guardians would govern any potential disclosure to the school and should be considered and discussed with the school prior to initiating the research.

If the information to be collected in the study includes criminal activity (drug use/sale, violence to others), and it cannot be collected anonymously, then the principal investigator may need to apply for a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). This document protects the data from subpoena, and thus removes the risk of use in criminal proceedings. Receipt of a Certificate of Confidentiality does not alleviate legal or ethical requirements to report child abuse. It should be noted that even in cases where a Certificate of Confidentiality is not presumed to be needed, access to research data may be sought via subpoena. For example, one can imagine that the child's responses could be of value in the context of a custody dispute.

In most studies, the likelihood of a litigant wanting to look at the data is low and confidentiality can be adequately protected by coded the data and destroying the code upon completion of data collection.

School Concerns

One could argue that the concerns of the school are not within the purview of the IRB as a school is not a "subject" since it is not a "living individual." Nor is the school part of the research team since the school often will not be involved in the design and conduct of the research. However, since a school study cannot, by definition, be conducted without the approval of the school, sensitivity to a school's concerns will facilitate a researcher's ability to complete the proposed data collection and produce valid results.

The primary function of a school is to educate students. Involvement in a research study will necessarily compete for the limited time that a school has to perform its primary function. The moment an investigator enters a school, the education function of the school has been disrupted. Such disruption will only be tolerated by the school if it anticipates receiving some benefit from participation. In agreeing to participate and to allow access to its students, the school must weigh the disruption of the study against the expected benefits. To do so, the school must be fully informed about the details of the study, much like the requirement for an individual participant's informed consent. It is imperative that the principal investigator clearly describes the roles of all parties, the risks and benefits of the study, as well as the purpose and procedures of the study.

Define who is responsible for what: There is a broad spectrum of the intrusiveness of a study. At one extreme are observational studies in which the investigator is interested in discreet observation and thus approval only to enter the schools is needed. Purely observational studies would not require parental consent, although the school may require that the parents be informed of the research.

Most common, however, are studies in which the data are collected interactively on school grounds during the school day. The responsibility of the schools may include distribution and collection of parental consent documents. The testing session itself may occur during normal classroom time, either with the class being testing *en masse* or by individuals being excused from the class to meet with the investigator. When the data is collected *en masse*, it is frequently the responsibility of the school to determine appropriate alternate activities for those students who decline to participate. It should be noted, however, that in some cases it is preferable to have a "filler" activity for the non-participants. In this way, the confidentiality of those who chose not to participate can be respected by allowing the appearance of participation in front of their peers and teachers while completing an unrelated task.

In defining the roles of the research team and the schools, the research personnel who will be on site should be identified to the school along with their qualifications and role. The school should be notified, in advance, who will be present in the schools, when they will be present and in what capacity. This includes undergraduates on the project as well as graduate students and postdoctoral fellows. To facilitate the school's ability to monitor who is present in their facility, the IRB recommends that all research personal wear a visible form of identification that includes their name and affiliation with the research project.

Define benefits to the school: Schools may be willing to relinquish classroom time only if they feel that the benefits of the study are worthwhile. A realistic description of the benefits for the school should include not only the benefits that will be provided but also the limitations of those benefits. For example, the types of reports that will be provided to the schools must be outlined—will there be information specific to an individual school or to schools in general? Are there circumstances in which the study will be terminated early and thus reports not be provided? This latter instance must be addressed if a study commences prior to securing adequate funding. The IRB recommends that the school be provided with a timeline showing when the data will be collected and when the school can expect to see any promised reports or other benefits.

Define disclosure risks: Public schools in particular have legal and moral requirements which they must fulfill to ensure the safety of their students. For example, school personnel in Connecticut are mandated to report suspected child abuse to state authorities. Conn. Gen. Stat. §17a-101b. Such reports are frequently followed by an investigation by Department of Children and Families (DCF) and have the potential to have a child removed from the home. The threshold of required reporting is low and schools are put into a difficult situation when informed of suspected abuse of an identified student. Investigators should consider the potential to obtain information that would necessitate DCF reporting and whether such information should be shared with the school or handled directly by the investigator.

Another area where the school would be expected to act is threats to student safety. Information suggesting that a student may harm another student or him/herself would require the school to further assess the threat. In the event that such a threat is substantiated, the school would be expected to mitigate the situation. Although it is difficult to identify all situations in which a response would be necessary, investigators should be prepared when the study queries about depression, possession of weapons, or threatening behavior, either directly or indirectly. The IRB protocol should propose a plan for handling such information including to whom the information will be disclosed.

To protect the school from having to implement its mandated procedures, it is generally better for the investigator to take responsibility for information uncovered in a study and present the school with generalized results. Reporting would then be performed by the investigator directly to the relevant authorities. Note that many reporting requirements are defined by each individual state. Investigators are urged to be aware of what they as researchers would be legally required to report, as well as what they as individuals may feel ethically required to report. In cases where it would be absolutely necessary to inform the school, the school and the participants must be informed from the start that this would be a potential risk involved in the study. This risk must be stated clearly and in writing, including what types of actions the school would be required to take and whether or not the information would become part of the student's school record. The investigator must discuss reporting expectations with the school personnel prior to the initiation of a study.

Define other site specific risks: Each school is a unique environment about which the school personnel are experts. Survey instruments and other measures, which are of little concern in one school, may be of great concern in another, based on the local culture. It is essential that investigators provide school administrators with a full set of the measures to be used so that they may assess the likelihood of problems for their school. The investigator should ask the school if the measures are appropriate for their students and if any problems can be anticipated during or after the research procedure. Note that highly sensitive topics may promote discussion of these issues by the students during the remainder of the school day. Depending on the nature of the issues, the school may want to be prepared for any subsequent repercussions arising from the research participation. Hence, the school must be aware of what measures will be administered and when.

Define appropriate contacts: Communication is essential to maintaining rapport with the schools. Not only does the school need to be informed as to who it should contact with questions and concerns, but also, the investigator will need to know who the appropriate contacts are for various aspects of the study.

The individual with authority to allow access to the students is usually different from the person who should be contacted about the logistics of data collection. In any case, these individuals should be defined up front to facilitate future communication.

Obtaining approval to work in the schools is a multi-step process. In the end, written approval should come from the highest level. In public schools this may be the superintendent. For private schools, the headmaster may be the appropriate official. This individual will be required to sign a letter indicating that they agree to allow access and have been shown all the required materials.

Schools as Research Partners

Occasionally, the study will call for the school to play an active role in the design and/or conduct of the research. Once the school moves beyond merely providing access, it is considered to be “engaged in research” and must meet additional requirements under the regulations for federally funded research. In particular, the school would be required to file an assurance with OHRP, indicating their plans to comply with 45 CFR Part 46. The IRB will assist in determining when such an assurance is needed and how the school can comply with this requirement.

Reporting Issues Arising in the Course of the Research

Occasionally, there may be problems that arise during data collection. Problems can range from complaints or distress of a participant to identification of participants at risk of harm. All such events should be evaluated by the principal investigator and reported to the IRB, if applicable, in accordance with the HRPP Policy. Note that the IRB has experience in ways to handle such events and is available to assist the investigator determine the appropriate course of action.

11.2. Deception in research

Deception in the context of human research refers to both providing false information as well as to withholding some pertinent aspect of the research that concerns the real purpose or nature of the research. The use of either form of deception is inconsistent with fully informed consent and hence must be scientifically and ethically justified. If the deception/incomplete disclosure impacts the consent process, the deceptive aspects of the study must meet the requirements for waiver or alteration of consent. Any proposal to involve deception or incomplete disclosure must be justified and necessary to carry out the research and must not adversely affect the subjects’ rights and welfare.

Instances when deception may be allowable

- There are no undisclosed risks to subjects that are more than minimal.
- The deception will not adversely affect the rights and welfare of the subjects.
- The research could not practicably be carried out without the deception. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

- The study intends to measure behaviors or responses that are likely to be different if the participants were fully informed

Examples of studies that may necessitate the use of deception/incomplete disclosure include:

- Psychology studies examining spontaneous behaviors which would be inhibited by informing the participant of the trait being observed.
- Psychology studies involving confederate(s) who are used to elicit comments/responses as if to a peer of the participant.

Instances when deception is not allowable

- The deception regards significant aspects of the study that would affect the participants' willingness to participate in the research.
- The deception/incomplete disclosure itself could cause harm to the participants.
- The deceptive techniques are intended solely to entice or lure an individual to participate in a research study.
- When false information is incorporated into the consent materials.

Debriefing due to deception

- Participants in a study involving the use of deception or incomplete disclosure should be debriefed about the nature of the deception and/or incomplete disclosure after completion of the study unless debriefing is not possible or would cause unacceptable risk to the subjects.
- A description of the debriefing process, including any written materials, should be included in the protocol submitted to the IRB. The debriefing process should include a clear description of what information was withheld or false as well as an explanation for why it was necessary to deceive the participant. During the debriefing, subjects must have the opportunity to ask questions about the new information and, if able, be given the opportunity to withdraw from the study or have their data removed.
- Debriefing may not be advisable in certain limited situations, for example, if the research reveals information about the participant that s/he might find disturbing (such as a personality disorder, aggressive behavior tendencies, etc.). If an investigator believes that debriefing will be inappropriate, the explanation as to the basis for this belief should be explained in the protocol submitted to the IRB. The IRB will determine whether debriefing is appropriate.

11.3. Oral history and humanities projects

Although oral history projects do not meet criteria for research subject to IRB review, there are important considerations when conducting oral history or humanities projects:

- Although each participant will have their own unique area of expertise to lend to the project, the goals of the project define what general areas will be the focus of the interviews and this can usually

	<p>Human Research Protection Program Investigator Manual</p>	<p>Version 2.1 07/24/2023</p>
---	--	-----------------------------------

be defined broadly if not by specific questions. In some cases, the populations to be interviewed can be categorized and the information to be gained from each group can be described.

- Unlike consent which can be obtained without a signed form under appropriate circumstances, release forms are required if transcripts will be published verbatim or if video testimonies will be shown publicly. Publication release forms require signature and serve to notify the interviewee that they will not retain rights or control in the final dissemination of the interview.
- There is no requirement that the information be anonymous, only that the participants be made aware of whether or not their names will be associated with their responses and any inherent risks associated with such disclosure. It must be noted, however, that projects that pose significant risk to the participants from disclosing their responses without a counterbalancing benefit anticipated from the project would be considered unethical.

12. Special Considerations for Drug/Device Research

12.1. Emergency use of an unapproved drug, biologic, or device

Contact the IRB Office (hrpp@yale.edu) or IRB chair immediately to discuss the situation. If there is no time to make this contact, see the "WORKSHEET: Emergency Use (HRP-322)" for the regulatory criteria allowing such a use and make sure these are followed. You will need to submit a report of the use to the IRB within five days of the use and for drugs and biologics. **If you fail to submit the report within five days, you may be restricted from submitting new Human Research until the report has been received.**

Emergency use of an unapproved drug or biologic in a life-threatening situation without prior IRB review is "research" as defined by FDA, the individual getting the test article is a "subject" as defined by FDA, and therefore is governed by FDA regulations for IRB review and informed consent. Emergency use of an unapproved device without prior IRB review is not "research" as defined by FDA and the individual getting the test article is not a "subject" as defined by FDA. However, FDA guidance recommends following similar rules as for emergency use of an unapproved drug or biologic. Individuals getting an unapproved drug, biologic, or device without prior IRB review cannot be considered a "subject" as defined by DHHS and their results cannot be included in prospective "research" as that term is defined by DHHS.

13. Using External IRBs for Review of Research

Yale investigators may wish to use an external Institutional Review Board (IRB) in lieu of the Yale IRB to oversee a research study. Ceding IRB review requires an IRB Authorization Agreement, often referred to as a reliance agreement. Yale has entered into several agreements with outside institutions for review of research studies e.g., SMART IRB, master agreement with some of the commercial IRBs. The Yale Human Research Protection Program (HRPP) may authorize use of an external IRB for review of research studies. The HRPP will work with the proposed external IRB on a reliance agreement if one is not yet in place.

External IRBs may include commercial IRBs (e.g., WIRB, Advarra, BRANY, etc.), academic or non-academic IRBs where research is occurring (e.g., Harvard, Greenwich Hospital, UCONN, etc.), or other IRBs such as mandated IRBs for network studies and federal IRBs (e.g., FDA IRB, DCF IRB, NCI CIRB, etc.).

When an external IRB reviews the study on behalf of Yale, only the actual IRB review is ceded to that IRB. The local requirements regarding research remain Yale's institutional responsibility. As such, the Principal Investigator (PI) will continue working with the Yale HRPP to ensure that investigators and research staff meet the Yale training and COI disclosure requirements, all ancillary reviews (e.g. PPRC, PRC, MRRC) are obtained, the record is updated in IRES IRB, etc.

13.1. Initial Submission

In order to submit a research protocol to an external IRB for review, you must first obtain authorization from the Yale HRPP office. All external IRB review requests must be submitted to the Yale HRPP via IRES IRB prior to submitting the research to the IRB for review. Please note, the Yale HRPP office may independently determine that a study submitted to the Yale IRB will be reviewed by an external IRB. If that occurs, the PI will be notified and the HRPP will work with the PI and the research team on the submission to the proposed IRB of record.

With the exception of studies under NCI CIRB purview, no research may be submitted to an external IRB without the prior approval of the Yale HRPP. When submitting a request for approval to use an external IRB, the PI or designee must submit the following to the Yale HRPP office:

- Request to Use External IRB,
- Approval letters from all ancillary committees required to review the study unless the ancillary committee used IRES IRB to issue approvals,
- Any documents received from the coordinating center or the proposed IRB for the study that require completion by the HRPP such as local context questionnaires, and
- All required study-related documents (e.g., protocol, consent form templates and the version proposed for use at Yale, IB, recruitment materials, etc.).

Once the submission is received, the HRPP will verify compliance with local requirements such as:

- PI eligibility to serve as the PI on the project,
- Ancillary committee approvals,
- Completeness of initial submission documents that will be sent to the external IRB,
- PI and staff compliance with training and Conflict of Interest (COI) requirements,
- Whether the study was previously reviewed or is in the process of being reviewed by the Yale IRB or another IRB,

- For industry-sponsored trials, consistency between the terms of “In Case of Injury” language (and any other Yale University preferred and/or negotiated language) in the consent form and the contract with the sponsor,
- For federally funded studies, congruency between the grant proposal and protocol to be submitted to the IRB.

Once the submission is reviewed and approved for review by an external IRB, the HRPP will provide you with an authorization letter in IRES IRB. When applicable, the letter will list specific requirements regarding consent language, any recommendations from the ancillary committees, and instructions to the reviewing IRB where to send invoices for their IRB review service. You must attach that letter to your submission to the IRB.

13.2. Ongoing Responsibilities

After the initial approval, the Investigator must update the submission in IRES IRB to reflect the approved status of the protocol. Study changes must be reviewed by the IRB of Record. In addition, changes that affect the local context information must also be submitted in IRES IRB. See the table below for examples for study updates that must be submitted to the HRPP for review and acknowledgment.

Changes that require submission in IRES IRB	Notes:
Change of PI	HRPP must review for eligibility to serve as the PI, training, COI, etc.
Change of Personnel	HRPP must review for training, COI, etc.,
Addition of a new consent form	If non-commercial IRB serves as the IRB of record, a new local context form may need to be completed
Revision of language in the ‘In Case of Injury’ or ‘Economic Considerations’ sections of the consent form	May require OSP review or HRPP review that the subject injury provisions are consistent with Yale policies
Changes in Funding	HRPP conducts consistency/congruency review to ensure the grant matches the protocol and that there are no conflicts of interest with the new sponsor
Changes that require a re-review by an ancillary committee that uses IRES IRB	See the Appendix C on ancillary committees
Changes that require an initial review by an ancillary committee (regardless of whether IRES IRB is used)	See the Appendix C on ancillary committees
Changes in recruitment plans at Yale (does not include recruitment materials)	Recruitment must conform to local policies, commercial IRBs often do not review recruitment plans; if non-commercial IRB serves as the IRB of record, a new local context form may need to be completed

Changes in research location for Yale site	Some sites have additional requirements, Yale needs to keep track of where research takes place
Updates in approval status (continuing review, closures)	Approval letters for continuing review and closures must be submitted to HRPP via site modification
Changes in information reported in IRES IRB electronic application - pages in IRES IRB	Information in IRES IRB is used for running reports, e.g., how data is shared with other institutions or countries

13.3. Transfer of studies approved by Yale IRB

At time, studies under purview of Yale IRB need to be transferred to an external IRB for oversight. It may be as a result of an investigator moving to another institution, funder’s requirements, or new application of revised Common Rule, which requires sIRB review for multi-site or cooperative research studies. The request for transfer of the IRB oversight follows the same steps as the initial request for use of an external IRB. You can make a copy of the existing study record in IRES IRB and submit it as a request to use an external IRB. Do not close out the study under Yale IRB purview until the external IRB approves the research for Yale site.

13.4. Studies under NCI CIRB purview

Investigators who are approved by NCI as Principal Investigators, can open a trial under the NCI CIRB purview by following these steps:

- Identify a study from the NCI CIRB website that you wish to join,
- Obtain NCI CIRB approval for Yale participation (by submitting a Study Specific Worksheet),
- Revise the consent documents with Yale boilerplate language,
- Obtain approval from YCC Protocol Review Committee (see [Appendix C](#) on the ancillary reviews),
- Submit to the HRPP the following documents in IRES IRB:
 - NCI CIRB approval of the Study Specific Worksheet,
 - Yale modified CIRB consent form (the only changes that are allowed are the additions included in the approved boilerplate language that is posted on the NCI website and uploaded in IRES IRB for your reference),
 - All internal approvals (PRC, etc.),
 - The CIRB approval letter for the study,
 - When applicable, completed Request for a HIPAA waiver,
 - HIPAA Research Authorization Form

Upon receipt, the HRPP will review the submission for compliance with local requirements. When requested, in its role as the Privacy Role, Yale IRB will issue any applicable HIPAA waivers. The result of the review will be communicated to you in an acknowledgement letter.

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

14. Requesting Use of Yale IRB as sIRB

14.1. HRPP agreement to serve as the sIRB for external sites

Yale IRB generally does not serve as an sIRB for multi-site research. Exceptions can be made for federally funded non-exempt multi-site research or collaborative research with limited number of sites. When Yale serves as the sIRB for multiple sites, Yale may charge for sIRB services. Before deciding to take on the role as the overall PI and/or coordinating center, review '[Investigator's responsibilities when serving as the overall PI.](#)' You should also be aware that aside from IRB review and approval, you will need to develop and facilitate other non-IRB logistics, such as billing for study procedures, redistributing funds to sites for performance of study procedures, etc.

If you wish to designate Yale IRB as the sIRB in your grant proposal, you must first contact the Yale Human Research Protection Program (HRPP) to discuss the project and level of engagement of the proposed relying sites. The Yale IRB must prospectively agree to serve as the sIRB prior to the investigator's selecting Yale as the sIRB during the grant application process.

To request Yale to serve as the sIRB, complete [sIRB Request Form](#) and send it to central.irb@yale.edu or hrpp@yale.edu. One of the HRPP representatives will contact you to set up a meeting to discuss your request. The HRPP will provide you with a letter of support for the grant submission. If Yale determines that it is not in a position to serve as the sIRB for your project, the HRPP will help facilitate selection of another IRB that can serve in that role e.g., one of Yale's commercial IRB partners. It will require you to budget adequately for sIRB review fees. It is recommended that you begin the process a month prior to your grant application.

14.2. Investigator's responsibilities when serving as the overall PI

Adapted from SMART IRB Resources

As the Overall PI for a study for which research activities involving human subjects will be overseen by Yale IRB for all or most sites, you should be aware of your additional responsibilities in assuming that role. Once you have agreed to collaborate with investigators at other institutions and intend to use Yale as the single IRB for oversight of the study, you must agree to the following:

- Identify who will act in the role of the Lead Study Team e.g., your own study team, [YCCI clinical trials project management team](#), or an external coordinating center. If none of the Yale research teams is to serve as the Lead Study Team, then you will need to obtain Yale NetIDs for the external coordinators and train them on use of the electronic submission system, IRES IRB.
- Develop a plan for communicating with collaborators across the lifetime of the study (i.e., regular conference calls, site initiation procedures and training materials). Ensure that the Relying Site Principal Investigator and Relying Site Teams understand and agree to the communication plan and the [Relying Site responsibilities](#).

- Provide the Site Investigators with the Yale IRB policies and procedures. This includes, but is not limited to, policies for reporting unanticipated problems, noncompliance, and subject complaints.
- Promptly respond to questions or requests for information from study teams and IRB/Human Research Protection Program personnel at institutions who are relying on Yale IRB.
- Participate in conference calls regarding a study as requested.
- Have a mechanism in place to obtain and collate information from Relying Site Study Teams and/or Relying Site Points of Contacts (POCs), depending on who is designated to provide that information at the Relying Institution, regarding local variations in study conduct, such as recruitment materials and process, consent process and language, and subject identification processes.
- Prepare and submit materials on behalf of all sites, including initial reviews, local amendments, personnel updates, local reportable events, and studywide information for continuing review.
- Assist Relying Site Study Teams and/or POCs at the Relying Institution(s), depending on who is designated to provide that information, in ensuring consent documents follow the Yale IRB's template form and include applicable site-specific required language from each Relying Institution.
- Provide participating Relying Site Study Teams with the IRB-approved versions of all study documents (e.g., consent and authorization forms, protocol, recruitment materials).
- Notify Site Investigators of all Reviewing IRB determinations and communications, including those for initial review, continuing review, amendments, and reportable events.
- When agreed upon in coordination with the Yale IRB, promptly report to the Site Investigator (or designee on the Relying Site Study Team) any unanticipated problems involving risks to subjects or others research-related subject injuries, or significant subject complaints that are related to or may affect subjects participating in the research (i.e., the specific study or studies ceded to Yale IRB) at the Relying Institution.
- If a Relying Site Study Team does not provide the Lead Study Team (or designee) with the required information before the continuing review application is submitted to Yale IRB, report the absence of this information as part of the continuing review and notify affected Relying Site Study Team of lapse in approval for their site and any applicable corrective action plans.
- Provide access, upon request, to study records for audit by the Relying Institution, Yale IRB, and other regulatory or monitoring entities.
- Follow all requirements of the Relying Institution with regard to ceded review, such as ensuring administrative requirements for documenting ceded review have been met before study activation occurs at a Relying Institution.

14.3. Relying Investigator Responsibilities and Guidance

Adapted from SMART IRB Resources

As Principal Investigator at the Relying Institution (Site PI) for a study that may be overseen by Yale IRB, you should be aware of your responsibilities. Once you have agreed to collaborate with an investigator at another institution and intend to use an external IRB for oversight of this study:

- You should contact the IRB administration or relevant Human Research Protection Program (HRPP) personnel at your institution to:
 - Discuss whether ceding IRB oversight to an external IRB is appropriate.
 - Provide them with details about the study (including your study team's role), the proposed reviewing IRB, and the lead investigator's name and institution.
- Obtain a copy of the studywide protocol and template consent documents(s), which will help facilitate the discussion with your local IRB/HRPP.
- Register the study at your institution according to local processes, such as creating a shell study in the local electronic system and uploading documents received and listing the names and roles of all key study personnel on the local study team.
- Promptly respond to questions or requests for information from the Lead Study Team (or their designee) as well as from the Yale IRB.
- Participate, as required, in conference calls regarding a study as requested by the Lead Study Team, Yale IRB, or your local IRB/HRPP.
- Become familiar with the reportable event policy of the Yale IRB to ensure that you appropriately report protocol deviations, noncompliance, significant subject complaints, subject injuries, unanticipated problems, or other events required by the Yale IRB to be reported and within the timeframes required.
- Ensure that all local reviews and sign offs that, in addition to IRB approval, are in place before a study is activated, such as coverage analysis, department approvals, data use agreements, material transfer agreements, ancillary committee reviews (e.g., radiology, nursing, and pharmacy).
- Work with the Lead Study Team and the IRB/HRPP point of contact from your institution to incorporate locally required language into the consent template to be used by the local study team, such as institutionally required compensation for injury language, local study team contact information, and additional costs that subjects may incur that differ from those identified in the template consent form.
- Notify local IRB administration/HRPP personnel of any staff changes so they can confirm their training is current and help ensure any relevant COI management plans are communicated to the Reviewing IRB.
- Notify the lead PI of:
 - Any reportable events that occur locally, according to regulations and the Yale IRB's policy.
 - Any changes (including those related to funding and personnel) in accordance with the Yale IRB's policies and procedures for timing and content of such submissions.
 - Any management plans, including any updates to these plans, as relevant to the study.

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

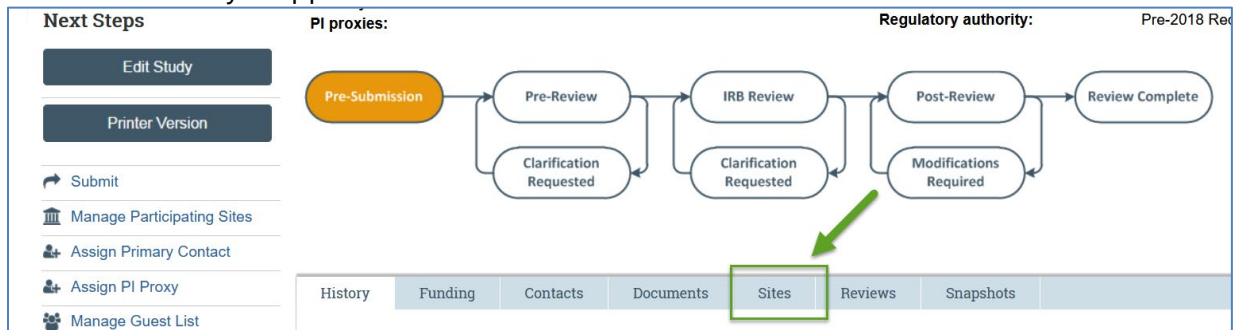
- Any applicable information for continuing review progress reports in accordance with the Yale IRB's policies and procedures for timing and content of such submissions.
- Follow all determinations of the Yale IRB.
- Only implement changes of protocol, including local variations, after the Yale IRB has approved them, except in cases where a change is required to avoid an apparent immediate hazard to participants.
- Provide, upon request, access to study records for audit by the local institution, the Yale IRB's institution, and other regulatory or monitoring entities.

14.4. Initial IRB Approval

When Yale IRB serves as the IRB for non-Yale sites, there will be two levels of IRB review and approval:

1. Review and approval of the protocol and Yale site, and
2. Review and approval of the non-Yale site.

Generally, the study protocol and Yale documents live in the main study workspace. Documents related to non-Yale sites live in the **SITES** space, as shown in the screenshot below. Sites can be added to the protocol after the study is approved as a multi-site research.



Sequence of the actions to obtain initial IRB approval for the study and participating sites:

Obtain initial IRB approval for multi-site research

Note: If the study is already approved as a single site research project and you wish to add a site, you will need to submit a modification for the study to be approved as a multi-site or cooperative research project. Review the section below describing the approval process for multi-site research and prepare and submit a modification to edit the IRES IRB pages and revise the IRB Submission Form to allow for the sites to be added.

The following section describes:

- Preparing documents for multi-site research
- Submitting multi-site research for IRB review

- Working with the sites to obtain site-specific information (Local consent forms, Local context form, Local recruitment materials)
- Submitting site information for approval
- Distributing the approval documentation to the sites

Preparing documents for multi-site research

In addition to the study protocol and documents to be used by Yale site, you will need to create the following:

- **IRB Submission Form**

The information in the IRB Submission Form generally pertains to the conduct of the study at Yale. Section titled 'Supplement II - Multicenter Management' must be completed to provide the IRB with information about how Yale team will manage the sites.

- **Consent templates**

Most of the time, each site will need its own consent form for recruitment. You need to create a generic consent template that will indicate which sections of the consent can be modified by the site. Consent templates are not used for recruitment – they serve as the basis for each site consent document. Generally, the following sections should be allowed to be modified by each site:

- Name of the institution conducting the study in the header of the consent document,
- Subject Injury Provisions ('In Case of Injury' language),
- Payments for Participation, if the amount for participation differs between sites,
- Contact information to local investigator, HRPP, etc.
- HIPAA Authorization, if applicable – the template can propose authorization language with the understanding that each site may require their own templated authorization to be used instead,
- Locally required reporting requirements, if applicable, *and*
- Local version control date or number.

There can also be a section included for specific site information where each site can add their own locally required language.

In addition to the generic consent template, you should create Yale version of the consent form and include it with the initial submission. Alternatively, you can initially submit only the consent template for review to allow for revisions that may be required by the IRB. In that case, once the template receives final IRB approval, you would submit the Yale version of the consent as a modification.

Submitting the multi-site protocol for IRB review

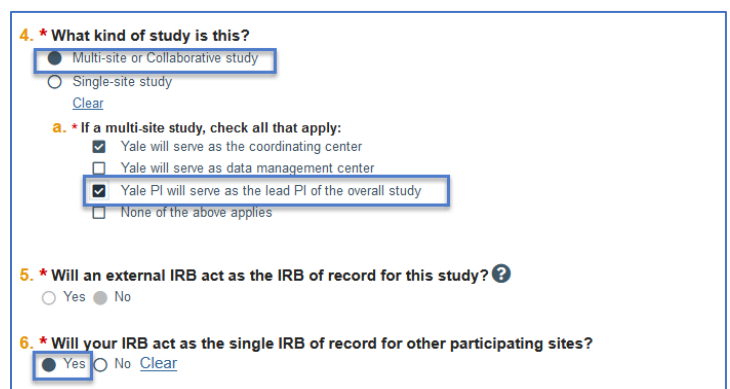
Create a study record in IRES IRB system. Some pages will ask for information that pertains to the overall study and some will ask for information specific to Yale site only. Pay attention to the following:

Basic Study Information

- Indicate in question # 4 that you are submitting a 'Multi-site or Collaborative study',
- In question 4a, select Yale's role in this research,
- Question #6 must indicate that Yale will serve as the sIRB for other participating sites.

Study Funding Sources

Questions on this page ask about the funding for the overall study and Yale as a site. If a participating site has additional funding that will be used for the study, it will need to be entered later in the submission process, in the workspace for the site.



4. * What kind of study is this?
 Multi-site or Collaborative study
 Single-site study
[Clear](#)

a. * If a multi-site study, check all that apply:
 Yale will serve as the coordinating center
 Yale will serve as data management center
 Yale PI will serve as the lead PI of the overall study
 None of the above applies

5. * Will an external IRB act as the IRB of record for this study? ?
 Yes No

6. * Will your IRB act as the single IRB of record for other participating sites?
 Yes No [Clear](#)

Local Research Locations

Do not list non-Yale sites that will rely on Yale as the sIRB. They will be listed separately in their own workspaces. Local Research Locations should include names of the Yale affiliated locations.

Study-Related Documents

This page should include materials relevant to the overall research, not only Yale. Included here should be consent template, any templates for recruitment materials that could be modified for site use (e.g., allow for inclusion of local phone numbers and contact names), and any materials that will be used by all sites e.g., interview or focus group guides, etc.

Local Site Documents

This page should include Yale specific documents, for example, Yale consent forms, Yale specific recruitment ads (if they are different from the overall study recruitment), IRB Submission Form, Special Permission to Serve as PI, if applicable, and any other form relevant to Yale as a site.

Technology-Data-Specimens

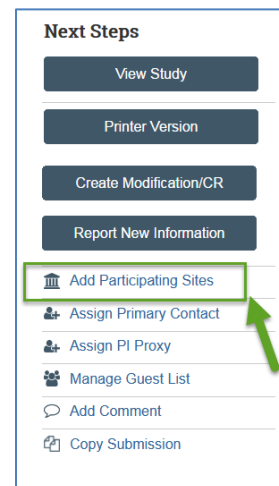
Questions 1 and 4, regarding research locations, refer to the entire study. Questions related to use of technology and sharing of data and specimens refer to Yale only. If the research includes plans for sharing of the data from other sites, it will need to be accounted for in SITE specific submission.

	<p>Human Research Protection Program Investigator Manual</p>	<p>Version 2.1 07/24/2023</p>
---	--	-----------------------------------

Once the study record is created in IRES IRB, submit the protocol for review by clicking **Submit** under **Next Steps** in the study workspace. The HRPP will conduct initial review of compliance with institutional requirements (which may include reviews by ancillary committees) and will triage the submission to IRB for review.

When you receive final IRB approval, contact central.irb@yale.edu to begin the reliance process with the non-Yale sites. Provide the name of the site and the name and the contact information for the local investigator (site PI). A record will be created in IRES IRB for the site PI so that their name appears in the site approval letter.

Note: The final IRB approval at this stage will pertain to the protocol and Yale’s activities. Additional sites are not authorized to begin enrollment or engage in human subjects research until the site is added and approved by the IRB. A site specific approval letter will be issued by the IRB.



Working with the sites to obtain site-specific information

The final IRB approval along with the WORD versions of the approved consent documents and the Local Context Questionnaire (available in IRES IRB) along with the proposed communication plan describing who is responsible for providing information about the study to local investigator, site’s HRPP, Yale IRB, etc. must be provided to the local investigator (Site PI). Site PI must review the documents, complete a portion of the Local Context document, modify the applicable sections of the consent documents, and submit the documents to the local HRPP (or in some cases local IRB) requesting a reliance agreement according to the local policies. Most of the time, the local HRPP will issue a letter of authorization to the local investigator that indicates that the materials are ready for Yale IRB review.

The Yale HRPP will work with the local sites’ HRPPs on the best reliance agreement for the study. Reliance with sites that signed SMART IRB Agreement can be documented using SMART IRB portal or SMART IRB documentation of reliance document outside of the electronic portal. Reliance with sites that have not signed SMART IRB Agreement may be documented using other IRB Authorization Agreement Forms. Generally, a reliance agreement will be negotiated directly between Yale HRPP and the site. You will receive a copy of the executed reliance agreement.

Submitting site information for approval

Once you receive tracked versions of the local consent forms and the completed and signed Local Context questionnaire, you are ready to add a site to the protocol.

- In the main study workspace, click on **Add Participating Sites** Under Next Steps.

- In the window that will appear, click on **Add** and select the name of the institution (in *Institutional Profile* field) and the name of the Site PI (in *Principal Investigator* field). If you cannot locate the name of the institution or the name of the site PI, contact central.IRB@yale.edu.

- Once added, the site will appear in the Sites tab in the study workspace. Click on the name of the site to begin completing the site-specific information.

ID	Name	SmartForm	Institution	Principal Investigator	State	FWA Number
SITE00000004	UCONN Health Center Participating Site for Multi-site Study		UCONN Health Center	Brandy Lagner	Invitation Pending	

- You now opened site workspace. If at any point you wish to return to the main study workspace, you can click on the double arrow next to Dashboard. To complete site information, click on **Edit Site**.

Invitation Pending
Last updated: 9/12/2022 11:47 AM

Principal investigator: Brandy Lagner
Submission type: IRB Site
Primary contact:
PI proxies:
Institution: UCONN Health Center

IRB office: Yale IRB
IRB coordinator: Monika Lau
Regulatory authority: 2018 Requirements
Study: 2000022220

Activity	Author	Activity Date
Site Created	Infoed, Test 13	9/12/2022 11:47 AM

- There will only be three pages for you to complete:
 - **Basic Site Information:**
 - Verify with the local site PI whether there is any financial interest related to the study;
 - Describe activities that will be conducted at the site in Question #4, if the site will be engaged in all research activities, you can simply state 'ALL'. The IRB will be reviewing this section to understand the nature of engagement of the site.
 - **Additional Local Funding Sources:**
 - Complete only if the site will use additional funds that are not already reported in the main study record,
 - **Local Site Documents:**
 - Local consent forms showing track changes of the edits made to the approved consent template must be uploaded in Question # 1;
 - Completed and signed Local Context questionnaire must be uploaded in Other Attachments, question # 3.
- Once all documents are uploaded, contact central.irb@yale.edu to notify the HRPP that the site information is ready. Ensure to include the number of the main protocol and the site number.

The HRPP will verify that the information is uploaded appropriately and that the reliance agreement is pending or completed. The site documents will be then submitted for the Yale IRB review. You will receive an email to your Yale email address notifying you when site documents are approved.

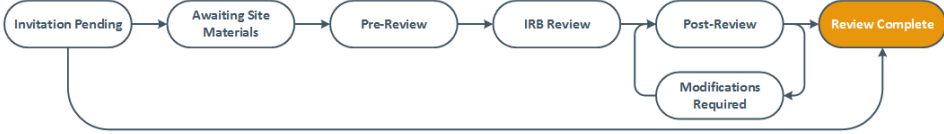
Distributing the approval documentation to the sites

Once approved by the IRB, the site approval letter and site consent form will live in the SITE space. Site consent forms will receive an approval watermark. Download and review the initial site approval letter. It may contain important information about the activities that are approved and any IRB findings relevant to the site. Send the approval letter and the consent forms to the local research team – site PI and the coordinator. Keep the proof of the delivery of the documents in your study file – all your communications with the sites should be part of your regulatory binder. The site PI may need to provide the letter to the local HRPP per local institutional requirements. You are now approved to begin the research activities at the site.

SITE00000004: UCONN Health Center Participating Site for Multi-site Study

Principal investigator: Brandy Lagner
Submission type: IRB Site
Primary contact: Test 13 Infoed
PI proxies:
Institution: UCONN Health Center

IRB office: Yale IRB
IRB coordinator: Monika Lau
Letter:  Initial SITE Approval_UCONN(0.01) ...
Regulatory authority: 2018 Requirements
Study: 2000022220 



- History
- Funding
- Documents
- Follow-on Submissions
- Snapshots

Study Related Documents				
Draft	Category	Final	Last Finalized	Document History
Study Protocol	IRB Protocol	Study Protocol	9/12/2022 11:38 AM	History
Consent Template	Consent Form	Consent Template	9/12/2022 11:38 AM	History
Site Related Documents				
Draft	Category	Final	Last Finalized	Document History
Consent Form_UCONN	Consent Form	Consent Form_UCONN	9/12/2022 12:06 PM	History
Local Context_UCONN	Local Context Questionnaire	Local Context_UCONN	9/12/2022 12:06 PM	History

14.5. Modification Request Process

There will be three different types of modifications that can be submitted for review:

- Modifications affecting the overall protocol and Yale site,
- Modifications affecting both the protocol (and/or Yale site) and site,
- Modification affecting site information only.

Site only modifications are submitted directly in the site workspace. The following is the sequence of actions to obtain IRB approval for modifications affecting the study and participating sites:

Obtain IRB approval for modification to protocol documents and Yale site

This section of the manual describes the following:

- Submitting modification to protocol and Yale site,
- Submitting materials for site modification,
- Distributing approval documents to sites.

Submitting modification to protocol and Yale site

The first step for modifications that only affect the protocol/Yale site and those that affect the protocol/Yale site and other non-Yale sites is to submit the modification in the main study workspace. During this modification, study related documents and documents pertaining to Yale activities can be modified and uploaded for review. Follow the regular procedure for submitting modification requests in IRES IRB.

Submitting materials for site modifications

Once the protocol modification is approved and revised consent templates are available, you will need to prepare site documents for submission. If the site consent needs to be revised, you need to:

- Download the WORD version of the approved consent form from the site workspace,
- Accept any existing changes, and
- With tracked changes function ON, edit the site consent form to incorporate the changes made to the approved consent template. Remember to use version control to distinguish the version of the consent template vs. version of the site consent. If you need to make additional changes beyond those in the consent template, ensure to include an explanation in the Modification Summary as shown in the screenshot below.

In the Site workspace, click on **Create Site Modification** under Next Steps.

Active

Entered IRB: 9/12/2022 12:06 PM
Initial approval: 9/12/2022
Initial effective: 9/12/2022
Effective: 9/12/2022
Approval end: 9/11/2023
Last updated: 9/12/2022 12:08 PM

Principal investigator: Brandy Lagner
Submission type: IRB Site
Primary contact: Test 13 Infoed
PI proxies:
Institution: UCONN Health Center

IRB office: Yale IRB
IRB coordinator: Monika Lau
Letter: Initial SITE Approval_UCONN(0.01) ...
Regulatory authority: 2018 Requirements
Study: 2000022220

Next Steps

- View Site
- Printer Version
- Create Site Modification**
- Report New Information

History Funding Documents Follow-on Submissions Snapshots

Filter by: Activity [dropdown] Enter text to search for [input] + Add Filter X Clear All

Activity Author Activity Date

In the screen that opens up, explain the nature of the modification and plan for obtaining continued consent for participation from currently or previously enrolled participants at the site.

Modification Information

1. Study enrollment status:

- No subjects have been enrolled to date
- Subjects are currently enrolled
- Study is permanently closed to enrollment
- All subjects have completed all study-related interventions
- Collection of private identifiable information is complete

2. * Notification of subjects: (check all that apply)

- Current subjects will be notified of these changes
- Former subjects will be notified of these changes
- No re-consent/modification needed

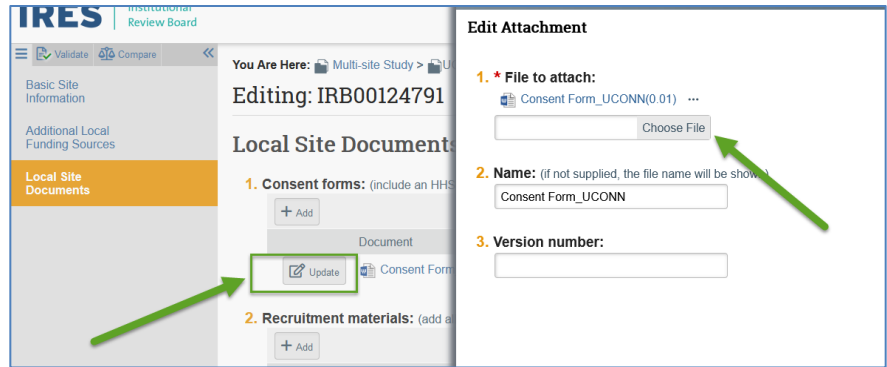
3. * Summarize the modifications, provide rationale for the changes, address impact on subject safety, and explain where in the study record the changes have occurred (including sections of the documents that are modified).
Note: insufficient information may lead to rejection of the modification request.

Changes to the site consent form include changes approved by the IRB to the consent template in MOD000123.
In addition, the contact phone number for the site PI is revised.
Currently enrolled participants will not be re-consented but they will be provided with a new phone number.

Exit Save Continue

After clicking **Continue** at the bottom of the screen, go to the page where local information needs to be revised. If existing documents are being revised (e.g., consent forms), use **Update** to upload the new versions.

Once documents are uploaded, submit the site modification for review. HRPP will triage it to the IRB for review. When approved, you will be notified via email sent automatically to your Yale email address.

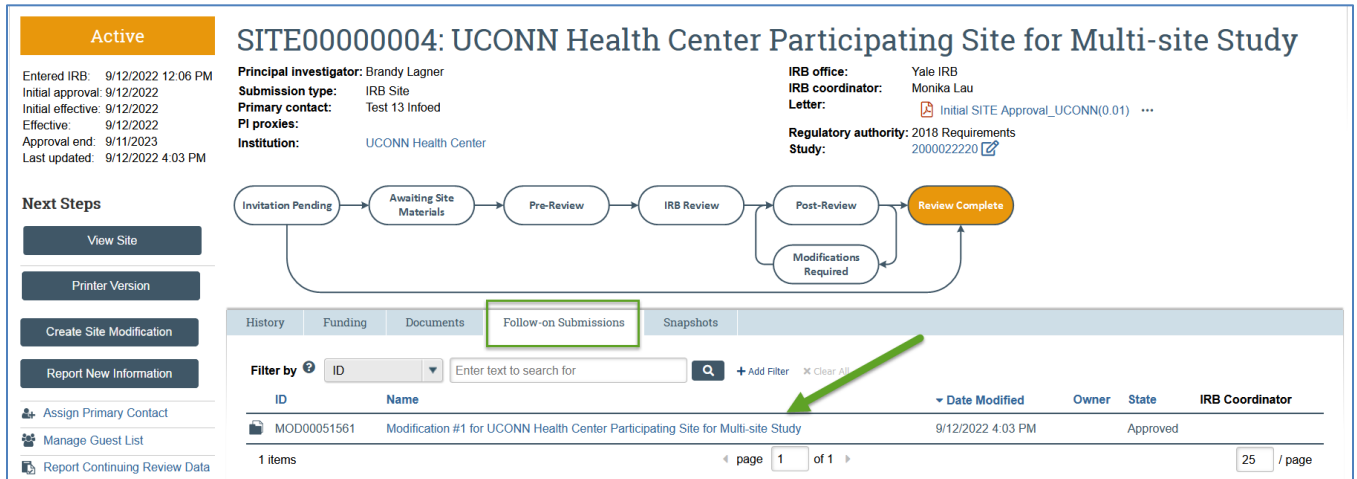


Distributing approval materials to sites

If the modification did not affect the site consent forms or local documents, you can send the approved version of the protocol and the main approval letter for the modification to the sites along with explanation of the approved changes.

If the modification included site changes, you need to first download the site approval documents, which will live in the site workspace. Open the site workspace by clicking on the name of the site in the SITES tab.

Once in the Site workspace, click on **Follow-on Submissions** to select and open the approved modification. The most recently approved consent forms for the site are available in the **Documents** tab.



The approval letter for the site modification is available in the modification workspace, as shown in the screenshot below.

When sending documents to the sites, ensure that track versions are included along with the clean approved documents. Site consent forms will receive an approval watermark. Keep the proof of the delivery of the documents and associated training provided on the modification in your study file – all your communications with the sites should be part of your regulatory binder. Depending on the local requirements, the site PI may need to provide the approval letter and/or approved documents to the local HRPP according to their procedures.

14.6. Continuing Review Submission Process

Continuing Review is approved for the entire study, inclusive of all participating sites. There will be only one IRB approval letter for the study. If there are any modifications that may also affect site-specific documents, you should submit them separately from the continuing review. You can combine the continuing review request with modifications to the study that do not affect consent forms or other site-specific materials. There are two steps to submitting the continuing review report to the IRB:

- Obtaining and submitting site continuing review report,
- Submitting study continuing review report to the IRB for review and approval.

Obtaining information from sites for continuing review report

You will need the following information from each of the sites:

- Total enrollment # at the site,
- Total enrollment # since the last approval (initial approval or last continuing review, whichever happened last),
- Verification of whether certain statements are true for the site,
- Any supporting information e.g., explanation of the progress,
- Any additional comments about the study.

To obtain the information from the site, you can copy a table with the questionnaire below and email it to the sites with a request to complete it.

1.	Specify enrollment totals at this investigator's sites:
2.	Specify enrollment totals at this investigator's sites since last approval:
3.	Check the items that are true for this site since the last IRB approval: (initial review or last continuing review):
<input type="checkbox"/>	NO subjects experienced unexpected harm
<input type="checkbox"/>	Anticipated adverse events have NOT taken place with greater frequency or severity than expected
<input type="checkbox"/>	NO subjects withdrew from the study
<input type="checkbox"/>	NO unanticipated problems involving risks to subjects or others
<input type="checkbox"/>	NO complaints about the study
<input type="checkbox"/>	NO publications in the literature relevant to risks or potential benefits
<input type="checkbox"/>	NO interim findings
<input type="checkbox"/>	NO multi-center trial reports
<input type="checkbox"/>	NO data safety monitoring reports
<input type="checkbox"/>	NO regulatory actions that could affect safety and risk assessments
<input type="checkbox"/>	NO other relevant information regarding this study, especially information about risks
<input type="checkbox"/>	In the opinion of the PI, the risks and potential benefits are unchanged
<input type="checkbox"/>	All modifications to the protocol have been submitted to the IRB
<input type="checkbox"/>	All problems that require prompt reporting to the IRB have been submitted
4.	Supporting Documents:
5.	<p>Comments: <i>Include any additional relevant information about research progress at the site, any changes in the site PI status, qualifications, and resources to conduct the study, changes in the status of the conflicts of interest (COIs) for the research team that could affect the study, any relevant information about safety monitoring that should be submitted to the IRB, any changes in the acceptability of the proposed research for the site in terms of institutional commitments and applicable regulations, state and local law, or standards of professional conduct or practice, etc.</i></p>

Submitting continuing review report

Once you obtain the continuing review information from the sites, you will need to submit the report to the IRB in two steps:

- **Report Continuing Review Data** for the sites – in each site workspace, under Next Steps, click on Report Continuing Review Data. In the window that will appear, transfer the information you received from the site. You can also upload any relevant documents received from the site.

- **Create and submit Continuing Review for the study** – once the site information has been submitted, you can return to study workspace and create study Continuing Review by clicking on Create Modification/CR under Next Steps. In the window that will open, select Continuing Review/Study Closure. Provide the following information as it applies to:

- **Questions #1 and #2** apply only to Yale sites,

- **Questions #3 and #4** apply to the overall study e.g., do not report that the study is closed to enrollment if there are sites that are still enrolling participants,

- **Questions #5, #6, and #7** apply to all sites, e.g., if a statement in question # 6 is only is NOT true for any site participating in the research under Yale IRB purview, the statement must remain unchecked.

5. * Do any investigators or research staff have a financial interest related to the research that was not described in a previous application?

Yes No [Clear](#)

6. Check the items that are true since the last IRB approval for all sites involved in the study: (initial review or last continuing review)

- NO subjects experienced unexpected harm
- Anticipated adverse events have NOT taken place with greater frequency or severity than expected
- NO subjects withdrew from the study
- NO unanticipated problems involving risks to subjects or others
- NO complaints about the study
- NO publications in the literature relevant to risks or potential benefits
- NO interim findings
- NO multi-center trial reports
- NO data safety monitoring reports
- NO regulatory actions that could affect safety and risk assessments
- NO other relevant information regarding this study, especially information about risks
- In the opinion of the PI, the risks and potential benefits are unchanged
- All modifications to the protocol have been submitted to the IRB
- All problems that require prompt reporting to the IRB have been submitted

- Save the information and exit the CR screen. Click on **Sites** tab in the CR workspace. Verify that the enrollment numbers are accurate, if so, check off the box in the Report Completed column to indicate YES.
- Now you are ready to submit the study CR for review. Click **Submit** under Next Steps.

Execute Activity	Institution	Report Date	Total Enrollment	Enrollment Since Last Approval	Potential Concerns	Documents	Report Completed?
	UCONN Health Center	9/12/2022	15	15	None	None	<input checked="" type="checkbox"/> yes

1 items < page 1 of 1 > 10 / page

The HRPP will review the submission and triage it for IRB review. Once approved, you will be notified via email sent to your Yale email address.

Distributing approval materials to sites

There will be no separate IRB approval letter for the site at the time of Continuing Review. The approval letter from the IRB should reference which sites are approved in the letter itself. Documents do not receive an approval watermark at the time of continuing review unless there was a modification that involved revision to the documents. As such, at the time of continuing review, you may only have a study approval letter to provide to the site. Keep the proof of the delivery of the approval documents in your study file – all your communications with the sites should be part of your regulatory binder. Depending on the local requirements, the site PI may need to provide the approval letter to the local HRPP according to their procedures.

14.7. Reportable New Information Submission Process

Reportable New Information (RNI) can be submitted from the main study workspace or directly from the workspace of the site where the reportable event occurred. Both types of reports will ask for the same information:

- **Related Study** - Main study and any associated modifications, if applicable, should be listed here.
- **Reporting Site** - Site reporting the issue, which should be the original site where event originated from, if Yale is the site where the event occurred, the field can be left empty.
- **Affected Sites** - Any participating sites that have been affected by the issue should be listed here. Yale does not appear as a separate site so the field may be left empty.

6. Related studies and modifications:

...

ID	Short Title	Investigator	State	IRB Office
2000022220	Multi-site Study	Test 13 Infoed	Approved	Yale IRB

7. Reporting participating site:

...

8. Affected participating sites:

...

ID	Short Title	Investigator	State	IRB Office
SITE00000004	UCONN Health Center Participating Site for Multi-site Study	Brandy Lagner	Active	Yale IRB

RNI reports will live in the main study workspace. If the RNI also affects a participating site, the RNI will also appear in the Follow-on Submissions in the site workspace.

History	Funding	Documents	Follow-on Submissions	Reviews	Snapshots
Filter by <input type="text" value="Enter text to search for"/> <input type="button" value="Q"/> <input type="button" value="+ Add Filter"/> <input type="button" value="X Clear All"/>					
ID	Name	Date Modified	Owner	State	IRB Coordinator
RNI00002631	Potential Serious Noncompliance at UCONN	9/12/2022 8:22 PM	Lau, Monika M.	Acknowledged	Monika Lau
MOD00051561	Modification #1 for UCONN Health Center Participating Site for Multi-site Study	9/12/2022 4:03 PM		Approved	
2 items		page 1 of 1		25 / page	

Distributing IRB determination to sites

The IRB determination regarding the RNI must be sent to the site investigators (local PIs). Keep the proof of the delivery of the determination in your study file – all your communications with the sites should be part of your regulatory binder. Depending on the local requirements, the site PI may need to provide the IRB determination letter to the local HRPP according to their procedures.

If the IRB makes a determination of Serious or Continuing Noncompliance or an Unanticipated Problem, the Yale HRPP will also contact the institution’s HRPP (or IRB). If the research is subject to FDA or OHRP

regulations, the Yale IRB will report the finding to the regulatory agencies on behalf of the affected institutions. You will receive a copy of the letter for your records.

14.8. sIRB Questionnaire

The answers to the following questions should be sent to the HRPP when requesting Yale IRB to serve as the sIRB for multi-site research. The request can be submitted via Qualtrics survey or via email sent to HRPP@yale.edu.

Please select the option that most closely fits your request for Yale to serve as the sIRB for a multi-site research project:

- Multi-site federally funded research project
- Multi-site, not-federally funded research project (i.e., other funding or no funding)
- Currently approved research project that seeks to add new sites.

Name of Yale Principal Investigator(s) (PI): [Type here]

Funding Agency: [Type here]

Funding Opportunity Announcement (FOA) Number: [Type here]

What Organization is the prime awardee?: [Type here]

Project Title: [Type here]

Provide a brief research summary: [Type here]

In the table below, list all research sites that Yale will serve as the sIRB for (add more rows as needed):

Name of the site	Name of the local PI	Research Activities occurring at the site (e.g., recruitment, enrollment, data analysis only)	Number of consent forms for the site

What is the estimated duration of the study? [Type here]

How many modifications do you expect every year? [Type here]

Is there anything else the Yale IRB should know when considering this request? [Type here]

15. Appendices

Appendix A-1 Additional Requirements for DHHS-Regulated Research¹⁶

1. When a subject decides to withdraw from a clinical trial, the investigator conducting the clinical trial should ask the subject to clarify whether the subject wishes to withdraw from all components of the trial or only from the primary interventional component of the trial. If the latter, research activities involving other components of the clinical trial, such as follow-up data collection activities, for which the subject previously gave consent may continue. The investigator should explain to the subject who wishes to withdraw the importance of obtaining follow-up safety data about the subject.
2. Investigators are allowed to retain and analyze already collected data relating to any subject who chooses to withdraw from a research study or whose participation is terminated by an investigator without regard to the subject's consent, provided such analysis falls within the scope of the analysis described in the IRB-approved protocol. This is the case even if that data includes identifiable private information about the subject.
3. For research not subject to regulation and review by FDA, investigators, in consultation with the funding agency, can choose to honor a research subject's request that the investigator destroy the subject's data or that the investigator exclude the subject's data from any analysis.
4. When seeking the informed consent of subjects, investigators should explain whether already collected data about the subjects will be retained and analyzed even if the subjects choose to withdraw from the research.
5. When research is covered by a certificate of confidentiality, researchers:
 - a. May not disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
 - b. May not disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.
 - c. May disclose information only when:
 - i. Required by Federal, State, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding.
 - ii. Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;

¹⁶ <http://www.hhs.gov/ohrp/policy/subjectwithdrawal.html>

- iii. Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
 - iv. Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human participants in research.
- d. Researchers must inform participants of the protections and limitations of certificates of confidentiality (see language in Consent Glossary, IRES IRB Library).
- i. For studies that were previously issued a Certificate and notified participants of the protections provided by that Certificate, NIH does not expect participants to be notified that the protections afforded by the Certificate have changed, although IRBs may determine whether it is appropriate to inform participants.
 - ii. If part of the study cohort was recruited prior to issuance of the Certificate, but are no longer activity participating in the study, NIH does not expect participants consented prior to the change in authority, or prior to the issuance of a Certificate, to be notified that the protections afforded by the Certificate have changed, or that participants who were previously consented to be re-contacted to be informed of the Certificate, although the IRB may determine whether it is appropriate to inform participants.
- e. Researchers conducting research covered by a certificate of confidentiality, even if the research is not federally funded, must ensure that if identifiable, sensitive information is provided to other researchers or organizations, the other researcher or organization must comply with applicable requirements when research is covered by a certificate of confidentiality.

Appendix A-2 Additional Requirements for FDA-Regulated Research

1. When a subject withdraws from a study:¹⁷
 - a. The data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.
 - b. An investigator may ask a subject who is withdrawing whether the subject wishes to provide 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 continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.
 - c. If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, 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 informed consent form). IRB approval of informed consent documents is required.
 - d. If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent.
 - e. 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.
2. For FDA-regulated research involving investigational drugs:
 - a. Investigators must abide by FDA restrictions on promotion of investigational drugs:¹⁸
 - i. An investigator, or any person acting on behalf of an investigator, must not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.
 - ii. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.
 - iii. An investigator must not commercially distribute or test market an investigational new drug.
 - b. Follow FDA requirements for general responsibilities of investigators¹⁹

¹⁷ <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf>

¹⁸ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.7>

¹⁹ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.60>

	<p style="text-align: center;">Human Research Protection Program Investigator Manual</p>	<p style="text-align: center;">Version 2.1 07/24/2023</p>
---	--	---

- i. An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.
- ii. An investigator must, in accordance with the provisions of 21 CFR §50, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 21 CFR §50.23 or §50.24 of this chapter.
- iii. Additional specific responsibilities of clinical investigators are set forth in this part and in 21 CFR §50 and 21 CFR §56.
- c. Follow FDA requirements for control of the investigational drug²⁰
 - i. An investigator must administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator.
 - ii. The investigator must not supply the investigational drug to any person not authorized under this part to receive it.
- d. Follow FDA requirements for investigator recordkeeping and record retention²¹
 - i. Disposition of drug:
 - 1. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects.
 - 2. If the investigation is terminated, suspended, discontinued, or completed, the investigator must return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR §312.59.
 - ii. Case histories.
 - 1. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.
 - 2. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.
 - iii. Record retention: An investigator must retain required records 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.

²⁰ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61>

²¹ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62>

- e. Follow FDA requirements for investigator reports²²
 - i. Progress reports: The investigator must furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained.
 - ii. Safety reports: An investigator must promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator must report the adverse effect immediately.
 - iii. Final report: An investigator must provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.
 - iv. Financial disclosure reports:
 - 1. The clinical investigator must provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under 21 CFR §54.
 - 2. The clinical investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.
- f. Follow FDA requirements for assurance of IRB review²³
 - i. An investigator must assure that an IRB that complies with the requirements set forth in 21 CFR §56 will be responsible for the initial and continuing review and approval of the proposed clinical study.
 - ii. The investigator must also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- g. Follow FDA requirements for inspection of investigator's records and reports²⁴
 - i. An investigator must upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 312.62.
 - ii. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.
- h. Follow FDA requirements for handling of controlled substances²⁵
 - i. If the investigational drug is subject to the Controlled Substances Act, the investigator must take adequate precautions, including storage of the investigational

²² <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64>

²³ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.66>

²⁴ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.68>

²⁵ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.69>

drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

3. For FDA-regulated research involving investigational devices:
 - a. General responsibilities of investigators.²⁶
 - i. An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR §50.
 - b. Specific responsibilities of investigators²⁷
 - i. Awaiting approval: An investigator may determine whether potential subjects would be interested in participating in an investigation, but must not request the written informed consent of any subject to participate, and must not allow any subject to participate before obtaining IRB and FDA approval.
 - ii. Compliance: An investigator must conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
 - iii. Supervising device use: An investigator must permit an investigational device to be used only with subjects under the investigator's supervision. An investigator must not supply an investigational device to any person not authorized to receive it.
 - iv. Financial disclosure:
 1. A clinical investigator must disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under 21 CFR §54.
 2. The investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
 - v. Disposing of device: Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator must return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
 - c. Maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:²⁸
 - i. All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.

²⁶ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.100>

²⁷ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.110>

²⁸ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.140>

- ii. Records of receipt, use or disposition of a device that relate to:
 - 1. The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
 - 2. The names of all persons who received, used, or disposed of each device.
 - 3. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.
 - iii. Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. Such records must include:
 - 1. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent.
 - 2. Documentation that informed consent was obtained prior to participation in the study.
 - 3. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
 - 4. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
 - iv. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
 - v. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
- d. Inspections²⁹
- i. Entry and inspection: A sponsor or an investigator who has authority to grant access must permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).
 - ii. Records inspection: A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, must permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

²⁹ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.145>

- iii. Records identifying subjects: An investigator must permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.
- e. Prepare and submit the following complete, accurate, and timely reports³⁰
 - i. Unanticipated adverse device effects. An investigator must submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
 - ii. Withdrawal of IRB approval. An investigator must report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
 - iii. Progress. An investigator must submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
 - iv. Deviations from the investigational plan:
 - 1. An investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency.
 - 2. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency occurred.
 - 3. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB also is required.
 - v. Informed consent. If an investigator uses a device without obtaining informed consent, the investigator must report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
 - vi. Final report. An investigator must, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
 - vii. Other. An investigator must, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

³⁰ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.150>

Appendix A-3 Additional Requirements for Clinical Trials (ICH-GCP-E6 (R2))

1. Investigator's Qualifications and Agreements
 - a. The clinical trial should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice and the applicable regulatory requirements.
 - b. The investigator 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 requirements, 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.
 - c. The investigator should be thoroughly familiar with the appropriate use of the investigational product, as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.
 - d. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
 - e. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authorities.
 - f. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
2. Adequate Resources
 - a. The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.
 - b. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
 - c. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
 - d. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product, and their trial-related duties and functions.
3. Medical Care of Trial Subjects
 - a. A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
 - b. During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illnesses of which the investigator becomes aware.

- c. It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
 - d. Although a subject is not obliged to give his/her reasons for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reasons, while fully respecting the subject's rights.
 4. Communication with IRB
 - a. Before initiating a trial, the investigator/institution should have written and dated approval 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.
 - b. As part of the investigator's/institution's written application to the IRB, the investigator/institution should provide the IRB with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB.
 - c. During the trial the investigator/institution should provide to the IRB all documents subject to review.
 5. Compliance with Protocol
 - a. The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authorities and which was given approval opinion by the IRB. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.
 - b. The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazards to trial subjects, or when the changes involves only logistical or administrative aspects of the trial (e.g., change in monitors, change of telephone numbers).
 - c. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
 - d. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to trial subjects without prior IRB approval opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendments should be submitted: a) to the IRB for review and approval opinion, b) to the sponsor for agreement and, if required, c) to the regulatory authorities.
 6. Investigational Product
 - a. Responsibility for investigational product accountability at the trial site rests with the investigator/institution.
 - b. Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product accountability at the trial site to

an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

- c. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product received from the sponsor.
 - d. The investigational product should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.
 - e. The investigator should ensure that the investigational product is used only in accordance with the approved protocol.
 - f. The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.
 - g. Randomization Procedures and Unblinding: 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 any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product.
7. Informed Consent of Trial Subjects
- a. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB's written approval opinion of the written informed consent form and any other written information to be provided to subjects.
 - b. 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 opinion in advance of use. The subject or the subject's legally acceptable representative 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.
 - c. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.
 - d. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or

appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

- e. The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval opinion by the IRB.
- f. 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 legally acceptable representative and the impartial witness, where applicable.
- g. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative 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 legally acceptable representative.
- h. 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 legally acceptable representative, and by the person who conducted the informed consent discussion.
- i. If a subject is unable to read or if a legally acceptable representative 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 legally acceptable representative, and after the subject or the subject's legally acceptable representative 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 legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.
- j. Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:
 - i. That the trial involves research.
 - ii. The purpose of the trial.
 - iii. The trial treatments and the probability for random assignment to each treatment.
 - iv. The trial procedures to be followed, including all invasive procedures.
 - v. The subject's responsibilities.
 - vi. Those aspects of the trial that are experimental.
 - vii. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

- viii. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- ix. The alternative procedures or courses of treatment that may be available to the subject, and their important potential benefits and risks.
- x. The compensation and/or treatment available to the subject in the event of trial related injury.
- xi. The anticipated prorated payment, if any, to the subject for participating in the trial.
- xii. The anticipated expenses, if any, to the subject for participating in the trial.
- xiii. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- xiv. That the monitors, the auditors, 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 the subject's legally acceptable representative is authorizing such access.
- xv. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- xvi. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- xvii. The persons to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- xviii. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- xix. The expected duration of the subject's participation in the trial.
- xx. The approximate number of subjects involved in the trial.
- k. Prior to participation in the trial, the subject or the subject's legally acceptable representative 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 legally acceptable representative 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.
- l. When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to

the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

- m. Except as described above, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.
 - n. Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled: a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally. b) The foreseeable risks to the subjects are low. c) The negative impact on the subject's well-being is minimized and low. d) The trial is not prohibited by law. e) The approval opinion of the IRB is expressly sought on the inclusion of such subjects, and the written approval opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.
 - o. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval opinion by the IRB, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.
8. Records and Reports
- a. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
 - b. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.
 - c. Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.
 - d. The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory

requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

- e. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.
 - f. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.
 - g. Upon request of the monitor, auditor, IRB, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.
9. Progress Reports
- a. The investigator should submit written summaries of the trial status to the IRB annually, or more frequently, if requested by the IRB.
 - b. The investigator should promptly provide written reports to the sponsor, the IRB and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.
10. Safety Reporting
- a. All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authorities and the IRB.
 - b. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
 - c. For reported deaths, the investigator should supply the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).
 - d. Premature Termination or Suspension of a Trial If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirements, should inform the regulatory authorities. In addition:

- i. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB, and should provide the sponsor and the IRB a detailed written explanation of the termination or suspension.
 - ii. If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.
 - iii. If the IRB terminates or suspends its approval opinion of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.
11. Final Reports by Investigator: Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the trial's outcome, and the regulatory authorities with any reports required.

Appendix A-4 Additional Requirements for Department of Defense (DOD) research

1. When appropriate, research protocols must be reviewed and approved by the IRB prior to the Department of Defense approval. Consult with the Department of Defense funding component to see whether this is a requirement.
2. Civilian researchers attempting to access military volunteers should seek collaboration with a military researcher familiar with service-specific requirements.
3. Employees of the Department of Defense (including temporary, part-time, and intermittent appointments) may not be able to legally accept payments to participate in research and should check with their supervisor before accepting such payments. Employees of the Department of Defense cannot be paid for conducting research while on active duty.
4. Service members must follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty or off-duty.
5. Components of the Department of Defense might have stricter requirements for research-related injury than the DHHS regulations.
6. There may be specific educational requirements or certification required.
7. When assessing whether to support or collaborate with this institution for research involving human subjects, the Department of Defense may evaluate this institution's education and training policies to ensure the personnel are qualified to perform the research.
8. When research involves U.S. military personnel, policies and procedures require limitations on dual compensation:
 - a. Prohibit an individual from receiving pay of compensation for research during duty hours.
 - b. An individual may be compensated for research if the participant is involved in the research when not on duty.
 - c. Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to \$50 for each blood draw.
 - d. Non-Federal persons may be compensated for research participating other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.
9. When research involves large scale genomic data (LSGD) collected on DOD-affiliated personnel, additional protections are required:
 - a. Additional administrative, technical, and physical safeguards to prevent disclosure of DoD-affiliated personnel's genomic data commensurate with risk (including secondary use or sharing of de-identified data or specimens)
 - b. Research will apply an HHS Certificate of Confidentiality
10. DoD Component security review
11. When conducting multi-site research, a formal agreement between institutions is required to specify the roles and responsibilities of each party.
12. Other specific requirements of the Department of Defense research be found in the "Additional Requirements for Department of Defense (DOD) Research" section in the IRB's HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

Yale	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
------	--	---------------------------

Appendix A-5 Additional Requirements for Department of Energy (DOE) Research

(See DOE Order 443.1C)

1. Research that involves one or more of the following must be submitted to the appropriate IRB for human subjects research review and determination :
 - a. Study of humans in a systematically modified environment. These studies include but are not limited to intentional modification of the human environment:
 - i. Study of human environments that use tracer chemicals, particles or other materials to characterize airflow.
 - ii. Study in occupied homes or offices that:
 1. Manipulate the environment to achieve research aims.
 2. Test new materials.
 3. Involve collecting information on occupants' views of appliances, materials, or devices installed in their homes or their energy-saving behaviors through surveys and focus groups.
 - b. Use of social media data.
 - c. Human Terrain Mapping (HTM).
 - d. All exempt HSR determinations must be made by the appropriate IRB and/or IRB office.
2. Personally identifiable information collected and/or used during HSR projects must be protected in accordance with the requirements of DOE Order 206.1, Department of Energy Privacy Program, current version. The Central DOE IRBs require submission of DOE's HRP- 490-CHECKLIST-Reviewing Protocols that use Personally Identifiable Information (PII) if your research includes PII.
3. You must report the following to the DOE human subjects research Program Manager (and, when an NNSA element is involved, the NNSA HSP Program Manager) prior to initiation of any new human subjects research project, even if it meets the regulatory definition of exempt human subjects research as outlined in 10 CFR Part 745.104, involving:
 - a. An institution without an established Institutional Review Board (IRB);
 - b. A foreign country;
 - c. The potential for significant controversy (e.g., negative press or reaction from stakeholder or oversight groups);
 - d. Research subjects in a protected class (prisoners, children, individuals with impaired decision making capability, or DOE/NNSA federal or DOE/NNSA 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; or
 - e. The generation or use of classified information.
4. The IRB must be notified immediately and the DOE HSP Program Manager (and, when an NNSA element is involved, the NNSA HSP Program Manager) must be notified within 48 hours and consulted regarding planned corrective actions if any of the following occur:
 - a. Adverse events. Notify the IRB for all adverse events and the DOE/NNSA HSP Program Manager if the IRB determines them to be significant, as defined in DOE Order 443.1C.
 - b. Unanticipated problems and complaints about the research.

- c. Any suspension or termination of IRB approval of research.
 - d. Any significant non-compliance with HSP Program procedures or other requirements.
 - e. Any finding of a suspected or confirmed data breach involving PII in printed or electronic form. Report immediately to the IRB, the DOE/NNSA HSP Program Manager(s), and the DOE-Cyber Incident Response Capability, in accordance with the requirements of the CRD associated with DOE O 206.1.
 - f. Serious adverse events and corrective actions taken must be reported immediately to the IRB and the DOE/NNSA HSP Program Manager(s). The time frame for "immediately" is defined as upon discovery.
5. Requirements for human participant protections for classified research apply to all classified research conducted or supported by the DOE and its national laboratories, including contracts, and including Human Terrain Mapping research.
 6. Researchers conducting human subjects research in any other country or on citizens or other individuals residing in that country must be cognizant of country-specific human subjects research requirements and consult the IRB regarding applicability of such requirements.
 7. No human subjects research conducted with DOE funding, at DOE institutions (regardless of funding source), or by DOE or DOE contractor personnel (regardless of funding source or location conducted), whether done domestically or in an international environment, including classified and proprietary research, may be initiated without both a Federalwide Assurance (FWA) or comparable assurance (e.g., Department of Defense assurance) of compliance and approval by the cognizant Institutional Review Board (IRB) in accordance with 10 CFR §745.103. Human subjects research involving multiple DOE sites (e.g., members of the research team from more than one DOE site and/or data or human subjects from more than one DOE site) must be reviewed and approved by one of the Central DOE IRBs prior to initiation, or if authorized by the DOE and/or NNSA HSP Program Manager, other appropriate IRB of record. In all cases, an IRB Authorization Agreement (IAA) or Memorandum of Understanding (MOU) must be in place between the organization(s) conducting the HSR and the organization responsible for IRB review.
 8. Human subjects research that involves DOE Federal and/or contractor employees must first be reviewed and approved by the appropriate DOE IRB (the DOE site IRB or one of the Central DOE IRBs), or if deemed more fitting by the Federally assured DOE site or Headquarters, other appropriate IRB of record, in accordance with an IAA or MOU negotiated between the DOE site or Headquarters and the organization responsible for IRB review.
 9. Classified and unclassified human subjects research that is funded through the Strategic Intelligence Partnership Program (SIPP) must be reviewed and approved by the Central DOE IRB-Classified.
 10. If applicable, federally funded HSR must comply with the requirements of the Paperwork Reduction Act.
 11. Other specific requirements of the DOE research can be found in the "Additional Requirements for Department of Energy (DOE) Research" section in the IRB's HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

Appendix A-6 Additional Requirements for Department of Justice (DOJ) Research**Additional Requirements for DOJ Research conducted in the Federal Bureau of Prisons**

1. Implementation of Bureau programmatic or operational initiatives made through pilot projects is not considered to be research.
2. The project must not involve medical experimentation, cosmetic research, or pharmaceutical testing.
3. The research design must be compatible with both the operation of prison facilities and protection of human subjects.
4. Investigators must observe the rules of the institution or office in which the research is conducted.
5. Any investigator who is a non-employee of the Bureau of Prisoners must sign a statement in which the investigator agrees to adhere to the requirements of 28 CFR §512.
6. The research must be reviewed and approved by the Bureau Research Review Board.
7. Incentives cannot be offered to help persuade inmate subjects to participate. However, soft drinks and snacks to be consumed at the test setting may be offered. Reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research subjects who are both: No longer in Bureau of Prisons custody. Participating in authorized research being conducted by Bureau employees or contractors.
8. A non-employee of the Bureau may receive records in a form not individually identifiable when advance adequate written assurance that the record will be used solely as a statistical research or reporting record is provided to the agency.
9. Except as noted in the consent statement to the subject, you must not provide research information that identifies a subject to any person without that subject's prior written consent to release the information. For example, research information identifiable to a particular individual cannot be admitted as evidence or used for any purpose in any action, suit, or other judicial, administrative, or legislative proceeding without the written consent of the individual to whom the data pertain.
10. 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.
11. If you are conducting a study of special interest to the Office of Research and Evaluation but the study is not a joint project involving Office of Research and Evaluation, you may be asked to provide Office of Research and Evaluation with the computerized research data, not identifiable to individual subjects, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the project.
12. Required elements of disclosure additionally include:
 - a. Identification of the investigators.
 - b. Anticipated uses of the results of the research.
 - c. A statement that participation is completely voluntary and that the subject 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, an investigator

- may not guarantee confidentiality when the subject indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the subject is an inmate, indicates intent to leave the facility without authorization.
- e. A statement that participation in the research project will have no effect on the inmate subject's release date or parole eligibility.
13. You must have academic preparation or experience in the area of study of the proposed research.
14. The IRB application must include a summary statement, which includes:
- a. Names and current affiliations of the investigators.
 - b. Title of the study.
 - c. Purpose of the study.
 - d. Location of the study.
 - e. Methods to be employed.
 - f. Anticipated results.
 - g. Duration of the study.
 - h. Number of subjects (staff or inmates) required and amount of time required from each.
 - i. Indication of risk or discomfort involved as a result of participation.
15. The IRB application must include a comprehensive statement, which includes:
- a. Review of related literature.
 - b. Detailed description of the research method.
 - c. Significance of anticipated results and their contribution to the advancement of knowledge.
 - d. Specific resources required from the Bureau of Prisons.
 - e. Description of all possible risks, discomforts, and benefits to individual subjects or a class of subjects, and a discussion of the likelihood that the risks and discomforts will actually occur.
 - f. Description of steps taken to minimize any risks.
 - g. Description of physical or administrative procedures to be followed to: Ensure the security of any individually identifiable data that are being collected for the study.
 - h. Destroy research records or remove individual identifiers from those records when the research has been completed.
 - i. Description of any anticipated effects of the research study on institutional programs and operations.
 - j. Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.
16. The IRB application must include a statement regarding assurances and certification required by federal regulations, if applicable.
17. You must assume responsibility for actions of any person engaged to participate in the research project as an associate, assistant, or subcontractor.
18. At least once a year, you must provide the Chief, Office of Research and Evaluation, with a report on the progress of the research.

19. At least 12 working days before any report of findings is to be released, you must distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the warden of each institution that provided data or assistance.
20. You must include an abstract in the report of findings.
21. In any publication of results, you must acknowledge the Bureau's participation in the research project.
22. You must expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
23. Prior to submitting for publication the results of a research project conducted under this subpart, You must provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons.
24. Other specific requirements of the Department of Justice (DOJ) Research Conducted within the Federal Bureau of Prisons (BOP) can be found in the "Additional Requirements for Department of Justice (DOJ) Research Conducted within the Federal Bureau of Prisons (BOP)" section in the IRB's HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

Additional Requirements for DOJ Research Funded by the National Institute of Justice

1. The project must have a privacy certificate approved by the National Institute of Justice Human Subjects Protection Officer.
2. All investigators and research staff are required to sign employee confidentiality statements, which are maintained by the responsible investigator.
3. The confidentiality statement on the consent document must state that confidentiality can only be broken if the subject reports immediate harm to subjects or others.
4. Under a privacy certificate, investigators and research staff do not have to report child abuse unless the subject signs another consent document to allow child abuse reporting.
5. A copy of all data must be de-identified and sent to the National Archive of Criminal Justice Data, including copies of the informed consent document, data collection instruments, surveys, or other relevant research materials.
 - a. At least once a year, the researcher shall provide the Chief, Office of Research and Evaluation, with a report of the progress of the research.
 - b. At least 12 working days before any report of findings is to be released, the researcher shall distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the warden of each institution that provided data or assistance. The researcher shall include an abstract in the report of findings.
 - c. In any publication of results, the researcher shall acknowledge the Bureau's participation in the research project.
 - d. The research shall expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

- e. 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
- 6. Other specific requirements of the Department of Justice (DOJ) Research Funded by the National Institute of Justice can be found in the "Additional Requirements for Department of Justice (DOJ) Research" section in the IRB's HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

Yale	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
------	--	---------------------------

Appendix A-7 Additional Requirements for Department of Education (ED) Research

1. Each school at which the research is conducted must provide an assurance that they comply with the Family Educational Rights and Privacy Act (FERPA) and the Protection of Pupil Rights Amendment (PPRA).
2. Provide a copy of all surveys and instructional material used in the research. Upon request parents of children³¹ involved in the research³² must be able to inspect these materials.
3. The school in which the research is being conducted must have policies regarding the administration of physical examinations or screenings that the school may administer to students.
4. Other specific requirements of the Department of Education (ED) Research can be found in the "Additional Requirements for Department of Education (ED) Research" section in the IRB's HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

³¹ Children are persons enrolled in research not above the elementary or secondary education level, who have not reached the age or majority as determined under state law.

³² Research or experimentation program or project means any program or project in any research that is designed to explore or develop new or unproven teaching methods or techniques.

Yale	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
------	--	---------------------------

Appendix A-8 Additional Requirements for Environmental Protection Agency (EPA) Research

1. Research conducted, supported, or intended to be submitted to EPA is subject to Environmental Protection Agency Regulations.
2. Intentional exposure of pregnant women or children to any substance is prohibited.
3. Observational research involving pregnant women and fetuses are subject to additional DHHS requirements for research involving pregnant women (45 CFR §46 Subpart B) and additional DHHS requirements for research involving children (45 CFR §46 Subpart D.)
4. Research involving children must meet category #1 or #2.
5. Other specific requirements of the Environmental Protection Agency (EPA) Research can be found in the "Additional Requirements for Environmental Protection Agency (EPA) Research and Research Intended to be Submitted to the Environmental Protection Agency" section in the IRB's HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

Appendix A-9 Additional Requirements for Veterans Administration (VA) Research

- VA research is research that is conducted by researchers (serving on VA compensated, WOC, or IPA appointments) while on VA time or on VA property. The research may be funded by VA, by other sponsors, or be unfunded. VA research must have Research and Development (R&D) Committee approval before it is considered VA Research and before it can be initiated. All research activities approved by the R&D Committee are considered VA Research.
- VA-affiliated nonprofit research and education corporations (NPC) are authorized by Congress under 38 U.S.C. 7361-7366 to provide flexible funding mechanisms for the conduct of research and education at one or more VA facilities. Research approved by a facility R&D Committee are considered to be a VA research project or a VA education activity respectively, regardless of the source of funding, the entity administering the funds, or the research or education site (see VHA Handbook 1200.17, Department of Veterans Affairs Nonprofit Research and Education Corporations Authorized by Title 38 U.S.C. Sections 7361 Through 7366, dated April 27, 2016 and revised May 9, 2017).
- VA research includes VA-approved research conducted at international sites not within the United States, its territories, or Commonwealths; and includes research where human tissues are sent outside the United States.
- The investigator must follow this institution's procedures to ensure reporting in writing to the IRB within 5 business days of becoming aware of unanticipated problems involving risks to subjects or others (local SAEs or serious problems that are unanticipated and related to the research), apparent serious or continuing non-compliance, suspension of IRB approval, termination of IRB approval. Any unanticipated problem involving risks to subjects or others that is a local research death must be reported orally to the IRB immediately upon becoming aware of the information. VA personnel must ensure that the appropriate IRB of Record is notified, in writing, within five (5) business days after becoming aware of any apparent serious and/or continuing noncompliance with applicable laws, regulations, policies, and agreements pertaining to non-exempt human participants research. This includes, but is not limited to, serious or continuing noncompliance with the Common Rule, local VA medical facility policies and SOPs related to human participants research, if developed, IRB-approved protocols, and the requirements or determinations of the IRB.
- In the event of a local research participant death, VA personnel must ensure that the appropriate IRB of Record is notified:
 - Immediately (i.e., within one hour) upon becoming aware of any local research death of a human participant that is believed to be both unexpected and related or possibly related to participating in a VA non-exempt human participant study. VA personnel must also provide follow-up written notification to the IRB within one (1) business day.
 - In the event of any apparent UPIRTSO, VA personnel must ensure that the appropriate IRB of Record is notified, in writing, within five (5) business days after becoming aware of any apparent UPIRTSO.
 - Definitions:

Serious non-compliance is a failure to follow requirements for conducting human research that may reasonably be regarded as:

- Presenting a genuine risk of substantive harm to the safety, rights, or welfare of research personnel who conduct research.
- Presenting a genuine risk of substantive reputational harm to VA.
- Substantively compromising a VA facility's HRPP.

Continuing non-compliance means repeated instances of noncompliance with applicable laws, regulations, policies, agreements, or determinations of a research review committee or the prolonged persistence of noncompliance occurring after its identification, awareness, or implementation of a corrective action intended to effectively resolve the noncompliance.

The determination that non-compliance is "serious" or "continuing" rests with the IRB.

An unanticipated problem involving risks to participants or others (UPIRTSO) in human participants research is an incident, experience, or outcome that is: unexpected; related or possibly related to participation in the research; and indicative of the research placing participants or others at substantively greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

- The term "unexpected" refers to an incident, experience, or outcome that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.
- The phrase "related to participation in the research" means a logical sequence of cause and effect shows that the study procedures were the reason for the incident, experience, or outcome.
- The phrase "possibly related to participation in the research" implies a lesser degree of certainty about causality and refers to an incident, experience, or outcome for which there is some evidence to reasonably suggest a causal relationship between study procedures and the incident, experience, or outcome.

A serious adverse event (SAE) in human participants research is an untoward occurrence, whether or not considered related to a participant's participation in research, that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly or birth defect, or that requires medical, surgical, behavioral, social, or other intervention to prevent such an outcome.

- An unexpected SAE that is related or possibly related to participation in human participants research constitutes a UPIRTSO.

- The investigator must give first priority to the protection of research subjects, uphold professional and ethical standards and practices, and adhere to all applicable VA and other federal requirements, including the local VA facility's policies and procedures, regarding the conduct of research and the protection of human subjects. The investigator must hold a current VA appointment to conduct VA research.
- The responsibilities of the investigator may be defined in the protocol or IRB application. Specifically, the principal investigator's and local site investigator's responsibilities include, but are not limited to
 - Qualifications to Conduct Human Subjects Research. VA investigators must have the appropriate training, education, expertise, and credentials to conduct the research according to the research protocol.
 - PIs must ensure that all research staff are qualified (e.g., including but not limited to appropriate training, education, expertise, and credentials) to perform procedures assigned to them during the course of the study.
 - Investigators and their staff conducting human subjects research must be credentialed and privileged as required by current local and VA requirements (see VHA Handbook 1100.19 and VHA Directive 2012-030, Credentialing of Health Care Professionals, or successor policy). Investigators and their research staff may only perform those activities in a research study for which they have the relevant credentials and privileges.
 - Investigators and co-investigators must be identified on the IRB application and must provide credentials, conflict of interest statements or other documentation required by VA and local facility policies.
 - All individuals involved in conducting VA human subjects research are required to complete training in ethical principles on which human subjects research is to be conducted. Specific requirements regarding the type and frequency of training are found on ORD's Web site at: <http://www.research.va.gov/pride/training/options.cfm>. All other applicable VA and VHA training requirements at the local and national level must be met (e.g., privacy and information security training).
 - Investigators must prospectively document their research with their supervisor in writing.
 - Investigators must submit exempt protocols that require limited IRB review to the IRB for limited IRB review/approval.
 - Research Protocol. The investigator must develop and submit a research protocol that is scientifically valid, describes the research objectives, background and methodology, provides for fair and equitable recruitment and selection of subjects, minimizes risks to subjects and others, and describes a data and safety monitoring plan consistent with the nature of the study. The research must be relevant to the health or welfare of the Veteran population. When relevant, the protocol must include the following safety measures:
 - The type of safety information to be collected including AEs;
 - Frequency of safety data collection;
 - Frequency or periodicity of review of cumulative safety data;

- Statistical tests for analyzing the safety data to determine if harm is occurring; and
- Conditions that trigger an immediate suspension of the research, if applicable.
- Approvals. The investigator must submit the protocol for initial review and obtain written approvals from the IRB, other applicable committees, and from the R&D Committee. In addition, the investigator must receive written notice from the ACOS/R&D that the research may commence before initiating the research.
- An investigator may not self-certify that a study is exempt.
- Once approved by the IRB, the protocol must be implemented as approved. All modifications to the approved research protocol or consent form must be approved by the IRB prior to initiating the changes except when necessary to eliminate apparent immediate hazards to the subject.
- The investigator must also obtain continuing review and approval at a frequency established by the IRB, but not less than once every year and is expected to submit all materials required for continuing review in sufficient time to assure approval prior to the expiration date. No research activities may be conducted at any time without a currently valid IRB approval.
- Conflict Of Interest. The investigator must disclose to the IRB any potential, actual, apparent, or perceived conflict of interest of a financial, professional, or personal nature that may affect any aspect of the research, and comply with all applicable VA and other federal requirements regarding conflict of interest.
- Initial Contact. During the recruitment process, members of the research team must make initial contact with potential subjects in person or by letter prior to initiating any telephone contact, unless there is written documentation that the subject is willing to be contacted by telephone about the study in question or a specific kind of research as outlined in the study. (NOTE: This does not apply to situations where a Veteran calls in response to an advertisement. If existing information from sources such as a medical record or database, research or non-research, are used to identify human subjects, there must be an IRB approved HIPAA waiver for this activity in the new protocol.)
- Any initial contact by letter or telephone must provide a telephone number or other means that the potential subject can use to verify that the study constitutes VA research.
- If a contractor makes the initial contact by letter, the VA investigator must sign the letter.
- Informed Consent for Research. The investigator must obtain and document legally effective informed consent of the subject or the subject's LAR prospectively (i.e., no screening or other interaction or intervention involving a human subject can occur until after the IRB-approved informed consent requirements have been met) that is in alignment with ethical principles that govern informed consent for research. The only exceptions are if the IRB determines the research is exempt, or approves a waiver of the informed consent process, or approves a waiver of the signed informed consent document.
- The consent document must include all required disclosures, but does not need to use a specific template.

- The consent document must be signed and dated by the participant or legally authorized representative, and by the person obtaining consent.
- Consent may be obtained and documented electronically so long as there are appropriate authentication controls to provide assurance the consent is rendered by the appropriate individual, and the participant dates the consent, or software provides the current date when signed.
- The informed consent for research must include information describing any photographs, video, and/or audio recordings to be taken or obtained for research purposes; how the photographs, video, and/or audio recordings will be used for the research; and whether the photographs, video, and/or audio recordings will be disclosed outside VA.
- An informed consent to take a photograph, video, and/or audio recording cannot be waived by the IRB.
- The consent for research does not give legal authority to disclose the photographs, video, and/or audio recordings outside VA.
- Consent documents must include additional VA elements of disclosure:
 - A statement that in the event of a research-related injury the VA has to provide necessary medical treatment to a participant injured by participation.
 - Any payments the participant is to receive for participating in the study.
 - Any real or apparent conflict of interest by the researchers where the research will be performed.
 - A statement that VA will provide treatment for research-related injury in accordance with applicable federal regulations.
 - A statement that informs VA research participants that they or their insurance will not be charged for any costs related to the research.
 - A statement that a veteran-participant will not be required to pay for care received as a participant in a VA research project except in accordance with federal law and that certain veterans were required to pay co-payments for medical care and services provided by VA.
 - Consent for research must describe any photographs, video, or audio recordings obtained for research purposes; how they will be used, and whether they will be disclosed outside the VA.
- If the investigator does not personally obtain informed consent, the investigator must delegate this responsibility in writing (e.g., by use of a delegation letter) to research staff sufficiently knowledgeable about the protocol and related concerns to answer questions from prospective subjects, and about the ethical basis of the informed consent process and protocol.
 - If the investigator contracts with a firm, e.g., a survey research firm, to obtain consent from subjects, collect private individually identifiable information from human subjects, or are involved in activities that would institutionally engage the firm in human subjects research, the firm must have its own IRB oversight of the activity. In

addition, the PO must determine that there is appropriate authority to allow the disclosure of individual names and other information to the contracted firm.

- The investigator must ensure that all original signed and dated informed consent documents are maintained in the investigator's research files, readily retrievable, and secure.
- HIPAA Authorization. The investigator or designee must obtain HIPAA authorization for the use and disclosure of the subject's PHI, or obtain an IRB-approved waiver of HIPAA authorization unless there is a limited data set and appropriate DUA. The written HIPAA authorization may either be a standalone document or combined with the research informed consent approved by the IRB. If a standalone document is used as the written HIPAA authorization, VA Form 10-0493: Authorization for Use and Release of Individually Identifiable Health Information Collected for VHA Research, must be used to document the authorization.
- Reporting. The investigator is responsible for reporting unanticipated problems involving risks to subjects or others, serious unanticipated problems involving risks to subjects or others, apparent serious or continuing noncompliance, any termination or suspension of research; and privacy or information security incidents related to VA research, including: any inappropriate access, loss, or theft of PHI; noncompliant storage, transmission, removal, or destruction of PHI; or theft, loss, or noncompliant destruction of equipment containing PHI, in accordance with local facility or IRB SOPs and VHA Handbook 1058.01.
- Research Records. All written information given to subjects must be in the investigator's research file along with the consent form(s). All records regardless of format (paper, electronic, electronic systems) must be managed per NARA approved records schedules found in VHA RCS 10-1 and therefore must be retained until disposition instructions, as approved by NARA, are published in VHA RCS 10-1. NOTE: Once the disposition schedule is determined, records should be disposed in accordance with VHA RCS 10-1. If the investigator leaves VA, all research records must be retained by the VA facility where the research was conducted.
- VHA Health Record. A VHA health record must be created or updated, and a progress note created, for all research subjects (Veterans or Non-Veterans) who receive research procedures or interventions as inpatients or outpatients at VA medical facilities that are either used in or may impact the medical care of the research subject at a VA medical facility or at facilities contracted by VA to provide services to Veterans (e.g., Community-Based Outpatient Clinics or nursing homes). Informed consent and HIPAA authorization documents are not required to be in the health record.
- Investigational Drugs and Devices. The investigator must conduct VA human subjects research involving investigational drugs and devices in accordance with all applicable VA policies and other federal requirements including, but not limited to: VHA Directive 1200.05, VHA Handbook 1108.04, and applicable FDA regulations. The storage and security

- procedures for test articles used in research must be reviewed and approved by the IRB and follow all applicable federal rules.
- The PI or Local Site Investigator (LSI) must provide the Pharmacy Service with the following:
 - Written approval letter signed by the ACOS for R&D that all relevant approvals have been obtained and that the study may be initiated at the site (VHA Directive 1200.01);
 - An IRB approval letter;
 - A copy of the approved study protocol;
 - A copy of VA Form 10-9012, when appropriate;
 - An IB, when appropriate;
 - Any sponsor-provided documents relating to the storage, preparation, dispensing, and accountability of the investigation products;
 - Copies of all correspondence addressed to the Researcher from the FDA specific to the investigational drugs as appropriate;
 - A copy of the consent document for each participating participant with all appropriate signatures;
 - Protocol revisions, amendments, and updates after IRB approval and after the IRB approved the amendment;
 - Updates and changes to authorized prescribers after IRB approval;
 - Documentation of IRB continuing review approval;
 - Notice to the Chief, Pharmacy Service, the research pharmacy when applicable and the IRB in writing and the Research and Development Committee when a study involving investigational drugs has been suspended, terminated, or closed.
 - The PI or LSI must provide Pharmacy Service and/or the Research Service Investigational Pharmacy, investigational drug information on each patient receiving an investigational drug through the electronic medical record or other locally-approved means. This documentation is to include allergies, toxicities, or adverse drug events related to the investigational drug, or the potential for interaction with other drugs, foods, or dietary supplements (herbals, nutraceuticals).
 - The PI or LSI must place the completed VA Form 10-9012, or electronic equivalent, in the subject's medical record.
 - The PI must comply with all dispensing and documentation requirements and the dispensing log must be made accessible to the investigational drug pharmacist upon request.
 - Initiation of Research Projects. IRB approval is for a specified time period based on the degree of risk of the study, not to exceed 1 year except for research subject to the 2018 Requirements where continuing review is not required. The IRB determines the expiration date based upon its date of review and communicates that date to the investigator in the written approval letter. The investigator must not initiate the IRB approved research protocol until all applicable requirements in VHA Directive 1200.01 have also been met including obtaining R&D Committee approval.

- Expiration of IRB Approval. There is no provision for any grace period to extend the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur on or before the date when IRB approval expires. If approval expires, the investigator must:
- Stop all research activities including, but not limited to, enrollment of new subjects, analyses of individually identifiable data, and research interventions or interactions with currently participating subjects, except where stopping such interventions or interactions could be harmful to those subjects; and
- Immediately submit to the IRB Chair a list of research subjects who could be harmed by stopping specified study interventions or interactions. The IRB Chair must determine within 2 business days whether or not such interventions or interactions may continue.
- Documentation of Informed Consent
 - When documentation of informed consent is not waived by IRB, the investigator or designee must ensure that the informed consent document is signed and dated by the subject or the subject's legally authorized representative,
 - If consent is obtained electronically, the following must be met:
 - Authentication controls on electronic consent provide reasonable assurance that such consent is rendered by the proper individual; and
 - The subject dates the consent as is typical or that the software provides the current date when signed.
- Other specific requirements of Veterans Administration (VA) research be found in the "Additional Requirements for Veterans Administration (VA) Research" section in the IRB's HRP-318 - WORKSHEET - Additional Federal Agency Criteria.
- Vulnerable Subjects
 - The following populations are considered categorically vulnerable and have specific VA requirements for their inclusion in research:
 - Pregnant Women, Human Fetuses and Neonates
 - Prisoners
 - Children
 - Subjects who Lack Decision-making Capacity.
- Research Involving Prisoners
 - Research involving prisoners cannot be conducted by VA investigators while on official VA duty, at VA facilities, or at VA-approved off-site facilities unless a waiver has been granted by the CRADO.
 - Waiver requests must be submitted electronically to the CRADO by the VA medical facility Director with the following documents:
 1. A letter from the VA medical facility Director supporting the conduct of the VA study involving prisoners;

2. Rationale for conducting the research involving prisoners to include additional ethical protections taken by the proposed research for prisoners to make voluntary and uncoerced decisions whether or not to participate as subjects in research;
 3. Documentation of the VA investigator's qualifications to conduct the research involving prisoners, such as a biosketch and a list of all research team members;
 4. Location of institutions where the research is proposed to be conducted;
 5. A copy of the IRB approval letter specifically documenting its review determinations according to 45 CFR 46.305(a);
 6. A copy of the IRB minutes approving the research with documentation that at least one member of the IRB included a prisoner or a prisoner representative for the review of the research;
 7. A copy of the IRB-approved research study;
 8. A copy of the IRB-approved informed consent document; and
 9. A copy of the written HIPAA authorization.
 - If such a waiver is granted, the research must comply with the requirements of 45 CFR 46.301 - 46.306.
- Research Involving Children
 - Research involving children must not present greater than minimal risk.
 - The VA medical facility Director must approve participation in the proposed research that includes children.
 - Research involving biological specimens or data obtained from children is considered to be research involving children even if de-identified. If the biological specimens or data were previously collected, they must have been collected under applicable policies and ethical guidelines.
 - The IRB must have the appropriate expertise to evaluate VA research involving children and must comply with the requirements of 45 CFR 46.401 - 46.404 and 46.408.
 - Research Involving Pregnant Women, Human Fetuses and Neonates as Subjects
 - Neonates: Interventional research enrolling neonates cannot be conducted by VA investigators while on official duty, or at VA facilities, or at VA approved off-site facilities. VA investigators may conduct research involving noninvasive monitoring of neonates if the research is determined by the IRB to be minimal risk. Prospective observational and retrospective record review studies that involve neonates or neonatal outcomes are permitted. The VA medical facility Director must certify that the medical facility has sufficient expertise in neonatal health to conduct the proposed research.
 - Pregnant Women: The VA medical facility Director must certify that the medical facility has sufficient expertise in women's health to conduct the proposed research if the research includes interventional studies or invasive monitoring of pregnant women as subjects.
 - Research that involves provision of in vitro fertilization services can be conducted by VA investigators while on official VA duty, at VA facilities, or at VA-approved off-site facilities. This includes prospective and retrospective research involving provision of or the

enhancement of FDA-approved methods of in vitro fertilization for studies involving consenting subjects, both male and female, undergoing or who have undergone in vitro fertilization for the treatment of certain forms of human infertility. In vitro fertilization is any fertilization of human ova that occurs outside the body of a female, either through a mixture of donor human sperm and ova or by any other means.

- Prospective and retrospective studies that enroll or include pregnant subjects who conceived through in vitro fertilization or other artificial reproductive technologies are permitted.
- Research that uses human fetal tissue or that focuses on either a fetus, or human fetal tissue, in-utero or ex-utero cannot be conducted by VA investigators while on official VA duty, at VA facilities, or at VA-approved off-site facilities. Use of stem cells shall be governed by the policy set by NIH for recipients of NIH research funding.
- Research Involving Persons Who Lack Decision-Making Capacity
 - The protocol must include a plan, that it is appropriate given the population and setting of the research, for how investigators will determine when a legally authorized representative will be required to provide informed consent. In general, the research staff must perform or obtain and document a clinical assessment of decision-making capacity for any subject suspected of lacking decision-making capacity.
 - When the potential subject is determined to lack decision-making capacity, investigators must obtain consent from the LAR of the subject (i.e., surrogate consent). NOTE: Investigators and IRBs have a responsibility to consult with the Office of General Counsel (OGC) regarding state or local requirements for surrogate consent for research that may supersede VA requirements.
 - The following persons are authorized to consent on behalf of persons who lack decision-making capacity in the following order of priority:
 - (1) Health care agent (i.e., an individual named by the subject in a Durable Power of Attorney for Health Care);
 - (2) Legal guardian or special guardian;
 - (3) Next of kin: a close relative of the patient 18 years of age or older, in the following priority: spouse, child, parent, sibling, grandparent, or grandchild; or
 - (4) Close friend.
 - If feasible, the investigator must explain the proposed research to the prospective research subject even when the legally authorized representative gives consent. Although unable to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may a subject be forced or coerced to participate in a research study even if the LAR has provided consent.
 - Legally authorized representatives must be told that their obligation is to try to determine what the subjects would do if able to make an informed decision. If the potential subjects' wishes cannot be determined, the legally authorized representatives must be told they are responsible for determining what is in the subjects' best interest.

- Research Involving Certificates of Confidentiality
 - If information about the subject's participation will be included as part of the VHA medical record that information must be given to the prospective subject as part of the informed consent process that information regarding study participation will be included in the medical record.
 - In instances where a written informed consent form is used, inclusion of a statement that the study has been issued a CoC is required.
 - Investigators should work with the research office in their facility to assure that when Veterans are enrolled in a study protected by a Certificate of Confidentiality, they are not simultaneously enrolled in other interventional studies unless it is absolutely clear that this enrollment does not raise safety issues.
- Collaborative Research
 - Collaborative research is human participants research activities involving researchers from VA and at least one non-VA institution. Collaborative Research includes VA and non-VA institutions.
 - This addresses collaborations between VA and non-VA investigators. Collaboration is encouraged when VA investigators have a substantive role in the design, conduct, and/or analysis of the research. VA may also serve as a Coordinating Center for collaborative studies. NOTE: Collaborative studies do not include studies conducted under a CRADA with pharmaceutical companies or other for-profit entities.
 - IRB of Record Approval. Each institution is responsible for safeguarding the rights and welfare of human subjects and providing oversight of the research activities conducted at that institution.
 - Each collaborating institution engaged in human subjects research must obtain approval from its IRB of Record and hold a FWA or another assurance acceptable to VA, e.g. DoD assurance.
 - VA investigators must submit a protocol or other documentation to their VA IRB of Record that delineates which research activities will be conducted by VA.
 - Each institution engaged in the collaborative research must use the informed consent document and HIPAA authorization required by their respective institutional policies for subjects recruited from that institution, or procedures requiring participation of the subject at that institution. The informed consent document may contain information on the project as a whole as long as the document clearly describes which procedures will be performed at VA and which will be performed at other institutions.
 - The VA informed consent document must clearly state when procedures mentioned at other institutions are part of the VA's portion of the study.
 - The informed consent document and HIPAA authorization must be consistent and include information describing the following:
 - PHI to be collected and/or used by the VA research team;

- PHI to be disclosed to the other institutions; and
 - Purpose for which the PHI may be used.
 - Waivers. PHI obtained in research for which the IRB of Record has waived the requirements to obtain a HIPAA authorization and a signed informed consent document may not be disclosed outside VA unless the VA facility Privacy Officer ensures and documents VA's authority to disclose the PHI to another institution. A waiver of HIPAA authorization is not sufficient to fulfill the requirements of other applicable privacy regulations such as the Privacy Act of 1974 (5 U.S.C. 552a).
 - Research Data. The protocol, addendum, and/or IRB of Record application must describe the data to be disclosed to collaborators, the entity(ies) to which the data are to be disclosed, and how the data are to be transmitted. This includes data from individual subjects as well as other data developed during the research such as the analytic data and the aggregate data.
 - Each VA facility must retain a complete record of all data obtained during the VA portion of the research in accordance with privacy requirements, the Federal Records Act, and VHA Records Control Schedule (RCS) 10-1.
 - All disclosures and data transmission must meet privacy and security requirements per VA Directive 6500, VHA Handbook 6500, and VHA Handbook 1605.1.
 - Written agreements. Collaborative research involving non-VA institutions may not be undertaken without a signed written agreement (e.g., a CRADA or a Data Use Agreement (DUA)) that addresses such issues as the responsibilities of each party, the ownership of the data and the reuse of the data for other research. NOTE: Any reuse must be consistent with the protocol, the informed consent document, and the HIPAA authorization.
- Photography, Video and/or Audio Recording for Research Purposes
 - The informed consent for research must include information describing any photographs, video, and/or audio recordings to be taken or obtained for research purposes, how the photographs, video, and/or audio will be used for the research, and whether the photographs, video, and/or audio will be disclosed outside the VA.
 - An informed consent to take a photograph, video, and/or audio recording cannot be waived by the IRB.
 - The consent for research does not give legal authority to disclose the photographs, video, and/or audio recordings outside the VA. A HIPAA authorization is needed to make such disclosures.
- International Research
 - VA international research is defined as any VA-approved research conducted at international sites (i.e., not within the United States (U.S.), its territories, or Commonwealths), any VA-approved research using either identifiable or de-identified human biological specimens or identifiable or de-identified human data originating from international sites, or any VA-approved research that entails sending such specimens or data out of the U.S. This definition applies regardless of the funding source (funded or unfunded) and to research conducted

through any mechanism of support including MOUs, CRADAs, grants, contracts, or other agreements. NOTE: Research conducted at U.S. military bases, ships, or embassies is not considered international research.

- Sending specimens or data to individuals with VA appointments at international sites (e.g., a WOC appointment, a VA investigator on sabbatical at an international site) is considered international research. Remote use of data that is maintained on VA computers within the U.S. or Puerto Rico and accessed via a secure connection is not considered international research.
- International research includes multi-site trials involving non-U.S. sites where VA is the study sponsor, a VA investigator is the overall study-wide PI, VA holds the Investigational New Drug (IND), or the VA manages the data collection and the data analyses.
- International research does not include studies in which VA is only one of multiple participating sites where the overall study-wide PI is not a VA investigator (i.e., the PI for the study as a whole is not a VA investigator).
- Before approving international research involving human subjects research, the IRB must ensure that human subjects outside of the U.S. who participate in research projects in which VA is a collaborator receive equivalent protections as research participants inside the U.S. (see OHRP guidance at <http://www.hhs.gov/ohrp/international/index.html>). NOTE: The VA medical facility Director must approve participation in the proposed international research.
- All international research must also be approved explicitly in a document signed by the VA medical facility Director, except for Cooperative Studies Program activities which must be approved by the CRADO.
- Use Preparatory To Research
 - VA investigators may use individually-identifiable health information to prepare a research protocol prior to submission of the protocol to the IRB for approval without obtaining a HIPAA authorization or waiver of authorization.
 - VA investigators must not arbitrarily review PHI based on their employee access to PHI until the investigator documents the following required information as “Preparatory to Research” in a designated file that is readily accessible for those required to audit such information (e.g., Health Information Manager or PO):
 - Access to PHI is only to prepare a protocol;
 - No PHI will be removed from the covered entity (i.e., VHA); and
 - Access to PHI is necessary for preparation of the research protocol.
 - Non-VA researchers may not obtain VA information for preparatory to research activities without appropriate VA approvals (see VHA Directive 1605.01).
 - During the preparatory to research activities the VA investigator:
 - Must only record aggregate data. The aggregate data may only be used for background information to justify the research or to show that there are

- adequate numbers of potential subjects to allow the investigator to meet enrollment requirements for the research study;
- Must not record any individually identifiable health information; and
 - Must not use any individually identifiable information to recruit research subjects.
 - Preparatory activities can include reviewing database output (computer file or printout) containing identifiable health information generated by the database owner, if the investigator returns the database output to the database owner when finished aggregating the information.
- Contacting potential research subjects and conducting pilot or feasibility studies are not considered activities preparatory to research.
 - Activities preparatory to research only encompass the time to prepare the protocol and ends when the protocol is submitted to the IRB.
- Posting of Clinical Trial Consent Forms
 - For studies subject to the 2018 Requirements, if a VA research study is a clinical trial, one IRB-approved informed consent form used to enroll subjects, unless the IRB waived documentation of informed consent, must be posted by either the investigator or the Federal department or agency conducting or supporting the study. The informed consent form must be posted after the clinical trial is closed to recruitment and no later than 60 days after the last study visit by any subject as described in the IRB-approved protocol. For multi-site studies, it applies when the entire study has closed to subject recruitment. Any proprietary or personal information (such as names and phone numbers) must be redacted prior to posting the informed consent form.
 - For any ORD-funded clinical trial, the applicable ORD funding service will be responsible for posting the informed consent form.
 - For a clinical trial funded or supported by a Federal agency or department other than VA, the awardee is responsible for posting the informed consent form.
 - For a clinical trial funded or supported by a non-Federal agency or department (e.g., university, industry, nonprofit organization) or not funded, the VA Investigator conducting the clinical trial is responsible for ensuring that the informed consent form is posted. If the clinical trial includes multiple sites engaged in the clinical trial, an agreement must exist specifying who is responsible for posting the informed consent form.

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

Appendix A-10 Additional Requirements for Research Subject to EU General Data Protection Regulations (GDPR)

1. Human Research involving personal data about individuals located in (but not necessarily citizens of) European Union member states, Norway, Iceland, Liechtenstein, and Switzerland is subject to EU General Data Protection Regulations.
2. For all prospective Human Research subject to EU GDPR, contact HRPP or Yale Data Protection Officer to ensure that the following elements of the research are consistent with institutional policies and interpretations of EU GDPR:
 - a. Any applicable study design elements related to data security measures.
 - b. Any applicable procedures related to the rights to access, rectification, and erasure of data.
 - c. Procedures related to broad/unspecified future use consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens.
3. Where FDA or DHHS regulations apply in addition to EU GDPR regulations, ensure that procedures related to withdrawal from the research, as well as procedures for managing data and biospecimens associated with the research remain consistent with Appendices A-1 and A-2 above.

Appendix B Emergency/Disaster Preparedness Considerations for Investigators Conducting Human Research

Investigators conducting human research should be aware of the following additional considerations associated with managing Human Research during an emergency/disaster scenario (e.g., extreme weather events, natural disasters, man-made disasters, infectious disease pandemics, etc.) related to investigators' ongoing interactions with research subjects and the institutional review board (IRB) in such cases.

During Emergency/Disaster Scenarios: Deciding Whether a Study-Specific Risk Mitigation Plan for Ongoing Research Is Needed

In general, investigators should develop a study-specific emergency/disaster risk mitigation plan for their research unless one of the following is true:

- Research does not involve in-person interaction with research subjects.
- Research can be conducted as written while adhering to additional institution-level and HRPP-level guidance and requirements regarding the emergency/disaster event.
- The research is externally sponsored, and the sponsor has developed a protocol-specific risk mitigation plan for the research.
- The research has been voluntarily placed on hold for recruitment and all research procedures (except for necessary follow-up procedures to be done consistently with additional institution-level and HRPP-level guidance and requirements regarding the emergency/disaster event).

Please refer to the HRPP [COVID-19 GUIDANCE Related to Human Subjects Research](#) for information related to the following topics:

1. Informed Consent – Using eConsent during the COVID-19 Pandemic
2. Informed Consent – Options for obtaining Consent During the COVID-19 Pandemic
3. Home Health Visits
4. Investigational Product Shipment
5. Remote Laboratories
6. Remote Visits
7. Research Participant Compensation or Reimbursement Options
8. Documentation of Changes Made to Research Due to COVID-19 Impacts
9. Sponsor Audits/Monitoring and Agency inspections (e.g., FDA, EMA, etc.)
10. Study Reactivation

Appendix C Ancillary Committees

#	Research Scenario	Applicable Ancillary Review	Quick instructions for obtaining approval	Example of changes that may require re-review	If changes are made to protocol that affect the review		Notes:
					Study under Yale IRB	Study under External IRB	
1.	Involves interactions with participants (including online)	HRPP	PI must complete 'Safety protocol during pandemic' form and upload it in the Local site documents, HRPP will document approval by requesting an ancillary review in IRES IRB	Significant changes in the pandemic status that allow more lenient safety protocols	Submit revised safety protocol as a modification in IRES IRB	Submit revised safety protocol as a site modification in IRES IRB, modification to the external IRB may not be required	Unless announced otherwise by Yale, studies do not need to be put on hold when the safety protocol is being reviewed
2.	Includes minors as research participants	Pediatric Protocol Review Committee	HRPP to request Ancillary Review at Pre-review; no additional documents needed from PI; approval must be obtained prior to IRB review	Adding minors to the study as a new subject group, changing the drug for minors completely (dose changes do not require re-review)	Submit revised protocol as a modification in IRES IRB; after the PPRC review, the modification will be routed to Yale IRB; occasionally, the reviews can be conducted concurrently	Submit revised protocol as an update (for protocol) and a site modification (for additional documents) in IRES IRB; after PPRC review, an acknowledgement letter will be issued	PPRC does not generally review modifications unless the IRB specifically requests a consultation or review
3.	Yale investigator serves as the IND/IDE holder for the drug/device used in this study	IND-IDE Management Office	HRPP to request Ancillary Review at Pre-review; additional Supplement is needed; approval must be obtained prior to IRB review	Changing the IND/IDE #, adding a new drug/device where Yale investigator holds the IND/IDE	Submit revised protocol and supplement as a modification in IRES IRB; after the approval is obtained, the modification will	Submit revised protocol and supplement as an update (for protocol) and a site modification in IRES IRB; after the approval is	For decide studies that were submitted as exempt or nonsignificant devices: If the IRB requires IDE for the device,

					be routed to Yale IRB	obtained, the acknowledgement letter will be issued	contact HRPP to initiate sign-off from IND-IDE Management Office
4.	Industry sponsored clinical trial or registry	Office of Sponsored Projects	HRPP to request Ancillary Review at Pre-review; no additional documents needed; IRB and OSP sign-off can be concurrent; approval must be obtained prior to final IRB approval OR authorization to use external IRB	Adding new consent forms, revising In Case of Injury or Economic Considerations language in the consent form, changing the PI of the study;	Submit revised and/or new consent forms as a modification in IRES IRB; after the OSP review is requested, the modifications will be routed to Yale IRB	Submit revised and/or new consent forms as a site modification in IRES IRB; after the OSP review is completed, an acknowledgement letter will be issued	Consent Glossary has preferred Injury language for different sponsors, study teams will need to negotiate the revisions with the sponsors/CROs
5.	Includes oncology patients at Smilow Hospital or area of research is related to oncology	Protocol Review Committee	PI obtains it via ePRMS Timing: For PI initiated research: prior to submitting the study in IRES IRB; For industry sponsored research: at the same time as the study is submitted in IRES IRB <ul style="list-style-type: none"> • PRC amendments • PRC 	Changes to drug (compound, dosage, or schedule); significant changes to eligibility, Study Objectives, Statistical/analysis plan	Changes that require IRB review must be submitted to the IRB, proof of PRC approval is required for IITs	Changes that require IRB review must be submitted to the IRB of Record, no action is required in IRES IRB, PI is responsible for obtaining PRC approval when required	
6.	Will include MRI scans at Magnetic Resonance Research Center (The Anlyan Center)	MRRC Protocol Review Committee	Researcher to complete the Proposal to use the MRRC Resources form and upload it in Local Site Documents; MRRC must be indicated in Research Locations; HRPP to verify consent language,	Addition of new or different intravenous infusions of any kind, new or different medications will be administered during the scan, the subject population change	Submit revised protocol as a modification in IRES IRB; after the MRRC review, the modification will be routed to Yale IRB;	Submit revised protocol as an update (for protocol) and a site modification (for additional documents) in IRES	

			approval must be obtained prior to the IRB review/authorization to use external IRB	significantly, the MR sequences will change; adding MRI scans	occasionally, the reviews can be conducted concurrently	IRB; after MRRC review, an acknowledgement letter will be issued; if scanning is added for the first time	
7.	Will include MRI scans at FAS Brain Imaging Center	Central Campus Scanner Governance Committee	Researcher to complete the Request for Scanner Access Faculty of Arts and Sciences (FAS) Brain Imaging Center (BIC) and upload it in Local Site Documents; must be indicated in Research Locations page; HRPP to verify consent language and request the ancillary review; approval must come prior to IRB review.	Adding/removing scans	Submit revised protocol and request form for scanner access as a modification in IRES IRB; after the FAS BIC review, the modification will be routed to Yale IRB;	Submit revised protocol and request form for scanner access as a study update and a site modification in IRES IRB; after the FAS BIC review, an acknowledgement letter will be issued	
8.	Will include research procedures at HRU or CSRU	YCCI Clinical Trial Services	PI to obtain approval prior to IRES IRB submission (YCCI HRU/CSRU/West Campus Clinic Reservation Form online) and upload the approval letter in the Local Site documents; must be indicated in Research Locations page	Adding HRU/CSRU/WCRU as a location	Submit a modification in IRES IRB to indicate the new location in Research Locations page	Submit a site modification in IRES IRB to indicate the new location in Research Locations page, acknowledgement letter will be issued	PI should not hold submission to IRB of record
9.	Includes use of radioactive drugs at PET Center that are FDA approved or exempt from IND requirements	Radioactive Investigational Drug Committee AND	PI completes three documents: • RIDC/RDRC application • Dosimetry calculator • Yale RSC cover page; Must be uploaded in the Local Site Documents; indicated in the Research	Changes to radiation doses or frequency, any information in the RIDC/RDRC or RSC applications	Submit revised protocol and RIDC/RSC application as a modification in IRES IRB; ancillary reviews will be initiated by HRPP and the	Submit revised protocol and RIDC/RSC applications as an update and a site modification in IRES IRB; ancillary reviews will be	For internal IRB consent forms will not be finalized unless both RIDC and RSC approvals are obtained

		Yale Radiation Safety Committee	Locations page; review can be concurrent; HRPP to request ancillary reviews from RIDC and YRSC, notify PET Center		modification will be routed to Yale IRB;	initiated by HRPP, once approvals are obtained, acknowledgement letter will be issued	
10.	Includes use of radioactive drugs at PET Center under RDRC purview	Radioactive Drug Research Committee AND Yale Radiation Safety Committee	PI completes three documents: <ul style="list-style-type: none"> • RIDC/RDRC application • Dosimetry calculator • Yale RSC cover page; Must be uploaded in the Local Site Documents; indicated in the Research Locations page; review can be concurrent; HRPP to request ancillary reviews from RDRC and YRSC, notify PET Center	Changes to radiation doses or frequency, increase # of participants , any information in the RIDC/RDRC or RSC applications	Submit revised protocol and RDRC/RSC applications as a modification in IRES IRB; ancillary reviews will be initiated by HRPP and the modification will be routed to Yale IRB;	Submit revised protocol and RDRC/RSC applications as an update and a site modification in IRES IRB; ancillary reviews will be initiated by HRPP, once approvals are obtained, acknowledgement letter will be issued	For internal IRB consent forms will not be finalized unless both RDRC and RSC approvals are obtained
11.	Includes research only scans with radiation at YNHH	Yale New Haven Radiation Safety Committee	PI completes two documents: <ul style="list-style-type: none"> • YNHH RSC application • Dosimetry calculator Must be uploaded in the Local Site Documents; HRPP to request ancillary review from YNHH RSC; review can be concurrent	Changes to radiation doses or frequency,	Submit revised protocol and RSC application as a modification in IRES IRB; ancillary review will be initiated by HRPP and the modification will be routed to Yale IRB;	Submit revised protocol and RSC application as an update and a site modification in IRES IRB; ancillary review will be initiated by HRPP, once approval is obtained, acknowledgement letter will be issued	For internal IRB consent forms will not be finalized unless YNHH RSC approval is obtained

	Human Research Protection Program Investigator Manual	Version 2.1 07/24/2023
---	--	---------------------------

12.	Targets Yale medical students as study participants	Committee on research on Yale medical students	PI obtains sign off from Andres Martin and uploads it in Local Site Documents	Addition of Yale medical students as study subjects	Submit a modification in IRES IRB with a proof of approval	Submit a site modification in IRES IRB with a proof of approval	
13.	Uses psychology pool for recruitment of psychology students as participants	Intro to Psych Pool Committee	PI obtains approval and uploads it in Local Site Documents; must be obtained prior to IRB review; HRPP to verify language in consent forms	Addition of Yale Psych Pool as study subjects	Submit a modification in IRES IRB with a proof of approval	Submit a modification in IRES IRB with a proof of approval and consent changes to include specific language	
14.	It is NIH funded clinical trial or applicable trials under FDA purview and Yale is responsible for registering the protocol at clinicaltrials.gov	YCAS	HRPP initiates sign-off from YCAS and notifies PI if registration is required or recommended	Certain changes to the protocol and status of the study require updates, See info on website	Changes requiring IRB review must be submitted for review, PI is responsible for updating the record	No actions are required in IRES IRB; PI is responsible for updating the record on clinicaltrials.gov	
15.	The study will be conducted at embargoed countries	Export Controls - OSP	PI must contact exports@yale.edu to obtain approval	Adding new location that is on the embargoed list, significant changes to what is imported/exported to and from the location	Submit a modification in IRES IRB to indicate the new location in Research Locations page, Data Sharing page may also need update	Submit a site modification in IRES IRB to indicate the new location in Research Locations page, Data Sharing page may also need update	
16.	Is conducted by nurses at YNHH	Nursing Research Committee	PI must contact Nursing Research Committee at NursingScientificReviewComm@ynhh.org and obtain approval, must be uploaded in Local Site Documents	N/A	N/A	N/A	N/A

17.	Enrolls at Emergency Department (adult)	Sign-off from Departmental Chair	PI must complete Emergency Department Approval form and obtain appropriate signature; upload it in Local Site Documents, must be indicated in Research Locations page, must be completed prior to IRB review	Adding ED as a new recruitment location	Submit a modification in IRES IRB to indicate the new location in Research Locations, provide proof of approval	Submit a site modification in IRES IRB to indicate the new location in Research Locations, provide proof of approval	
18.	Enrolls at Maternal Fetal Medicine at 1 Long Wharf (pregnant women)	Approval from Maternal Fetal Medicine , contact: Lauren.perley@yale.edu	PI must complete ' <i>Request to Conduct Research Activities, Including Recruitment, at Maternal Fetal Medicine: Outpatient Clinic at 1 Long Wharf</i> ' and upload it in Local Site Documents, HRPP will request Ancillary Review in IRES IRB, approval must be obtained prior to the IRB review	Adding MFM at Long Wharf as a new site	Submit a modification in IRES IRB to indicate the new location in Research Locations, upload the completed request	Submit a site modification in IRES IRB to indicate the new location in Research Locations, upload the completed request, when approval is obtained, acknowledgement letter will be issued	<i>Pending new process</i>
19.	Involves use of CMHC locations	Notification to CMHC	HRPP to initiate Ancillary Review notification to CMHC to allow for verification of training	Adding CMHC as a new site	Submit a modification in IRES IRB to indicate the new location in Research Locations	Submit a site modification in IRES IRB to indicate the new location in Research Locations	May require changes to the consent forms to indicate medical record creation
20.	Requires waivers of HIPAA authorization or stand-alone HIPAA RAF	HIPAA Privacy Board	The Yale IRB serves as the Privacy Board but the function may be delegated to another IRB; most of the time, requests for waivers and authorizations are reviewed at the same time as the IRB review; if Yale IRB serves as a Privacy Board for	Requesting a new waiver for HIPAA authorization, adding PHI that will be collected under a waiver,	Submit a modification in IRES IRB along with the IRB Submission form reflecting the revised or new waiver of HIPAA authorization	<u>Only when Yale IRB continues serving as the HIPAA Privacy Board</u> (e.g., NCI CIRB) - submit a site modification in IRES IRB along with the new or	If the external IRB serves as both IRB of record and Privacy Board, request for new or revised waivers are submitted to the IRB of record and

			a study under an external IRB purview, a separate Request Form for HIPAA waiver must be completed and submitted in IRES IRB			revised Request for a HIPAA waiver;	no submission is required in IRES IRB
21.	Includes use of any of the following: <ul style="list-style-type: none"> • Infectious agents (bacteria, fungi, viruses, parasites), • Recombinant DNA, • Insects, • Biological toxins 	Biosafety Committee	PI must obtain approval from IBC, https://ehs.yale.edu/biosafety-committee , must be uploaded in Local Site Information page; must be obtained prior to IRB approval	Adding a new biologic that requires IBC review, when the sponsor or IRB may specifically requests the re-review as a result of changes	Submit a modification in IRES IRB to add the new biologic, include proof of approval	Submit a site modification in IRES IRB to add the new biologic, include proof of approval	
22.	Is considered Dual Use Research of Concern as it uses one of the following: <ul style="list-style-type: none"> • Avian influenza virus (highly pathogenic) • Bacillus • Botulinum neurotoxin • Burkholderia mallei • Burkholderia pseudomallei • Ebola virus 	Biosafety Committee (Subcommittee for Dual Use Research of Concern)	PI must obtain approval from IBC, https://ehs.yale.edu/biosafety-committee , must be uploaded in Local Site Information page;	Adding a new biologic that requires DURC review, when the sponsor or IRB may specifically requests the re-review as a result of changes	Submit a modification in tIRES IRB to add the new biologic, include proof of approval	Submit a site modification in IRES IRB to add the new biologic, include proof of approval	

	<ul style="list-style-type: none">• Foot-and-mouth disease virus• Francisella tularensis• Marburg virus• Reconstructed 1918 Influenza virus• Rinderpest virus• Toxin-producing strains of Clostridium botulinum• Variola major virus• Variola minor virus• Yersinia pestis						
--	--	--	--	--	--	--	--

Appendix D Guide to Obtaining IRB Approvals to Conduct Research within the Yale New Haven Health System

Institution	Covered Clinics/Centers	Reliance Agreement/IRB Information	Instructions
Yale New Haven Hospital FWA00002577	Smilow Cancer Center, YNHH Shoreline Medical Center, YNHH Children's Hospital, Care Centers, St. Raphael Campus	Yale IRBs serve as IRB for YNHH research. Yale HRPP can designate non-Yale IRB (external IRB) as an IRB of Record for research engaging YNHH.	<p>IRES IRB steps:</p> <ul style="list-style-type: none"> Select Yale New Haven Hospital in the Local Research Location page Principal Investigators who are from YNHH only (with no affiliation with Yale) must upload a signed attestation from YNHH Human Protections Administrator (form available in IRES IRB, Library, Other Forms tab) into Local Site Documents page
Greenwich Hospital FWA00002560	N/A	<ul style="list-style-type: none"> Greenwich Hospital does not have its own IRB. All submissions for research engaging GH must be submitted to Bridgeport IRB for review. Existing agreements allow GH to rely on Yale in situations where research is conducted <u>by the Yale PI</u> at Greenwich Hospital. Submission to BH IRB is still required. 	<ol style="list-style-type: none"> If you wish to engage these institutions³³ in your research, first obtain approval for Yale research as Multi-site or Collaborative. Contact central.irb@yale.edu to obtain Local Context form and draft reliance agreement, which must be then submitted by the local investigator to BH IRB (see information below). You will also receive an sIRB guide that will provide steps for submission in IRES IRB and describe your responsibilities as an overall PI. Once the Local Context form is signed by BH IRB and the local PI, submit site documents (consent, recruitment materials, etc.) in IRES IRB using Add Participating Sites function. If you are adding multiple hospitals within YNHH System, use only one Local Context to cover all of them. <p>Information on BH IRB submission process:</p> <ul style="list-style-type: none"> Submissions must be completed by local PI in Axiom MENTOR. Investigators who do not have Axiom MENTOR account should contact Andriana Foiles at Andriana.Foiles@bpthosp.org Training on Mentor: Online training, starting around minute 8: https://player.vimeo.com/video/653830097?h=63728bd2d1 Training on forms and form selection at BH (12 minutes total): https://player.vimeo.com/video/653830130?h=fac19a073d See Communication Plan below for how the Yale HRPP, Yale Study Team, Local Study Team, and BH IRB must communicate with each other regarding actions on studies engaging YNHH System (with exception of Yale New Haven Hospital)
Lawrence & Memorial FWA00003097	Westerly Hospital	<ul style="list-style-type: none"> L&M does not have its own IRB. All submissions for research engaging L&M must be submitted to Bridgeport IRB for review. Existing agreements allow L&M to rely on Yale in situations where research is conducted by the Yale PI at L&M. Submission to BH is still required. 	
Northeast Medical Group FWA00002819	Component of Bridgeport Hospital	<ul style="list-style-type: none"> NMG does not have its own IRB. All submissions for research engaging NMG must be submitted to Bridgeport IRB for review. Existing agreement is limited to NEMG investigators engaged in research conducted by Yale or YNHH PI without any further engagement of Bridgeport Hospital personnel or another entity within YNHH System. 	
Bridgeport Hospital FWA00002819	Northeast Medical Group	<ul style="list-style-type: none"> BH has its own IRB. Research engaging BH must be submitted to BH IRB. 	

³³ To determine whether the institution is engaged, see the [OHRP guidance on engagement](#). You can also refer to HRP-311 Worksheet on Engagement Determinations posted in IRES IRB Library. If unsure, contact Yale HRPP or BH IRB to determine whether the proposed activity engages any of the YNHH System entities. Review of medical records that were created or are held by any of the YNHH entities does not automatically engage these entities in research. Chart reviews require determination and HIPAA waiver only from the PI's IRB unless investigators at the other entities are also engaged. All chart reviews must be requested through JDAT after obtaining IRB determination.

Communication Plan for Yale Reliance Agreements with YNHHS (Greenwich Hospital, Bridgeport, L&M, NEMG)

Definitions:

- **REVIEWING IRB** - Point of Contact (POC): Main person responsible for addressing questions related to the Reviewing IRB’s (Yale IRB) policies and procedures and review status for a ceded study
- **LEAD STUDY TEAM - POC:** Main person responsible for communication with the Reviewing IRB and facilitating communication between relying site study teams and the Reviewing IRB regarding the ceded study
- **RELYING SITE - POC:** Main person responsible for communication with the Reviewing IRB and local study team regarding the ceded study (e.g., personnel in the local IRB office or local human research protection program personnel)
- **RELYING SITE STUDY TEAM POC:** Main person responsible for communication with the Lead Study Team regarding the ceded study

Role	Name(s)	Contact Information
REVIEWING IRB POC	Monika Lau	monika.lau@yale.edu
RELYING SITE POC	Andriana Foiles	Andriana.Foiles@bpthosp.org

Process:

- Reliance on Yale IRB will be documented using SMART IRB documentation of reliance
- The protocol must be approved prior to adding any of the YNHHS sites (except Yale New Haven Hospital)
- The IRB will not approve the site until local context is completed and signed by BH POC, and SMART IRB Acknowledgement of Reliance is signed by both parties

Communication Plan

Communication Responsibility	Responsible Party	Notes
COI: Providing applicable conflict of interest management plans for relying site study teams to the Reviewing IRB	<input type="checkbox"/> Reviewing IRB <input checked="" type="checkbox"/> Lead Study Team <input checked="" type="checkbox"/> Relying Site Study Team(s) <input checked="" type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	<p>Relying Site POC will alert Yale IRB if there is a Significant Financial Interest (SFI) or Conflict of Interest (COI) related to the study. Relying Site Study Team will communicate to Lead Study Team about SFI or COI, which will then be communicated to Yale IRB.</p> <p>Yale IRB will communicate to Relying Site POC if SFI related to the study is disclosed to the IRB.</p>
STUDY TEAM TRAINING & QUALIFICATIONS: Providing confirmation to the Reviewing IRB that relying site study	<input type="checkbox"/> Reviewing IRB <input type="checkbox"/> Lead Study Team <input checked="" type="checkbox"/> Relying Site Study Team(s)	The relying site study team and/or POC are responsible for ensuring that relying study team members have the relevant training/credentials/qualifications to conduct the

Communication Responsibility	Responsible Party	Notes
teams have completed relevant training and are qualified to conduct the proposed research	<input checked="" type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	proposed research at their site. The reviewing IRB will generally not require list of personnel or changes to personnel, <u>except the local PI.</u>
CHANGE OF LOCAL PI: Notifying the Relying Site about the requested change of the Relying Site PI	<input checked="" type="checkbox"/> Reviewing IRB <input type="checkbox"/> Lead Study Team <input checked="" type="checkbox"/> Relying Site Study Team(s) <input type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	Yale IRB will communicate to Relying Site POC when a request for a change of the PI is submitted to the IRB for review.
LOCAL CONTEXT INFORMATION: Providing local context information to the Reviewing IRB regarding state laws and institutional requirements that pertain to the review of the ceded study	<input type="checkbox"/> Reviewing IRB <input type="checkbox"/> Lead Study Team <input checked="" type="checkbox"/> Relying Site Study Team(s) <input checked="" type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	By completing the Local Context Form, the relying site POC and Study Team are responsible for providing the reviewing IRB with local context information.
IRB APPLICATION – STUDYWIDE: Preparing and submitting the studywide application for initial IRB review and studywide amendments to the Reviewing IRB	<input type="checkbox"/> Reviewing IRB <input checked="" type="checkbox"/> Lead Study Team <input type="checkbox"/> Relying Site Study Team(s) <input type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	All protocol submissions will be completed by the Lead Study Team.
IRB APPLICATION – SITE-SPECIFIC: Preparing and submitting the site-specific applications and site-specific amendments to the Reviewing IRB that address site variations in study conduct, informed consent language, HIPAA Privacy Rule requirements, subject identification and recruitment processes (including recruitment materials), and any other applicable components of the research	<input type="checkbox"/> Reviewing IRB <input checked="" type="checkbox"/> Lead Study Team <input checked="" type="checkbox"/> Relying Site Study Team(s) <input type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	Lead and relying study teams will communicate regarding submitting any site-specific amendments or issues to the Yale IRB. All site submissions will be completed in the IRB electronic system by the Lead Study Team.
IRB DETERMINATIONS: Providing documentation of IRB determinations to relying site study teams	<input type="checkbox"/> Reviewing IRB <input checked="" type="checkbox"/> Lead Study Team <input type="checkbox"/> Relying Site Study Team(s) <input type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	The reviewing IRB provides documentation of IRB determinations to lead study team. Lead study team then distributes documentation of reviewing IRB's determinations to relying site study teams.
IRB-APPROVED DOCUMENTS: Providing copies of IRB-approved materials to the lead study team	<input checked="" type="checkbox"/> Reviewing IRB <input type="checkbox"/> Lead Study Team <input type="checkbox"/> Relying Site Study Team <input type="checkbox"/> Relying Site POC	Reviewing IRB provides documentation of IRB determinations to lead study team.

Communication Responsibility	Responsible Party	Notes
	<input type="checkbox"/> Other, specify:	
IRB-APPROVED DOCUMENTS – RELYING SITES: Providing copies of the most current versions of IRB-approved materials to relying site study teams in a timely manner	<input type="checkbox"/> Reviewing IRB <input checked="" type="checkbox"/> Lead Study Team <input type="checkbox"/> Relying Site Study Team(s) <input type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	The reviewing IRB provides approved documents to lead study team. Lead study team then distributes the approved documents to relying site study teams.
CONSENT FORM TEMPLATE: Providing the consent form template to relying site study teams	<input type="checkbox"/> Reviewing IRB <input checked="" type="checkbox"/> Lead Study Team <input type="checkbox"/> Relying Site Study Team(s) <input type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	Reviewing IRB (Yale) will review and approve consent form templates for each relying site (with input from relying site POCs). After approved consent forms are distributed, the lead study team is charged with ensuring the relying site study teams receive the approved documents.
CONSENT FORM LANGUAGE: Incorporating site-specific language into consent form(s) and providing these consent form(s) to the Reviewing IRB	<input type="checkbox"/> Reviewing IRB <input checked="" type="checkbox"/> Lead Study Team <input checked="" type="checkbox"/> Relying Site Study Team(s) <input checked="" type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	Lead study team, relying site study team, and relying site POCs should work in conjunction to ensure site-specific language is included in consent forms reviewed and approved by the Reviewing IRB (Yale).
REVIEWING IRB POLICIES: Providing relevant Reviewing IRB policies to the lead study team	<input checked="" type="checkbox"/> Reviewing IRB <input type="checkbox"/> Lead Study Team <input type="checkbox"/> Relying Site Study Team(s) <input type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	All SOPs are available online.
CONTINUING REVIEW INFORMATION: Obtaining and collating studywide information for continuing review to the Reviewing IRB	<input type="checkbox"/> Reviewing IRB <input checked="" type="checkbox"/> Lead Study Team <input type="checkbox"/> Relying Site Study Team(s) <input type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	Lead study team is responsible for providing studywide information (including relying site information) for continuing review submissions to the reviewing IRB (Yale). CR submission will be completed in the IRB electronic system by the Lead Study Team.
REPORTABLE EVENTS (RNI): Reporting reportable events to the Reviewing IRB (e.g., unanticipated problems, noncompliance, subject complaints) -	<input type="checkbox"/> Reviewing IRB <input checked="" type="checkbox"/> Lead Study Team <input checked="" type="checkbox"/> Relying Site Study Team(s) <input checked="" type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	Relying Site Study Team must communicate to Lead Study Team about any reportable events. RNI submission will be completed in the IRB electronic system by the Lead Study Team. Relying Site POC should communicate to Yale IRB directly if any RNI is discovered.

Communication Responsibility	Responsible Party	Notes
REPORTABLE EVENTS: Communicating to Relying Site POC about any reportable findings on events reported to Yale IRB	<input checked="" type="checkbox"/> Reviewing IRB <input checked="" type="checkbox"/> Lead Study Team <input checked="" type="checkbox"/> Relying Site Study Team(s) <input type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	In addition to the Lead Study Team, the Yale IRB will communicate directly to Relying Site POC about determinations of serious or continuing noncompliance or Unanticipated Problems, regardless of whether the study is regulated and the event is reportable to federal agencies.
CLOSURE REPORTS: Providing the Reviewing IRB with required information when a study is closed.	<input type="checkbox"/> Reviewing IRB <input checked="" type="checkbox"/> Lead Study Team <input type="checkbox"/> Relying Site Study Team(s) <input type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	Request for closure submission will be completed in the IRB electronic system by the Lead Study Team.
CLOSURE REPORTS: Notification to Relying Site	<input checked="" type="checkbox"/> Reviewing IRB <input checked="" type="checkbox"/> Lead Study Team <input checked="" type="checkbox"/> Relying Site Study Team(s) <input type="checkbox"/> Relying Site(s) POC(s) <input type="checkbox"/> Other, specify:	The Yale IRB will communicate to the Lead Study Team about closures. In addition, Yale IRB will communicate directly to the Relying Site POC about site closure and the site no longer being under IRB oversight.
Special Handling Instructions: <input type="checkbox"/> Initial Approval Language	<input checked="" type="checkbox"/> Reviewing IRB	Yale IRB will include the following language in the initial approval letter: 'You must follow your institutional requirements in conducting this research. Please, notify your IRB about the final approval of this study for your site.'

Appendix E Reports of New Information (RNI) versus Modifications (MOD)

The following table details what type of submission (RNI, MOD, or Both) for each category of information:

Category Identify the categories that represent the new information: (check all that apply)	Description of Information	RNI	MOD	Event When to Submit (# of Days from Receipt)
Report of New Information				
<input type="checkbox"/> RISK	Risk: Information that indicates a new or increased risk, or a safety issue. For example:	RNI	MOD also if change Required to ICF or Study	General Rule: Promptly and no later than 5 business days after the discovery/receipt of information
	a. New Information (e.g., Interim Analysis, Safety Monitoring Report, Publication in the literature, sponsor report, investigator finding) that indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.	RNI	MOD also if change Required to ICF or Study	5 business days after discovery/receipt of the information
	b. Investigator Brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or to describe a new risk.	RNI	MOD Always	5 business days after discovery/receipt of the information
	c. Withdrawal, Restriction, or modification of a marketed approval of a drug, device, or biologic.	RNI	MOD also if change Required to ICF or Study	5 business days after discovery/receipt of the information
	d. Protocol Violation (aka “Major Deviation”) that harmed subjects or others or that indicates subjects or others might be at increased risk of harm.	RNI	MOD also if change Required to ICF or Study	5 business days after discovery/receipt of the information
	e. Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm.	RNI	MOD also if change Required to ICF or Study	5 business days after discovery/receipt of the information
	f. Any changes significantly affecting the conduct of the research	RNI	MOD also if change Required to ICF or Study	5 business days after discovery/receipt of the information
	Any harm experienced by a subject or other individual that, in the opinion of the investigator, is unexpected and at least probably related to the research procedures.	RNI	MOD also if change Required to ICF or Study	Promptly – no more than 5 business days for events occurring at Yale and no more than 5 business days

Category Identify the categories that represent the new information: (check all that apply)	Description of Information	RNI	MOD	Event When to Submit (# of Days from Receipt)
<input type="checkbox"/> Harm ³⁴	<p>a. A harm is “unexpected” when its specificity or severity is inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.</p> <p>b. A harm is “probably related” to the research procedures if, in the opinion of the investigator, the research procedures more likely than not caused the harm.</p>			for external events ³⁵
<input type="checkbox"/> Non-Compliance	Non-compliance: Non-compliance with applicable laws, regulations, guidelines, or Yale policies governing human research, with the requirements or determinations of the IRB, or an allegation of such non-compliance.	RNI	MOD also if change Required to ICF or Study	5 business days from becoming aware of the event
<input type="checkbox"/> Audit	Audit: Audit, inspection, or inquiry by a federal agency	RNI	MOD also if change Required to ICF or Study	Within 2 business days of notification.
<input type="checkbox"/> Report	Report: Written reports of study monitors if the monitor finds non-compliance or research error.	RNI	MOD also if change Required to ICF or Study	5 business days from becoming aware of the event
<input type="checkbox"/> Research Error	Researcher Error Failure to follow the protocol due to the action or inaction of the investigator or research staff.	RNI	MOD also if change Required to ICF or Study	5 business days from becoming aware of the event
<input type="checkbox"/> Confidentiality, Privacy, and Security	Breach of confidentiality, privacy, or security	RNI	MOD also if change Required to ICF or Study	5 business days from becoming aware of the event

³⁴ **Unanticipated Problem Involving Risks to Participants or Others (UPIRSO):** A single event (or multiple occurrences of an event based on an aggregate analysis) must meet ALL THREE of the following criteria: 1. **Unexpected** (in terms of nature, severity or frequency given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied) 2. **Related or Possibly Related** to the research 3. **Harmful** ((The incident, experience or outcome suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.).

³⁵ An event that occurs at a study site NOT under the jurisdiction of a Yale IRB (e.g., at another institution in a multicenter clinical trial), **only if** the Yale PI or another monitoring entity has concluded that an immediate change to the protocol is necessary to address the risks raised by the event.

Category Identify the categories that represent the new information: (check all that apply)	Description of Information	RNI	MOD	Event When to Submit (# of Days from Receipt)
<input type="checkbox"/> Unreviewed Change	Unreviewed change: Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.	RNI	MOD also if change Required to ICF or Study	Promptly – no more than 5 business days
<input type="checkbox"/> Incarceration	Incarceration: Incarceration of a subject in a study not approved by the IRB to involve prisoners.	RNI	MOD also if study is to continue to involve prisoners	Promptly and no more than 5 business days from becoming aware of the event
<input type="checkbox"/> Complaint	Complaint: Complaint of subject or other person that cannot be resolved by research team.	RNI	MOD also if change Required to ICF or Study	No more than 5 business days from becoming aware of the event
<input type="checkbox"/> Suspension	Suspension: Premature suspension or termination of the research by the sponsor, investigator, or institution.	RNI	MOD also if change Required to ICF or Study	Promptly – no more than 5 business days
<input type="checkbox"/> Unanticipated Adverse Device Effect³⁶	Unanticipated adverse device effect: 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 relates to the rights, safety, or welfare of subjects.	RNI	MOD also if change Required to ICF or Study	Promptly – no more than 5 business days
<input type="checkbox"/> Emergency Use of a Test Article	Emergency use of a test article: 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.	RNI	N/A	Prior to administration with a follow-up report within 5 days of administration
<input type="checkbox"/> Other Information	Other information: The sponsor, CRO, or other has directed the PI to report to the IRB even if they do not meet any of the Yale University's IRB's reporting requirements.	RNI	MOD also if change Required to ICF or Study	Within 30 calendar days from receipt
<input type="checkbox"/> Addition of certificates of privacy/confidentiality	The PI received Certificate of Confidentiality for studies that are not automatically covered through funding (e.g. NIH or DOJ).	NO	YES	Within 30 calendar days from receipt

³⁶ Based on an aggregate analysis, multiple occurrences of an Event may also rise to the level of an UADE.

Category Identify the categories that represent the new information: (check all that apply)	Description of Information	RNI	MOD	Event When to Submit (# of Days from Receipt)
<input type="checkbox"/> Change to the protocol or consent forms	Revisions to any of the study related documents approved by the IRB	RNI – Maybe (See above)	YES	Prior to implementation of the change, within 30 calendar days from receipt from external sponsor, if RNI required, timeframe described above for the RNI
<input type="checkbox"/> Approvals from groups with oversight	External IRB/foreign IRB/equivalent Notices and Approvals, Ancillary review committee approvals (PRC, Nursing Committee)	NO	YES	As directed by the IRB
<input type="checkbox"/> Updated documents related to study drugs/devices	Investigator Brochures, package insert, or change to device labeling that replaces an older version (<i>with note from Sponsor stating updates do not change ICF or study – No Increased Risk</i>)	NO	YES	Within 30 calendar days from receipt
<input type="checkbox"/> Recommendations/letters issued by Data Safety Monitoring Boards	Recommendations from DSMB or another monitoring board following review of the study progress report.	RNI if recommendations include suspension of the trial	Yes – if changes are required	Within 30 calendar days from receipt; if no changes proposed by DSMB, report can be submitted at the time of <u>Continuing Review</u> ; if RNI is required, timeframe is described above for the RNI.
<input type="checkbox"/> Letters of Support	Letters of support from Non-Government Organizations (NGOs), Signed agreements/forms from participating schools (particularly with Psychology studies)	NO	YES	As directed by the IRB
<input type="checkbox"/> ‘Dear Investigator’ letters	Letters from the sponsor that provide clarification on aspects of the protocol prior to release of sponsor amendments.	Possible IF the letter indicates increased risk or otherwise falls into any of the RNI categories	YES	Within 30 calendar days from receipt, if RNI is required, timeframe is described above for the RNI.
<input type="checkbox"/> Sponsor Close Out Visit	The sponsor scheduled close out visit <u>prior to closing</u> the study.	NO	NO	N/A
<input type="checkbox"/> Changes related to research staff members	Addition or removal of investigators, PI Proxy, addition of unaffiliated investigators, changes of PIs, applicable research staff changes, etc.	NO	MOD	Prior to staff engaging in human subjects research; needs to be reconciled with the Delegation of Authority Log.

	<p>Human Research Protection Program Investigator Manual</p>	<p>Version 2.1 07/24/2023</p>
---	--	-----------------------------------

Revision History

Date	Version	Description
March 9, 2018	1.0	Initial Effective
December 16, 2020	1.1	Added section 'Management Plan for Research at Satellite Locations'; corrected training requirements to include GCP,
January 30, 2023	2.0	Overall updates and changes to the format of the manual
July 24, 2023	2.1	Updated the GDS process