



INVESTIGATOR MANUAL

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This document satisfies AAHRPP element I.1.A, I.1.C-I.1.E, I-3, I.4.C, I.5.C, I.5.D, I.6.B, I.7.A-I.7.C, I-9, II.2.A, II.2.C, II.2.G, II.2.E-II.2.E.2, II.2.F-II.2.F.3, II.2.I, II.3.C-II.3.C.1, II.3.E, II.3.F, II.3.G, II.4.A, II.4.B, II.5.A, II.5.B, III.1.A, III.1.B, III.1.D, III.1.E, III.1.F, III.2.A, III.2.C, III.2.D

Purpose

This Investigator Manual is designed to guide investigators and study staff through policies and procedures related to the conduct of Human Research that are specific to the Harvard University Area (HUA) IRB office. Additionally, the manual serves as a guide for the HUA research community when preparing and submitting materials to the HUA IRB.

General information regarding Human Research protections as well as relevant federal regulations and guidance has been incorporated throughout this manual where applicable.

Key Definitions and Terms

ESTR

Electronic Submission, Tracking & Reporting (ESTR) is the IRB's online e-submission system, available at irb.harvard.edu. Users must have an active HUID/[HarvardKey](#) to access ESTR. ESTR-specific reference materials and tutorials, including job aids and how-to instructions with screen captures, can be found on the [ESTR Support Website](#). A [Study Submission Guide](#) is available to guide investigators and study staff through the submission process.

To report technical problems with ESTR, contact the ESTR Help Desk at ESTRhelp@harvard.edu.

IRB

The Institutional Review Board (IRB) is a committee that is required by federal law to protect the rights and welfare of human subjects participating in research activities. The committee meets this mandate by reviewing proposed and ongoing human research activities, ensuring they meet specific criteria for approval. The HUA IRB office provides administrative support to the HUA IRB. Historically, the HUA IRB has been known as the Committee on the Use of Human Subjects, CUHS.

HIPAA

The Health Insurance Portability and Accountability Act (HIPAA) [Privacy Rule](#) establishes national standards for the protection of health information (called "protected health information" or [PHI](#)). It applies to organizations such as health plans, health insurance companies, health care clearinghouses, and health care providers that conduct health care transactions electronically.

These organizations are called "[covered entities](#)." At Harvard, the Harvard University Health Services and Harvard School of Dental Medicine are covered entities under the HIPAA Privacy Rule; other schools/units within Harvard are not HIPAA covered entities. Because of this, Harvard is referred to as a "hybrid covered entity"

To learn more about how the Rule may impact your research, see the section in this manual on *HIPAA* and refer to the NIH booklet [Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule](#).

Human Research

The HUA IRB follows the regulatory definitions of "Human Subjects Research". To determine whether proposed activities constitute the DHHS or FDA definitions of Human Subjects Research, investigators can refer to "WORKSHEET: Human Research Determination (HRP-310)". If requested, the IRB will review the proposed activities and make a formal "Not Human Subjects Research" determination. See *Submitting an Application in ESTR* for how to prepare this request.

Human Research Protection Program

The Harvard University Area Human Research Protection Program (HRPP) is a comprehensive system to ensure the protection of the rights and welfare of participants in Human Research. The Harvard

University Area is comprised of the Cambridge and Allston campuses and include the Faculty of Arts and Sciences, as well as the following schools: John F. Kennedy School of Government, Harvard Graduate School of Education, Harvard Law School, Harvard Divinity School, Harvard Graduate School of Design, Radcliffe Institute for Advanced Study, Harvard School of Engineering and Applied Sciences, and the Harvard Business School.

The HRPP is comprised of institutional leadership; Harvard University Area Administration, which includes the HUA IRB administrative support staff; Institutional Review Board (IRB); investigators and their study staff; Department Chairs, and other relevant offices. The document “HUMAN RESEARCH PROTECTION PROGRAM PLAN (HRP-101)” describes the HUA overall plan to protect participants in Human Research, including:

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

Worksheets/Checklists/Template/Forms

All Worksheets, Checklists, Templates, and Forms referenced within this document can be found in the ESTR Library.

IRB Determinations and Modes of Review

Not Human Subjects Research Determination

Activities must meet the definitions of “Human Subjects Research” to fall under the [HHS Protection of Human Subjects Regulations](#). Activities that do not meet these definitions are not subject to HUA IRB oversight. Refer to “WORKSHEET: Human Research Determination (HRP-310)” for guidance on whether the proposed activities constitute Human Research. Contact the [HUA IRB office](#) in cases where it is unclear whether an activity is Human Research. If an investigator would like the IRB to make a formal “Not Human Subjects Research” determination, see *Submitting an Application in ESTR*.

Not Engaged

Harvard is engaged in Human Subjects Research when its faculty, students, employees, or agents, as part of their Harvard or Harvard-commissioned activities, are interacting or intervening with Human Subjects for the purpose of conducting research or are obtaining individually identifiable private information for research purposes in a research study that is non-exempt and ***involves more than one institution***. Harvard University follows the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) Guidance on Engagement of Institutions in Human Subjects Research, which states “In general, an institution is considered ***engaged*** in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research.” Should a Harvard agent not meet the above threshold for engaging the institution, the IRB will issue a not engaged determination.

Exemption Determination

Certain categories of Human Research may be exempt from regulation. Investigators may not determine whether their proposed Human Research is exempt. Instead, formal determination is required by the HUA IRB office prior to implementation in the field. The IRB office uses “WORKSHEET: Exemption (HRP-312)” when determining whether a particular study meets one or more exempt criteria.

Most exempt submissions do not require a modification if the exempt determination does not change. You also do not need to submit a modification when study team members change.

When should an Exempt study submit a modification?

- Including children, prisoners, or other protected populations.
- Study procedures that fall outside the exempt category. For example, an intervention was initially going to take place in one sitting, but the research team decides to include longitudinal effects, so they implement a follow-up treatment.
- Increase in risk.
- Ancillary policy / regulations: GDPR, collection of sensitive information requiring a Limited IRB review, change in data security assessment.
- Change in Principal Investigator.
- Change in Faculty Sponsor.
- If there is new funding.

What about other changes?

- If an exempt study is changing the design of the study or major revision to the procedures, a new exempt determination request should be submitted.

When conducting exempt human research internationally, the Principal Investigator is required to comply with applicable local laws, legislation, regulations, and/or policies. Additionally, if local IRB/ethics review is required, it must be obtained before any Human Research activities are conducted in the field. If assistance with applicable local requirements is needed, contact the [HUA IRB office](#)

Expedited Review Procedure

Certain categories of non-exempt Human Research may qualify for review using the expedited procedure, meaning that the project may be approved by one or more designated reviewers, rather than by the convened IRB. Refer to “WORKSHEET: Expedited Review (HRP-313)” for reference on applicable categories of research. Protocols eligible for review using the expedited procedure are reviewed on a rolling basis.

Convened IRB Review (“Full Board”)

Non-exempt Human Research that does not qualify for expedited review and/or is greater than minimal risk must be reviewed by the convened IRB. The HUA IRB office supports the HUA IRB. The IRB meets monthly. The convened IRB meeting schedule and submission deadlines are available here: <https://cuhs.harvard.edu/cuhs-committee-deadline-and-meeting-dates>

Scope and Applicability of the Federal Regulations Governing Human Subjects Research

The Harvard University Area commits to apply its ethical standards to all Human Research regardless of funding. When Harvard University Area is engaged in DHHS Human Research that is conducted, funded, or otherwise subject to regulations by a federal department or agency who is a signatory of the Common Rule, the Harvard University Area commits to apply the regulations of that agency relevant to the protection of Human Subjects. When Harvard University Area is engaged in FDA Human Research, it commits to apply the FDA regulations relevant to the protection of Human Subjects.

Determining when an IRB Application is Required

HUA IRB is responsible for the review and oversight of Human Research conducted by its agents. Its oversight applies regardless of whether the Human Research is conducted at a Harvard University Area school, another institution, in another country, and/or in collaboration with non- Harvard affiliates. For research with non- Harvard collaborators, see *Conducting Research with Non-Harvard Collaborators* for additional considerations.

Some activities do not require HUA IRB review. Activities that do not meet the definition of “Human Research” do not fall under the [HHS Protection of Human Subjects Regulations](#). Activities that do not meet this definition are not subject to HUA IRB oversight. Refer to “WORKSHEET: Human Research Determination (HRP-310)” for guidance on whether the proposed activities constitute Human Research. Contact the [HUA IRB office](#) in cases where it is unclear whether an activity is Human Research. If you would like the IRB to make a formal “Not Human Subjects Research” determination, see *Submitting an Application in ESTR*.

IRB Review Process

Once an application is submitted in ESTR, it will be reviewed by an IRB staff person. After initial review, the IRB staff may request clarifications, revisions, and/or additional information in ESTR (“Clarifications Requested”). The Principal Investigator may “Submit Response” in ESTR to resolve these requests. When resolved, the IRB staff will either complete their review and issue a determination letter or assign the application to an IRB meeting for review. The convened IRB may request additional information following its review.

A determination letter will be issued in ESTR once the review is complete. System notifications are sent from ESTR throughout the review process to inform Principal Investigators when additional action is necessary. To check on the status of a submission, log in to ESTR at irb.harvard.edu. For questions or concerns, contact the [HUA IRB office](#) or use the comment feature in your study submission space in ESTR.

IRB Approval Criteria

The criteria for IRB approval of non-exempt Human Research can be found in “WORKSHEET: Criteria for Approval (HRP-314)”. Additional checklists may be applicable depending on the nature of the proposed Human Research, e.g., inclusion of children will prompt the use of “CHECKLIST: Children (HRP-416)”.

Worksheets and Checklists are used by IRB members and reviewers at the time of initial review, continuing review, during the review of modifications to previously approved Human Research, and when reviewing Reportable New Information. Investigators are also encouraged to use these materials as a reference or guide when writing the Research Protocol in a way that addresses the criteria for approval. Worksheets and Checklists can be found in the [ESTR Library](#) ([HarvardKey](#) log in required for access).

IRB Decisions

The IRB has the authority to approve Human Research, require modifications to secure approval, or defer/disapprove Human Research. When the IRB cannot approve the research at a convened meeting for reasons unrelated to the research, such as loss of quorum, the review will be tabled. Under those circumstances, the research will be reviewed at the next meeting.

Approval

If the IRB has approved the Human Research, it may commence once all applicable organizational and/or local approvals have been secured. IRB approval is granted for a limited period¹, not exceeding one year, which is noted in the approval notification letter.

Modifications Required to Secure Approval

If the IRB requires modification(s) to secure approval, the notification letter will outline specific revisions to the Human Research and/or study materials, e.g., Research Protocol, consent form, study tools, etc. Human Research may not commence until the IRB grants final approval.

If the Principal Investigator accepts the required modifications, s/he should submit the revised materials via ESTR to the IRB within 45 calendar days. If all requested modifications are made, the IRB will issue a final approval notification letter after which time the Human Research can begin.

If the Principal Investigator does not accept the modifications, s/he should write a response detailing why such modifications are not appropriate and/or feasible and submit it to the IRB within 45 calendar days. If the Principal Investigator does not respond to the IRB within 45 calendar days, the decision of approval with the requested modifications will be withdrawn.

Tabled

Made when the IRB cannot approve the research at a meeting for reasons unrelated to the research, such as loss of quorum. When taking this action, the IRB automatically schedules the research for review at an upcoming meeting.

Deferral

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.

¹ Continuing review is required only for most studies that are reviewed by the Convened IRB, expedited studies that fall under the Pre-2018 Requirements, and certain 2018 Requirement expedited studies in which the IRB determined that continuing review is required.

Principal Investigator Eligibility

The basis for determining who is eligible to be a Principal Investigator (PI) is grounded in who may receive funds through a grant, contract, or other funding mechanism on behalf of the University.

Who may be listed on an IRB application follows these same guidelines however there are exceptions. Those who are not PI eligible may still serve as a PI on an IRB application however there must also be a faculty sponsor listed. This is particularly true when the PI on the IRB application is a student. This requirement does not preclude any non-eligible member from being listed as a Co-Investigator on the project, or having certain research-related responsibilities delegated to them, but they may not be named as PI nor assume ultimate responsibility for the assurances listed in the Principal Investigator Assurance.

PI eligibility is generally delegated to the Harvard Schools who have developed eligibility criteria for their faculty as well as specific procedures for granting exceptions to their criteria. Below you will find policies relevant to who may serve as a PI as well as the process to grant an exception to these policies.

Faculty of Arts and Sciences (FAS)

According to FAS policy, only teaching members of the Faculty and a select number of other academic appointees are PI eligible. The policy, including a list of who is eligible may be found [here](#)

The FAS has also established a process by which “Harvard appointees who are not otherwise PI-eligible may on occasion be authorized to serve as PI with approval by the appropriate Divisional Dean. The department chair or center director can submit such requests using the [PI Rights Questionnaire form](#), and the justification must be compelling.”

Central Administration

Generally, only those who have an academic appointment may be considered PI eligible. However, there may be circumstances when individuals that do not have an academic appointment who report to the University Central Administrative Unit may have the opportunity to seek external funding for special projects that contribute towards the goals or the mission of the individual’s unit. The Office of the Provost for Central Administration has developed a process for such circumstances. The policy for this process may be found [here](#). The Request Form to use with this process may be found [here](#).

Graduate Schools

The Harvard Graduate Schools have incorporated different policies and procedures for determining PI eligibility. Some schools maintain a list of names of those that are eligible while others create policies according to faculty rank or title. Given the variability, it is recommended that researchers check in with their respective Harvard School.

Undergraduate students, Graduate Students, and Post-Doc’s

As previously mentioned, those that are affiliated with Harvard University Area, including undergraduate students, graduate students, or post-doctoral researchers, are permitted to be a PI on an IRB application however this designation is only valid if a PI eligible Faculty Sponsor is also listed on the IRB application.

What does it mean to be a Faculty Sponsor?

A Faculty Sponsor sponsors the PI who is listed on the IRB application and confirms that they will oversee the research and ensure that the PI complies with all IRB requirements. For more information on what it means to be a faculty sponsor, please see the [Ancillary Review Reference document](#).

What if my Faculty Sponsor is not PI eligible?

There may be times when the best person to oversee a student's research is not considered PI eligible. For example, faculty classified as lecturers, or similar titles, may serve as senior thesis advisors however they are ineligible to be named as a faculty sponsor on a student project as they are not considered PI eligible.

The FAS has "established a guideline that establishes a process for waiver for a particular lecturer, or other faculty appointment holder, to be PI eligible for the limited purpose of serving as a faculty sponsor for undergraduate student human subject research protocol submissions." Please see the [policy](#) as well as the [Waiver of PI Status for Human Subject Research Request Form](#) for more information.

For more information on what it means to be a faculty sponsor, please see the [Ancillary Review Reference document](#).

Principal Investigator Responsibilities

For each application submitted to the IRB, the Principal Investigator must acknowledge a "Principal Investigator Assurance Statement" in ESTR. The PI must adhere to each requirement throughout the duration of the study (from initial submission to study closure). See *Principal Investigator Responsibilities and ESTR Assurance Statement*.

Human Research Training

New investigators and study staff are expected to review the HUMAN RESEARCH PROTECTION PROGRAM PLAN (HRP-101) available on the IRB [website](#).

Human Subjects Protection Training

Anyone that will have direct interaction with research participants and/or access to identifiable information/specimens must complete human research training. In addition, Principal Investigators, Co- Investigators, and those meeting the definition of NIH “[Key Personnel](#)” must complete human research training regardless of whether or not they have direct interaction with participants and/or access to identifiable information/specimens.

Harvard University’s human research training curriculum is offered through the [Collaborative Institutional Training Initiative \(CITI\) Program](#). To access it, CITI Learners should affiliate with “Harvard University” and select the “Human Research (Protection of Human Subjects)” course. (The following courses will not satisfy the requirement to complete human research training: Conflicts of Interest, Export Compliance, Good Clinical Practice Course, Information Privacy and Security, Responsible Conduct of Research.) Within the “Human Research Protection of Human Subjects)” course, CITI Learners can select either the “Biomedical Research” or “Social & Behavioral Research” module. In addition to Harvard University’s CITI training, the IRB will also accept another institution’s (human research) CITI training or equivalent training.

Human research training certification is valid for a three-year period from date of completion, regardless of which institution it was completed through. When current training expires, a refresher course, or additional training, is required. Refresher training can be fulfilled by taking the Harvard University’s CITI refresher course, another institution’s CITI refresher course or equivalent course.

IRB approval may not be granted for proposed Human Research where any staff member’s human research training remains incomplete.

Human Subjects Research Training Guide for International Enumerators

The IRB office has developed a paper-based human subjects research training guide for use with international enumerators when it is not feasible to undertake online human subjects protection training such as CITI. As specified in the guide, “The content and language level of the guide is specifically worded to help the investigator convey basic research principles and behavior that accords with those principles to enumerators and/or field workers.”

NIH Good Clinical Practice Requirements

In effect since January 1, 2017, NIH's Good Clinical Practice (GCP) policy establishes the expectation that all NIH- funded investigators and staff who are involved in the conduct, oversight, or management of NIH clinical trials should be trained in Good Clinical Practice (GCP), consistent with principles of the International Conference on Harmonisation (ICH) E6 (R2).

For more information on training requirements and access to documents and online training, please see the IRB [website](#).

Reporting Financial Interests to the IRB

To minimize the actual or potential conflicts of interest in Human Research, the IRB requires that all individuals involved in the design, conduct, or reporting of the research report financial interests related to the research. Of note, in addition to principal investigators and co-investigators, individuals involved in the design, conduct, or reporting of the research may include study coordinators, data coordinators, and other support staff possibly not captured within the ESTR SmartForm: Study Team Members Page.

To disclose, submit “FORM: Financial Interest Disclosure (HRP-221)” at the time of initial review and each subsequent continuing review. In addition, investigators must report any change(s) to this disclosure to the IRB via Modification in ESTR within 30 business days of discovering or acquiring (e.g., through purchase, marriage, inheritance, filing a patent application, etc.) a new financial interest.

Financial Interest Related to the Research refers to any of the following interests in the sponsor, product or service being tested, or competitor of the sponsor held by the individual or the individual’s immediate family:

- Ownership interest of any value including, but not limited to stocks and options.
- Compensation of any amount including, but not limited to honoraria, consultant fees, royalties, or other income.
- Proprietary interest of any value including, but not limited to, patents, trademarks, copyrights, and licensing agreements.
- Board or executive relationship, regardless of compensation.
- Reimbursed or sponsored travel by an entity other than a federal, state, or local government agency, higher education institution or affiliated research institute, academic teaching hospital, or medical center.

Immediate Family means spouse, domestic partner, and dependent children.

With regards to intellectual property, patents, technology development, proprietary ownership, commercial or manufactured products, etc., the IRB recommends disclosure of intent to commercialize or license intellectual property, as it relates to the research, in the consent documents. This disclosure should include plans for any development, licensure, commercialization, and/or patentability of any intellectual property, technology, commercial or manufactured products, etc., and indicate how participant identifiers are used in this process, if at all. The disclosure should include a statement about if/when the PI would profit or benefit financially and indicate what additional compensation will be awarded to participants, if any, if/when the intellectual property results in commercialization. See *Additional Consent Form Language Requirements Relating to Conflict of Interest* for additional considerations.

Please see <https://vpr.harvard.edu/pages/financial-conflict-interest-policy> for additional information and resources pertaining to Harvard University’s policy on financial conflict of interest.

Conducting Research with Non-Harvard Collaborators

All HUA investigators engaged in Human Research must secure IRB review. This applies when the Human Research is conducted at a HUA school, another institution, in another country, and/or in collaboration with non-Harvard affiliates.

Non-Harvard collaborators are expected to inquire with their home/affiliate institution to determine whether local IRB review and oversight is required. If desired, their home/affiliate institution may consider entering into a reliance agreement with Harvard. Ceding review allows one institution to serve as the Reviewing Institution/IRB (“single IRB” or “sIRB”) while the others serve as the Relying Institution/IRB (“participating sites”).

Where non-Harvard collaborators do not have a home/affiliate institution, e.g., community member or independent contractor, they may be added to the HUA IRB-approved study as *Individual Investigators* using “FORM: Individual Investigator Agreement (HRP-225)”. Such collaborators will be required to complete human research training and should be listed in “FORM - Non-Harvard Study Personnel (HRP-220)”.

Cede Review (Designating a single IRB)

Reliance agreement, IRB Authorization Agreement (IAA), cede review, cede, or External IRB are all terms that refer to a situation where research is conducted at two (or more) institutions, and one is designated to serve as the Reviewing Institution/IRB (“single IRB” or “sIRB”) while the others serve as the Relying Institution/IRB (“participating sites”).

Non-exempt Human Research is eligible for such an Agreement, i.e., protocols reviewed on an expedited basis or by the convened IRB. Activities that do not constitute human subjects research or are determined to be exempt are ineligible for reliance agreement/cede review; the HUA IRB requires in-house review of those projects.

Conditions for Ceded Review

To avoid duplication of review, the IRB will consider accepting review responsibilities, or ceding review to another IRB, when the following conditions are met.

Accepting Review Responsibilities for another Institution

The IRB will accept reviewing responsibilities on a case-by-case basis, including but not limited to the following situations:

- When the primary work involving participants takes place on property under the jurisdiction of an Investigator from Harvard University Area, or
- When the study involves secondary institution or institution’s personnel but is initiated by an Investigator from Harvard University Area, or
- When one or more parts of the study are to be conducted at an institution or entity, or in a locale, that lacks a constituted IRB or other research ethics committee, or
- When Harvard University Area has been chosen to be the Reviewing IRB according to the terms of a Single IRB policy.

In all situations where an IAA is in place, the relying institution must hold a current FWA.

Ceding Review to other Institutions

The IRB may cede reviewing authority to another IRB under one or more of the following conditions, or for other reasons deemed appropriate:

- The IRBs are part of an AAHRPP accredited Institution.
- The IRBs are not part of an AAHRPP accredited institution or organization, but where reasonable steps have been taken to ensure that subjects are adequately protected. For example, for research that is no greater than Minimal Risk, there may be an assurance that the IRBs will adhere to applicable ethical standards and regulations. For research that is greater than Minimal Risk, the institutions may agree on more extensive oversight.
- The IRBs are part of an established reliance network (e.g., Smart IRB) that has established contractual and SOP-level procedures to clarify the roles and responsibilities associated with IRB reliance and to establish mechanisms to ensure quality and consistency in the review process among institutions.
- The sIRB has been pre-determined by study sponsor or grant or established by prior arrangement.
- This Institution's investigator is a collaborator on Human Research that is primarily conducted at another institution or organization and the investigator's role does not include interaction or intervention with subjects.
- The Institution is engaged in the Human Research solely because it is receiving federal funds. (Employees and agents of the institution do not interact or intervene with subjects, gather, or possess private identifiable information about subjects, nor obtain the consent of subjects.)

The IRB will ordinarily not cede review if any research activities conducted at Harvard University Area require direct intervention or interactions with study participants unless the research activities at Harvard are minimal risk and represent a small proportion of the study activities.

In all situations where an IAA is in place, the relying institution must hold a current FWA.

Requesting Cede Review/Submitting External IRB in ESTR

To request that the HUA IRB serve as the IRB of record, follow instructions on *Submitting an Application in ESTR*.

To request that HUA IRB rely on another institution, submit an External IRB application in ESTR by following [these instructions](#) on the ESTR Support website.

When the Cede Request involves a SmartIRB [participating institution](#), an additional application is required through the [SmartIRB Online Reliance System](#). Instructions on how to complete the SmartIRB reliance form are [available online](#).

When the Cede Request **only** involves a component of Harvard (Harvard University Area and Harvard Longwood Campus), the Harvard Master Agreement is used. The Harvard Master Agreement is a standing document between the Harvard IRBs that acts like a permanent reliance agreement: it outlines the conditions for reliance, the responsibilities for each researcher, as well as the general terms and conditions of the reliance. You do not need to create a separate reliance request through SmartIRB.

To submit any changes or updates to an External IRB ESTR record, follow the [Updating External IRB Review](#) instructions on the ESTR Support website.

Obligations as the overall study PI for an sIRB study

- 1) Coordinating with the HUA IRB to determine whether this institution's IRB can act as the single IRB for all or some institutions participating in the study or if an external IRB will assume oversight.
- 2) Identifying all sites that will be engaged in the human research and requiring oversight by the IRB.
- 3) Ensure that all sites receive a request to rely on the reviewing IRB and that all institutional requirements are satisfied before a study is activated at a relying site.
- 4) Collaborate with the reviewing IRB to document roles and responsibilities for communicating and coordinating key information from study teams and the IRB or HRPP at relying sites.
- 5) Respond to questions or information requests from study teams or the IRB or HRPP staff at relying sites.
- 6) Provide relying site investigators with the policies of the reviewing IRB.
- 7) Provide relying site investigators with the IRB-approved versions of all study documents.
- 8) Preparation and submission of IRB applications on behalf of all sites. This includes initial review, modifications, personnel updates, reportable new information and continuing review information for all sites.
- 9) Establishing a process for obtaining and collating information from all sites and submitting this information to the reviewing IRB. This includes site-specific variations in study conduct, such as the local consent process and language, subject identification and recruitment processes and local variations in study conduct.
- 10) Ensuring that consent forms used by relying sites follow the consent template approved by the reviewing IRB and include required language as specified by the relying sites.
- 11) Providing site investigators with all determinations and communications from the reviewing IRB.
- 12) Submitting reportable new information from relying sites to the reviewing IRB in accordance with the terms outlined in the authorization agreement or communication plan.
- 13) Reporting the absence of continuing review information from relying sites if they do not provide the required information prior to submission of the continuing review materials to the reviewing IRB. Notifying the relying site of their lapse in approval and applicable corrective actions.
- 14) Providing study records to the relying institution, reviewing IRB or regulatory agencies upon request.

Obligations as investigator when relying on an external IRB

- 1) Check in with the Harvard University Area IRB prior to seeking review by another IRB.
- 2) Comply with determinations and requirements of the reviewing IRB.
- 3) Provide the reviewing IRB with requested information about local requirements or local research context issues relevant to the IRB's determination prior to IRB review.
- 4) Notifying the reviewing IRB when local policies that impact IRB review are updated.
- 5) Cooperating in the reviewing IRB's responsibility for initial and continuing review, record keeping and reporting and providing all information requested by the reviewing IRB in a timely manner.
- 6) Disclosing conflicts of interest as required by the reviewing IRB and complying with management plans that may result.
- 7) Promptly reporting to the reviewing IRB any proposed changes to the research and not implementing those changes to the research without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to the participants.
- 8) When enrolling participants, obtain, document, and maintain records of consent for each participant or each participant's legally authorized representative.
- 9) Promptly reporting to the reviewing IRB any unanticipated problems involving risks to participants or others according to the requirements specified in the reliance agreement.
- 10) Providing the reviewing IRB with data safety monitoring reports in accordance with the reviewing IRB's reporting policy.
- 11) Reporting non-compliance, participant complaints, protocol deviations or other events according to the requirements specified in the reliance agreement.

- 12) Specifying the contact person and providing contact information for researchers and research staff to obtain answers to questions, express concerns, and convey suggestions regarding the use of the reviewing IRB.

ESTR Record Access

Principal Investigator

The Principal Investigator named in ESTR has full access to the corresponding record and all the SmartForm Pages. The PI can make edits, create modifications and continuing review applications, and will receive all notifications generated via ESTR.

Primary Contact

In addition to the Principal Investigator, a Primary Contact can create submissions (on behalf of the PI) and receive copies of all study-related notifications generated in ESTR. A PI may designate a Primary Contact by completing the “Assign Primary Contact” activity in ESTR. There can only be one Primary Contact at a time.

PI Proxy

A PI Proxy may perform system activities customarily carried out by the Principal Investigator, including management of follow-on submissions (Modification/Updates and Continuing Reviews). A PI Proxy will receive all system notifications. PI Proxy does not assume any responsibility for the conduct and oversight of the study. These responsibilities remain unique to the Principal Investigator, see *Principal Investigator Responsibilities* section.

A PI Proxy must be a member of the approved study team with current human research training certification. A PI may designate a proxy only after securing initial IRB approval by completing the “Assign PI Proxy” activity in ESTR.

Study Team Members and Others

Study Team Members named in ESTR have access to the record. If others need access to the ESTR record and submission documents, they can be added as a member of the guest list by completing the “Manage Guest List” activity in the main study workspace. This will allow any Harvard-affiliated individual read-only access to the ESTR record.

For further information about the various roles within ESTR and the associated permissions, see the [ESTR Role Permissions Chart](#) on the ESTR Support website.

Submitting an Application in ESTR

The IRB must review and approve all Human Research prior to the initiation of any activities. To create a new IRB application online using ESTR, [follow these instructions on the ESTR Support website](#).

The ESTR application is a series of SmartForms where information is entered, and documents are attached. [Click here to view the full ESTR SmartForm and the requested attachments](#).

The SmartForms may contain required information identified by a red asterisk (*). You cannot proceed without providing this information. You must attach a document to the Basic Information page before you can proceed any further with the application.

Additional documents should be attached to the SmartForms where appropriate, e.g. recruitment materials, consent forms, and study tools. ESTR supports all common file formats (e.g. Word, PDF, Excel, Publisher, JPEG) however unsupported file formats (e.g. audio, video, mp4, mp3, wav, etc.) should be attached within a zip file. Zip files should only be used for this purpose and not used to consolidate supported file formats.

For each attachment, ensure that the name and version number/date of the document are accurate and reflective of the document content/purpose. It is recommended that the file name and version number/date also appear in either a header or footer within each document. When uploading a revised version of any document, click 'Update' in ESTR rather than 'Delete' or 'Add.' Do not delete any documents from the ESTR record unless instructed to by your IRB staff member.

Specific details about how to navigate the IRB online submission system and complete an application can be found in the [“Study Submission Guide”](#) on the ESTR Support website.

Proposing Modification(s)

To change or update an active, IRB-approved Human Research protocol, a modification must be submitted in ESTR and approved by the IRB prior to implementation. If the activities were found not to constitute research with human subjects or determined to be exempt, changes do not require IRB review unless they might alter the IRB's original determination. You will also want to take note of any institutional requirements that would require a modification. For example, use of the Harvard Psychology Department Study Pool requires notation in the determination letter therefore requiring a modification. Contact the [IRB office](#) in cases where it is unclear whether a proposed modification might alter the IRB's original determination or if institutional requirements might apply.

To request modifications, [follow these instructions from the ESTR Support website](#). Attach all updated study documents within the SmartForm including a copy of any revised study materials. When applicable, indicate how current or former participants will be notified of protocol modifications.

Requesting Continuing Review

Continuing review is required only for most studies that are reviewed by the Convened IRB, expedited studies that fall under the Pre-2018 Requirements, and certain 2018 Requirement expedited studies in which the IRB determined that continuing review is required.

To request continuing review, [follow these instructions from the ESTR Support website](#). Attach any documents that contribute to the review of the submission (e.g., any progress reports, CITI refresher training). Do not attach any revised study documents (Research Protocol, consent forms, research tools, supporting documents, etc.). If modifications to the study need to be made at the time of continuing review, a Modification is required to submit these revisions for review and approval (see above section on “Proposing Modifications”). This should be done prior to creating a continuing review application so that revised study documents will be included in the approval for the upcoming approval period.

If continuing review is required for your study, you will have an approval period for your study. If IRB approval of the Human Research expires, no human subjects activities may occur. This includes recruitment, enrollment, interventions, interactions, and collection of private identifiable information. Continuing Human Research procedures during a lapse in approval for studies with an expiration date is a violation of federal regulations.

If your study is required to have a continuing review and it is necessary to continue Human Research activities to eliminate apparent immediate hazards to participants, prior notification is required. Contact the [IRB office](#) immediately and provide a written list of the currently enrolled participants and a justification supporting the continuation of such activities.

Requesting Study Closure

Study closure is appropriate when (a) the research is permanently closed to enrollment; (b) all participants have completed all research-related interventions/interactions; (c) collection of private identifiable information is completed, and (d) analyses of private identifiable information is completed. Under closure, analyses of de-identified data/specimens and manuscript preparation can occur indefinitely.

To request closure, [follow these instructions from the ESTR Support website](#).

Ancillary Review

[Ancillary Review](#) allows Harvard-specific departments and units the ability to document their review and oversight, when applicable. Review is triggered and obtained by the IRB and typically performed in parallel with the IRB review. IRB staff will inform the PI during their review if/when Ancillary Review is required.

Ancillary Review may be initiated at the time of an initial or continuing review, or modification request.

Some Ancillary Reviews may be required before the IRB can grant final approval. For example, as per [Harvard Research Data Security Policy](#), any protocol assigned a sensitive data designation requires IT review/approval prior to IRB approval.

Preparing the Research Protocol

General Requirements

A Research Protocol is required for any Human Research application (this includes application for an Exemption Determination). The HUA IRB uses the following forms as a “research protocol”:

- TEMPLATE - HUA Protocol (HRP-503): for use with exempt, expedited, and convened IRB submissions.
- TEMPLATE - HUA Repository Protocol (HRP-504): for use with repository submissions.
- FORM- Not Human Subjects Research Request Determination Form (HRP-213): for use with not human subjects or not research determination submissions.

The purpose of the Research Protocol is to provide IRB members and Designated Reviewers with sufficient information to conduct a substantive review. If a separate sponsor’s protocol exists, submit it in addition to this document via the Supporting Documents page in ESTR.

The below sections are general considerations to consider when preparing your IRB application. The HUA IRB forms will ask you questions relates to these topics.

Specific Aims

What are the specific aims, purpose, intent, and/or objectives of the Human Research? Is the study designed to test specific hypotheses? Understanding the purpose of the research enables the IRB to determine if the research project meets the federal definition of “research”: a systematic investigation that contributes to generalizable knowledge. The connection between the aim, study design, and expected outcomes should be established prior to completing an application.

Background and Significance

How does the research project fit into the current literature in the field? What is the relevant prior experience, gaps in current knowledge, and any relevant preliminary data that will help contextualize the research project is the research building on previous work? Testing a new theory? How have previous findings informed the approach that will be taken?

Research Sites and Study Team

Where will the research take place? This includes locations of the research as well as research sites. A location is the environment in which the research will occur. A site can be thought of as a “place/person” that implements research activities. For example, a Harvard researcher collaborates with ABC hospital in Cambridge, MA to conduct surveys of mental health patients. The hospital is responsible for consenting patients and obtaining their survey responses. In this case, the location of the research is Cambridge, MA and ABC hospital is the research site.

Additional considerations for International Research

When conducting international research, it important to understand the local context. This includes consideration of the following: Local requirements such as customs affecting the research, local age of majority, local scientific and ethical review structure (i.e., national, regional, local state law, institution- based model). For example, research conducted in Brazil requires IRB review by a local institution. Some international communities require researchers to receive permission from local government or community leaders prior to beginning research activities.

Socioeconomic factors that may impact study-related costs, compensation, and reimbursement, if any; consideration of provisions to minimize potential for undue influence resulting from economic benefit. Political factors such as the stability of local government; consideration of provisions to ensure physical safety for participants and/or local study staff.

Cultural beliefs, norms, attitudes as they relate to the proposed research. For example, survey/interview questions may be innocuous in one culture, but offensive to another; secular vs. religious cultures; expectations regarding autonomy; home dynamics (e.g., impact of parent-child relationship of consent procedures), etc.

Study Design

How much time will be needed to complete the study? Will research be expected to last over the course of several years, months, etc.?

Study Procedure Risks

What is the timeline of all procedures being performed, including follow-up visits and are there procedures being performed to monitor participants for safety or minimize risks? Will participants be asked to participate in one session or multiple? Will sessions be spread out over time? How will you re-contact participants for follow-up?

What risks will participants incur during participation? Risks can vary in type and magnitude. People often think of physical risks as the main risk of research participation. However, other risks can include:

- Emotional/mental-could procedures be upsetting?
- Reputational-could procedures negatively impact a participant's social standing in their community? At their job? Their academic standing?
- Undue Influence-are there any factors that could make a participant feel compelled to participate?
- Legal-could procedures have negative legal outcomes for participants?

In identifying the risks that may be associated with study procedures, also consider the procedures that can be taken to lessen the probability or magnitude of risks. For example, collecting as minimally needed data as possible, ensuring adequate data security, etc.

What data will be collected during study procedures, including long-term follow-up data? What kinds of information will be obtained and kept? Will that data be identifiable, coded, or de-identified? Will data be collected directly through an interaction or intervention with participants or received via a source?

Consider the documents and instruments that will be used to collect data (e.g., questionnaires, surveys, interview guides, fMRI, videotaping, etc.) For example, will participants be audio/video recorded? This includes both what may be thought of as traditional voice/in-person recording during an interview or completion of tasks as well as via interactions with technological equipment (e.g., eye-movement tracking, facial responses to stimuli).

Incomplete Disclosure & Deception

Do study procedures include the use of incomplete disclosure or deception? Incomplete disclosure occurs when information is withheld from participants at the time of consent or during study procedures. This information is often withheld to avoid introducing bias into the study but can be used for many reasons. Deception occurs when participants are purposefully provided false information or are misled about procedure and the study purpose. Deception can be used as a tool to avoid introducing bias into a study or it can be used as part of the study design to ensure a particular outcome.

For both incomplete disclosure and deception, the rationale for their use should be considered. In addition to why, whether participants will be provided with the previously withheld information or told the correct information after participation should be considered. This is a process known as "debriefing". Debriefing can be an important part of the risk mitigation process, ensuring participants feel comfortable with the outcome of their participation in the research. The debriefing process should include the opportunity for the participant to withdraw themselves, and all their data, from the study.

When using incomplete disclosure or deception, the protection of research participants' rights in the presence of these (tools) should be considered. Participants should still have sufficient information to make the decision to participate and procedures should still allow for the voluntariness of the research.

What measures can be taken to ensure these aspects of the research, while allowing for the use of incomplete disclosure/deception?

Research versus Standard Practice

In some research settings, there can be overlap between organizational practice and research procedures. It is important to differentiate between those activities that would be considered routine clinical/standard care (in medical settings) or standard business practice from activities conducted for research, or both. Another example is research conducted in partnership with a technology firm. The firm regularly emails users regarding their product and services. The researcher is interested in how different messaging may impact user behavior. Under standard business practice all users are sent the same email messages. The researcher implements a randomization so that email messages are sent to users randomly without changing the content of the email. The email would be considered standard business practice, the randomization of who receives the emails would be considered a research activity.

Understanding what activities are considered "standard practice" and those that are considered research activities is important for determining whether the organization is considered a collaborator. If the organization is considered a collaborator, they may need IRB review for their role on the project.

Similarly, differentiate between those procedures conducted by Harvard staff from those conducted by non-Harvard members of the research team. What activities will be implemented by Harvard researchers and what activities will be implemented by non-Harvard personnel?

Data & Safety Monitoring

A data and safety monitoring plan might be required when Human Research involves greater than minimal risk to participants or if required by the IRB. Will plans be needed to periodically evaluate the data collected regarding both harms and benefits to determine whether participants remain safe? What data will be reviewed, including safety and efficacy data, how safety information will be collected (e.g., with case report forms, at study visits, by telephone), the frequency of data collection, including when safety data collection begins, the person or entity (e.g., a Data and Safety Monitoring Board) responsible for reviewing the data, the frequency or periodicity of cumulative data review, statistical measures for analyzing safety data to determine whether harm is occurring, and any conditions that would trigger an immediate suspension of the research.

Recruitment Methods

Recruitment is the first point of contact with a potential participant, when they are provided with information to determine if they wish to participate in the research. This information can be delivered to participants via a variety of strategies. For example, flyers, advertisements, phone-calls, another participant, in-person, etc. How will participants be informed of the research project? Will the strategy be executed by the Harvard researcher or someone/something else? For example, if partnering with an organization, will they conduct recruitment on your behalf? Will participants be asked to refer others?

Obtaining Consent

Consent is often thought of as a singular activity; however, consent is a process that begins with recruitment. It is the process by which participants are provided information about the study and what is expected of them. This information is what individuals will use to decide to participate.

When designing the research project, the consent process should be considered. This includes the setting of the consent process. For example, will it be in a group setting or one-on-one? Identify who will be responsible for obtaining consent. Will someone other than a research team member be obtaining consent? What method(s) will be used to obtain consent (online, electronically, verbally, in-person via a document)? How much time is needed for the initial consent discussion? As a process, consent can occur over multiple time points with information delivered across recruitment, prior to participation, and during participation or afterwards in the case of debriefing. The timeline for consent should be established whether taking place only once or over time. Take into consideration the setting of consent and the role between researcher and participant and any other factors that may influence the voluntariness of the research. What measures will be taken to protect against the risk of undue influence?

If new information about study procedures, risks, and benefits to participation becomes available, how will participants be informed?

Also consider the participant population when designing the consent process. For example, if the research includes working with participants who speak a different language, consent information will need to be provided in their language either by the team or an interpreter.

If there is not enough time to translate prior to the research, the short form consent is typically used when the potential participant does not speak English. Please see the section on the Short Form Consent Process found in the section *"Consent Considerations"*.

Language differences are not the only issue to be considered when drafting the consent materials. For example, consent documents should be prepared at a reading level that matches the literacy capacity of participants. Also, do participants include individuals who may have limited capacity to consent such as children, individuals with mental/physical diagnoses that would impact their ability to consent, etc.? If the Human Research involves any special population such as these, what will be the process to obtain consent, permission, or assent, including:

- Persons who have not attained the local legal age for consent to treatments or procedures involved in the research ("children")?
- Will parental permission be obtained from both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child?
- One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child?
- Will permission be obtained from individuals other than parents, and if so, who will be allowed to provide permission?
- Will assent be obtained from all, some, or none of the children? If some children, which child population (e.g. age range) will be required to provide assent? Customarily, the IRB requires investigators to obtain assent from individuals ages 7 years or older; however, if this is not appropriate for the specific target population, please describe.
- When assent from children is obtained, describe whether and how it will be documented.
- What procedures will be put in place to obtain consent when, if any, children reach the local age of majority during the protocol?
- If the Human Research involves adults who may be unable to consent, describe the process to determine whether an individual is capable of consent and address the following, if applicable:
 - If permission of a legally authorized representative will be obtained.

- Who are the individuals from whom permission will be obtained?
- Which individuals are authorized under applicable law to consent on behalf of a prospective participant to their participation in the research procedure(s)? If necessary, contact the IRB who will consult with the Office of the General Counsel to review the definition of “legally authorized representative” in 45 CFR 46.102(c) or 21 CFR 50(l) to make this determination.
- Like consent, will assent be documented, if so, how?

Documentation of Consent

Consent of the participant is typically documented via signature line on the consent form. However, under certain circumstances, documentation of consent may be waived. Whether there are extenuating circumstances that make it impossible or inappropriate to meet this requirement should be considered. For example, is obtaining someone’s signature for participation in the project culturally appropriate given the local context? If study procedures occur completely online, is it possible to obtain an electronic signature? In other cases, it may be that the primary risk of participation would be a breach of confidentiality and a signed consent document would be the record of participation placing the participant at risk.

If the consent process will not be documented in writing, i.e., consent will be obtained, but the participant or representative will not sign a consent document, refer to “CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)” and consider each of the criteria.

If written documentation is waived under the criterion, “That the only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality” the federal regulations require that, “Each subject (or legally authorized representative) will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern”. If the research team does come across a situation where a subject wishes to have their name linked to a study, contact the IRB office as soon as possible as this may result in a different risk level and type of IRB review.

If the Human Research involves a waiver or alteration of the consent process (consent will not be obtained, required information will not be disclosed, or the research involves deception) review “CHECKLIST: Waiver or Alteration of the Consent Process (HRP-410)” and consider each of the criteria.

HIPAA Privacy Protections

At Harvard, the Harvard University Health Services and Harvard School of Dental Medicine are covered entities under the HIPAA Privacy Rule; other schools/units within Harvard are not HIPAA covered entities. Because of this, Harvard is referred to as a “hybrid covered entity”

If protected health information (PHI) is derived from a covered entity, e.g., a hospital or community health center, for purposes of the research project, plans to obtain authorization to access protected health information will be needed. Alternatively, a rationale for requesting a waiver of authorization for obtaining this information will be needed. If requesting the latter, consider why it is not practical to obtain an authorization from the covered entity and why the research cannot be conducted without obtaining PHI. Refer to “CHECKLIST: HIPAA Waiver of Authorization (HRP-441)”. Note: Standard Covered Entity Notice of Privacy Practices or Disclosure Statement documents are not considered authorization to access PHI for research purposes. A request for HIPAA authorization must be specific to the proposed research.

Vulnerable Populations

Certain participant populations may require additional protections when included in research. The Federal regulations note that pregnant women, prisoners, and children should be considered vulnerable and additional regulations have been put into place to ensure protection during research participation. For research conducted with prisoners, there are conditions regarding the purpose of the research, recruitment procedures, and study procedures to ensure a voluntary research environment. Note that the IRB must make additional regulatory findings for the inclusion of pregnant women, neonates, fetuses, children, and prisoners. The checklists referenced

below should not be submitted in ESTR, but rather used as a guide to ensure sufficient information is provided in the Research Protocol.

Adults Unable to Consent

If the Human Research involves adults unable to consent, refer to “CHECKLIST: Cognitively Impaired Adults (HRP-417)” and consider each of the criteria.

Children

If the Human Research involves persons who have not attained the legal age for consent for procedures involved in the research, refer to “CHECKLIST: Children (HRP-416)” and consider each of the criteria.

Neonates of Uncertain Viability

If the Human Research involves neonates of uncertain viability, refer to “CHECKLIST: Neonates of Uncertain Viability (HRP-414)” and consider each of the criteria.

Non-viable Neonates

If the Human Research involves non-viable neonates, refer to “CHECKLIST: Non-viable Neonates (HRP-413)” and consider the criteria.

Pregnant Women

If the Human Research involves pregnant women, refer to “CHECKLIST: Pregnant Women (HRP-412)” and consider each of the criteria.

Prisoners

If the Human Research involves prisoners, refer to “CHECKLIST: Prisoners (HRP-415)” and consider each of the criteria.

While the regulations specifically mention these populations, there are other factors that may make a population vulnerable to undue influence, coercion, or increased risk. These factors can include the relationship of the participant to the researcher (e.g., student/professor), economic circumstances (e.g., under housed/homeless), among others. Measures should be taken to mitigate any factors that could impact the voluntariness of the research and/or increase overall risk of participation as result of potential vulnerabilities. For example, in the case of a researcher who uses their own students as the participant population, someone other than the researcher could obtain consent of the students for participation. This would assist in students feeling free to decline participating. Inclusion of a sentence ensuring participation would not impact their grade or status in the course would also assist in mitigating the risk of students feeling compelled to participate because of their relationship with the researcher.

Risks

What will be the risks to participants because of participation in the research? While research is dynamic and situations can develop over time, during the design of the research and preparation of the protocol identify those risks that are foreseeable. These risks should not be limited to a discussion of possible physical harms (e.g., discomfort from a prolonged fMRI procedure), but should also include social, reputational, emotional, and confidentiality risks. Identify whether any of the information collected, if disclosed outside of the research, could reasonably place the participant at risk of criminal or civil liability or be damaging to the participant’s financial standing, employability, insurability, or reputation.

The magnitude of these risks may vary within a research project and could change over time. For example, the initial collection of interview data itself may be minimal risk, however, when combined with identifiable health records the overall data may become more sensitive— containing information that could negatively impact a participant’s reputation or employability.

Identify and outline measures that can be taken to reduce these risks or mitigate them to the extent researchers are able. For example, could data be de-identified and original identifiers (name, medical record number, etc.) deleted?

Participant Privacy

Maintaining participant privacy is often a primary means of mitigating any risk to participants. The research team should consider the provisions that will be implemented to protect participants' privacy during and after participation. Privacy is defined as a person having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. Privacy also refers to the right of individuals to limit access to/about themselves from/by others, especially information shared with researchers. This includes identifiable information, HIPAA-defined protected health information, research data, photos, video recording, even information contained in biological specimens. It involves consideration of whether the participants will be comfortable with the research procedures. For example, conducting interviews in a private room or visiting a participants' home in an unidentifiable manner, such as in an unmarked car, wearing plain street clothing. Identify the steps that will be taken to reduce any sense of intrusiveness that may be caused by study questions or procedures.

Data Confidentiality

Confidentiality pertains to the treatment of information that a participant has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission.

Genomic Data Sharing

If future open access (i.e., free availability and unrestricted use) is planned, this information should be included at the time of consent. If data is subject to the NIH [Genomic Data Sharing policy](#) or data will be voluntarily submitted to an NIH-designated repository, additional information will be needed. This includes a description of all data fields to be submitted to the repository, a copy of the consent form(s) used to enroll participants and collect underlying data, a description of the PI's plan for de-identifying datasets for transmission to the data repository, how the key linking the identity of each study participant will be maintained, and who will have access.

Data Security Policy

Data security plans developed to ensure data confidentiality must comply with protection requirements described in the Harvard Research Data Security Policy (HRDSP)* which can be found on the University security website <http://vpr.harvard.edu/pages/harvard-research-data-security-policy>.

Per the [Harvard Research Data Security Policy](#), research data can be stored electronically, however there are data security level specific requirements and investigators must consult with IT for data assigned as sensitive by the IRB before beginning their research activities. IT at Harvard is school-specific. The local IT Security Officer can assist with cloud-based computing environments, Share Point, file backup services, high-performance computing, and database platforms, etc. Additionally, this policy applies only to data stored at Harvard University or under the management and responsibility of a Harvard researcher.

Costs and Compensation

Consider how participants will be compensated for their time spent on study procedures. If participants will be compensated, identify the information that will be needed to pay individuals. Please consult the [Harvard University Financial Policy on Human Subject Payments](#) to make necessary arrangements for participants' payment. Describe the plan to securely transfer any financial paperwork to Accounts Payable for processing, if applicable. Refer to "WORKSHEET: Payments (HRP-316)".

Sharing Study Results

If you will be sharing results with research participants, consider what impact, if any, this could have on the ability to maintain confidentiality. Could participants potentially be able to identify others based on the information shared? Identify the plan to share study results with individual participants and/or the participant group/community, if applicable (e.g., what contact information will be needed and how will it be stored)

Devices

Refer to "WORKSHEET: Devices (HRP-307)" and "CHECKLIST: Non-Significant Risk Device (HRP-418)".

Drugs/Biologics

Refer to "WORKSHEET: Drugs (HRP-306)".

Consent Considerations

Creating a Consent Script for Exempt Human Research

Exempt Human Research does not require a long form, signed consent form. However, the ethical principles outlined in The Belmont Report, namely, respect for persons, emphasizes the importance of ensuring that participants are fully informed. Therefore, a consent process is recommended when exempt Human Research involves an interaction with human subjects. At a minimum, this process must disclose the following:

- That the activities involve research.
- The procedures to be performed.
- That participation is voluntary.
- The name and contact information for the investigator.

Please also refer to the “HUA Exempt Research Consent Script (HRP-502-c)”.

Creating Consent Forms for (non-exempt) Human Research

Consent documents must contain all the required and as appropriate, additional elements of informed consent. No informed consent (oral or written) should include exculpatory language whereby the participant or their representative is made to waive or appear to waive any of the participant’s legal rights, or releases or appears to release the Investigator, the sponsor, the Institution, or its agents from liability for negligence.

Documenting Consent

Use the signature block(s) approved by the IRB when obtaining informed consent. Ensure that all items in the signature block are complete, including dates and applicable checkboxes, e.g., future use, specimen storage, etc.

The following are the requirements for customary (long form) consent documents:

- The IRB-approved consent document is implemented in the field. IRB approval is evident by an ESTR watermark and/or reference to applicable version numbers/dates in IRB Notification letters. (IRB-approved consent documents can be accessed in ESTR under the Documents Tab within the main study workspace.)
- The participant or legally authorized representative signs and dates the consent document.
- The individual obtaining consent signs and dates the consent document, when required by the IRB.
- Whenever required by the IRB, the participant or legally authorized representative signature is to be witnessed by an individual who signs and dates the consent document.
- For participants who cannot read and whenever required by the IRB or the sponsor, a witness to the oral presentation signs and dates the consent document.
- A copy of the consent document is to be provided to the participant or legally authorized representative.
- A full copy of the signed and dated consent document is retained as part of the study documentation (usually contained within participant-specific files).

What is documented consent?

According to the federal regulations that protect human subjects, “informed consent shall be documented by the use of a written informed consent form approved by the IRB and signed (including in an electronic format) by the subject or the subject’s legally authorized representative. A written copy shall be given to the person signing the informed consent form.” (45 CFR 46.117)

While we are accustomed to think that documentation of consent is an in-person inked signature, there are many alternatives that satisfy these requirements.

Guidelines to document informed consent

The regulations that govern human subjects research and other state, local, and institutional laws, policies, and guidance do not directly outline what is considered acceptable documentation of an informed consent form, however they do provide guidelines to ensure that the documentation is valid:

- There must be a mark made by the study subject.
- The study team should have a reasonable way to verify the identity of the individual (“study subject”) signing the informed consent form.
- A copy of the informed consent form must be provided to the study subject.
- The Study Team must retain the study document for their records.

Mark made by the subject

The default “mark” made by a study subject is their signature however as noted by the federal regulations, “A person who speaks and understands English, but does not read and write, can be enrolled in a study by “making their mark” on the consent document, when consistent with applicable state law.” In this case, the mark may be a “X”, thumbprint, or other mark. If the study will be using an electronic signature capture method, know that there may be other requirements (see below).

Verifying identity

If a consent process occurs in-person, verification of the identity of the person is straight-forward but what if the consent process is taking place remotely? For example:

- **A virtual meeting or teleconference where the Study Team witnesses the signing of the informed consent form by the study subject.** Some study teams have found that conducting the consent process virtually or by teleconference is an effective way to not only ensure study subject understanding but also a way to verify the identity of the person signing the form.
- **Using technology that supports an electronic signature.** The use of an electronic signature is where things get a bit more complicated. Some regulations require a strict adherence to certain requirements such as with FDA regulated research (see 21 CFR 11.100(b)). Other laws suggest using a password or other security device to make sure the individuals signing electronically are indeed the individuals named in the document. Under the Massachusetts Uniform Electronic Transactions Act (“UETA”; see M.G.L. c. 110G § 9), the “efficacy of any security procedure” used in the e-signing process can be used to show that a record was attributable to the person who signed it.”

Other Examples

Examples of various methods that could be used include verification of state-issued identification or other identifying documents, or use of personal questions, biometric methods, or visual methods.

For Research Under the Sole Authority of 45 CFR Part 46 (otherwise known as the “Common Rule”)

Our most applied set of regulations realizes that it may not always be possible to verify that the person signing the informed consent is the study subject and therefore encourages a risk-based approach to the consideration of subject identity. For example, for some research if the consent form was mailed (by postal mail, email, fax, etc.) directly to the individual it may be sufficient verification if the signed informed consent form is sent back to the study team via the same method.

In these instances, it is recommended that the study team seek advice from the IRB.

A copy of the informed consent form must be provided to the person signing the form

According to the federal regulations, “...the person signing the informed consent (i.e., the subject or the subject’s LAR or the parents or guardians of subjects who are children) be given a copy of the written informed consent form (45 CFR 46.117(a) and 21 CFR 50.27(a)) ...”

The various federal, state, local, and institutional laws, policies, and guidance do not specify the required medium of the form and indicate that the copy provided to the subject can be paper or electronic and may be provided on an electronic storage device or via email.

The federal regulations go on to state that, “If the copy provided includes one or more hyperlinks to information on the Internet, the hyperlinks should be maintained, and information should be accessible until study completion.”

Massachusetts Law states that, “You must not use software or security settings that would prevent the recipient from printing or saving a document that the recipient has been asked to sign electronically.” (See M.G.L. c. 110G § 8(a)).

Retention of electronically signed document by the Research Team

While the federal regulations at 45 CFR 46 (again, the “Common Rule”) do not specify a research records retention period, other federal regulations such as FDA and HIPAA do. Moreover, Massachusetts state law and Harvard policy require a retention period for said documents.

Harvard University policy states that, “Researchers have certain obligations to record, maintain and retain research records, and to make those records available for grant monitoring and auditing purposes, as well as to enable investigators and the institution to respond to questions of research integrity and stewardship. See, e.g., 2 CFR 200, 42 CFR 93.106(b).” Moreover, according to the Harvard University General Records Schedule, all records associated with funded/sponsored projects must be retained for seven years after final project account closing unless a longer period is specified by the granting agency. For non-sponsored projects, records must be retained three years after final project account closing.

Exclusions

As the above guidelines demonstrate the flexibility in what is considered valid documented consent, there are certain regulations that require strict security requirements. As an IRB, we have determined that because of this, there are certain types of studies that require an in-person, inked signature as the only allowable method of documentation. These include studies that are regulated by the FDA and fall under 21 CFR 312 (drugs and biologics) and 21 CFR 812 (devices) and therefore require Part 11 compliance, as well as those studies regulated under HIPAA that require an individual authorization for research use/disclosure (45 CFR 164).

Short Form Consent Process

Participants who have limited English proficiency may be enrolled in your research if you have the resources to communicate effectively during the recruitment process, while obtaining consent, and for the duration of the study. The short form consent is typically used when the potential participant does not speak English and there is not enough time to translate the English version of the approved consent document into a language the potential participant understands.

A short form consent document attests that the elements of informed consent, as required by DHHS and the FDA, have been presented orally to either the participant or the participant's legally authorized representative. A short form consent may be used as described in "WORKSHEET: Short Form of Consent Documentation (HRP-317)". The IRB Office has a Short Form Consent Template available (see "TEMPLATE HUA Short Form Consent Form (HRP- 507)").

If you expect to enroll more than one participant with limited English proficiency or if your study is being conducted internationally, you are expected to translate all study documents provided to participants into the appropriate language(s). Please see section "Non-English-Speaking Subjects" below.

Requirements for Use

The investigator must provide the following to the IRB for review:

- A written summary of what is to be said to the participant or the participant's legally authorized representative. The summary must include all the required and appropriate elements in Section 7: Elements of Consent Disclosure in the "WORKSHEET: Criteria for Approval (HRP-314)". The PI may use the English version of the IRB- approved informed consent document.
- The short form document that will be signed by the potential participant.
- Confirmation that:
 - The oral presentation will be conducted in a language understandable to the participant.
 - The person obtaining consent is authorized by the IRB.
 - There will be a witness to the oral presentation (this cannot be the same person who is obtaining consent). If the participant does not speak English, the witness should be fluent in both English and the language of the participant. When the person obtaining consent is assisted by a translator, the translator may serve as the witness.
 - The short form will be signed by the participant and the witness.
 - The written summary will be signed by the witness and the person obtaining consent.
 - A copy of the oral summary and the short form will be given to the participant.

Responsibilities Afterward

The request to use the short form consent process is typically made because time is of the essence. As such, the IRB prioritizes the review of these requests to avoid denying an individual an opportunity to participate in research. However, once the participant is enrolled, the investigator is expected to adhere to the IRB's standard requirements for non-English speaking participants. This includes providing the IRB (in a timely fashion) with the plan for ensuring that ongoing communication with the participant is in a language understandable to the participant the following.

The Consent Process for Individuals With “Diminished Capacity” (adapted from the OHRP “Informed Consent FAQs”)

The HHS regulations are silent on the consent procedures specific to subjects with impaired decision-making capacity, for example, because of trauma, intellectual disability, some forms of mental illness, or dementia, whether temporary, progressive, or permanent. The regulations do require that the IRB ensure that “additional safeguards have been included in the study to protect the rights and welfare” of all subjects that are “likely to be vulnerable to coercion or undue influence.” The regulations include “mentally disabled persons” in this category (45 CFR 46.111(b)).

In research involving adult subjects with mental illnesses or cognitive impairments, the IRB and investigator(s) must be knowledgeable about the condition and any level of impairment that is likely to be present in the subject population. The regulations do speak to the fact that the IRB must possess “the professional competence necessary to review specific research activities” (45 CFR 46.107(a)). This is achieved either by having members with the appropriate experience and expertise or inviting consultants with competence in the special area to assist in the review of issues that require expertise beyond or in addition to that available on the IRB (45 CFR 46.107(a) and (f)). Ensuring such expertise on the IRB improves its ability to make determinations about subject recruitment, enrollment, and informed consent requirements that best match the needs of the subjects.

In some research, such as longitudinal studies involving progressive disorders or aging populations, enrolled subjects may be competent to consent on their own behalf at the outset yet may experience effects of progressive or intermittent disorders that lead to decisional impairment during the study. In these situations, IRBs and investigators should consider the need to discuss with the prospective subjects whether they should designate someone to serve as a legally authorized representative at the outset of the study, consistent with all applicable laws. Even if a subject has consented on his or her own accord, a designated representative would be ready to step in as the legally authorized representative if the subject’s ability to assess his or her own needs and interests becomes compromised during the study.

The Consent Process for Illiterate English-Speaking Subjects

A person who speaks and understands English, but does not read and write, can be enrolled in a study by “making their mark” on the consent document, when consistent with applicable state law.

A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if they are competent and able to indicate approval or disapproval by other means. If (1) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent) and (2) can indicate approval or disapproval to study entry, they may be entered into the study. The consent form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. The IRB may also recommend that an impartial third party should witness the entire consent process and sign the consent document.

Non-English-Speaking Subjects

The federal regulations require that the informed consent document be in language understandable to the subject (or authorized representative). When the study subject population includes non-English speaking people or the IRB anticipates that the consent process will be conducted in a language other than English, the IRB will require that the research have a translated consent document and provide assurance to the IRB that the translation is accurate. **The translated copy does not need to be submitted to the IRB.** A copy of the consent document must be given to each subject. In the case of non-English speaking subjects, this would be the translated document. While a translator may be helpful in facilitating conversation with a non-English

speaking subject, routine ad hoc translation of the consent document should not be substituted for a written translation.

Re-Consent of Subjects²

The regulations require that researchers provide participants with significant new findings developed during the research when those findings may impact a participant's willingness to continue participation in the research. Significant new information could include revised risk information or information related to an unanticipated problem, such as a data breach.

The provision of significant new information in the context of a given study will depend upon factors including the nature of the study, the nature and urgency of the new information, and the status of participants e.g., in screening phase, receiving an intervention, long term-follow-up, etc. Providing the new information creates an explicit opportunity for participants to exercise their ongoing right to continue their participation or withdraw from the research.

Possible approaches to providing new information include:

- Repeating the informed consent process with the revised informed consent document(s) and document consent following the requirements for documenting consent at 45 CFR 46.117.
- Presenting the new information using an addendum to the original informed consent document and either obtain documentation directly or describe the communication process in the participant's research records.
- Orally communicating the new information and document the communication process in each participant's research records.

Examples of Instances where changes to the study may affect a research participant's willingness to continue and therefore should be disclosed to participants are, but not limited to, the following:

- Identification of new research-related risks.
- Increase in the frequency or magnitude of previously described risks.
- Unanticipated problem that exposes subjects to new risks, such as a data breach.
- Decrease in expected benefits to participation.
- Change to the research that results in increased burden / discomfort.
- Change in duration of participation in the trial or other changes likely to increase the burdens or discomforts of participation.
- Significant changes in the research study design.
- Change in use of specimens obtained in the research (e.g., addition of genetic testing).
- Change in the financial burden of participation.
- Changes in the investigator's financial conflict of interest.

Please see "SOP: Informed Consent Process for Research (HRP-090)" for a complete overview of the consent process, including the short form consent process.

If your study is funded by a federal agency and meets the definition of a "clinical trial", please see the section "Additional Requirements for Studies Sponsored by a Common Rule Agency (45 CFR 46.116(h))" as the federal regulations require that for any clinical trial conducted or supported by a Common Rule department or agency, one consent form be posted on a publicly available federal website within a specific time frame.

² Adapted from materials developed by the Collaborative Institutional Training Initiative (CITI Program)

Do I need to obtain informed consent to screen, recruit, or determine the eligibility of prospective subjects?

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

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

The research protocol should include information about how potential subjects will be identified and recruited for the IRB to be able to determine whether informed consent for these activities is required.

Contact the IRB Office with additional questions or for further guidance regarding the requirement to obtain HIPAA authorization or a waiver to obtain HIPAA authorization for recruitment purposes.

Simplifying the Informed Consent Form

Readability Standards

Readability should be guided by the following standards:

- Materials should be written in a manner that is both understandable and sensitive to the target participant population(s).
- It is not the participant's responsibility to try to understand the study documents.
- Refer to your partner organization's or project site's readability policies and practices.
- When working with populations whose primary language is not English or who do not understand English, we recommend translating materials into their native language at the appropriate reading level.

Readability Requirements for Regulated Research

Readability requirements include:

Appropriate Reading Level

Write to the literacy level of your intended population, with a maximum reading level at 8th grade. Assent materials for minors should be written to the child's grade level but no higher than a 6th grade level.

- Use the Flesch–Kincaid and/or Fry scoring methods (embedded in Microsoft Word) or an app like Readable to estimate reading level.
- If your population includes a range of ages or literacy levels, write to the lowest level.

Clearly Written Materials

Tips to write clearly and directly include:

- Simplify, so long as it doesn't affect the information shared. This includes the study title.
- Write short, direct sentences. Divide sentences into two when necessary.
- Make your text logically sequenced and clear to understand.

- Keep paragraphs short and limited to one idea.
- Use active voice instead of passive. Write the information and consent materials the way that you would naturally speak.
- Keep words to three syllables or fewer. One-to-two syllable words are ideal.
- Spell out acronyms when first used.
- Use layman's terms and everyday language whenever possible. Use words familiar to the non-technical or non-scientific reader.

Examples:

- randomization = toss of a coin
- administer = give
- determine = find out
- in conjunction with = at the same time
- participate = take part, be in
- measure impact or evaluate or assess = learn about
- instruments = surveys and tests
- cognitive skills = thinking skills
- virtual = online
- discontinue = stop
- investigation = study
- utilize = use
- assessment = test
- Avoid contractions.
- Avoid repetition.
- Avoid large blocks of printed text.

Visual Ease

Make your materials visually appealing and easy to navigate.

- Use adequate spacing and white space to make the content inviting to read. Avoid crowding of words and letters.
- Use headings/subtitles. These reduce content density and serve as "road signs."
- Use lists rather than paragraphs when possible.
- Use friendly font.
- Use page numbers.
- Use at least 12-point font and consider a larger font based on your audience.
- Avoid excessive use of bold type, which can lead to subjects overlooking important information not in bold type.
- Use photos, graphics or tables if these will help clarify procedures.

Supporting Comprehension and Further Clarifications

Provide opportunities for subjects to ask questions and clarify what they have read or been told.

- This could be in-person or supported by phone or email.

Using Online and Manual Readability Tools to Assess the Reading Level of Informed Consent Documents

Note: This resource is provided to assist Informed Consent Document authors in assessing the readability of their documents. It is an optional resource. Adapted from:

https://ctep.cancer.gov/protocoldevelopment/docs/NCI_Informed_Consent_Template_Readability_Assessments.pdf

Readability formulas are used to estimate the reading difficulty of text. In general, they measure the average number of syllables in words and the average number of words in sentences. Most formulas provide results as grade levels, such as the 8th grade reading level. However, because readability depends on so many issues, achieving a certain grade level is not a guarantee of comprehension.

Types of readability formulas: There are numerous readability formulas including Flesch Kincaid, Flesch Reading Ease, SMOG, Fry, Fog Index, and Dale-Chall.³ They are generally accurate to ± 1.5 grade levels.

- **Flesch Reading Ease** – This formula uses a 100-point scale based on the average number of syllables per word and the average number of words per sentence. The higher the Flesch Reading Ease score, the easier it is to read the document. For example, a document that scores at 60 is easier to read than a document that scores at 40.
- **Flesch-Kincaid** – This formula is a modified version of the Flesch Reading Ease Formula. It assigns a grade level to a document. For example, you might see the results listed as 8th grade or 12th grade depending on the complexity of the text. Like the Flesch Reading Ease, the Flesch-Kincaid also measures the average number of syllables per word and the average number of words per sentence.
- **SMOG** – This formula measures the number of polysyllabic words (more than 2 syllables in a word) contained in a sample of 30 sentences. Like the Flesch-Kincaid, it assigns a grade level to a document based on its complexity.

Readability Level Guidelines for Informed Consent Documents: The 2015 IOM Informed Consent and Health Literacy Workshop Summary recommended that informed consent documents be written at the 8th grade reading level or lower.

Implementing Readability Assessments - Recommendations and Considerations: There are many online sites that perform readability analyses on a given document and provide a reading level score. The most used tool is the Microsoft Word Readability Statistics function. However, it is important to be aware of several limitations of this function which can result in underestimating the grade level of your document (below). To get the most accurate results from your online tool, you need to “clean up” your document.⁵ This means that before conducting the analysis, you need to:

- Delete titles, phrases, fragments, headers and lists that are not complete sentences. This includes lists of side effects that are not written as complete sentences (although you can include bulleted items that are written as complete sentences).
- Delete periods that don’t mark the end of a sentence, such as numerals in a number list (1. or 2.); abbreviations (Celeste B. Jones, M.D.); or periods used in decimals (10.3).
- Delete phone numbers and URLs.

Readability formulas were designed for use on narrative, flowing text that consists of complete sentences. They were not designed to measure phrases, fragments, or lists. If you include phrases, fragments, headers and lists that are not complete sentences, your readability software will not give you an accurate sentence count. If you don’t remove extra periods, your software may count more sentences than there are, giving you a lower readability score.

It is normal to see some variability across the tools. However, you will ideally see similar results from different tools. You can first put your document through MS Word's Readability Function, and then put it through the Online-Utility readability assessment tool at https://www.onlineutility.org/english/readability_test_and_improve.jsp Then, compare the results.

One good way to check the accuracy of your results is to conduct both an online and manual readability analysis of your document. NCI's Pink Book, "Making Health Communications Programs Work, available at <https://www.cancer.gov/publications/health-communication/pinkbook.pdf> provides instructions on how to conduct a manual SMOG readability analysis (pages 162-166). You can then compare your results to the SMOG reading level you got from the Online-Utility tool. MS Word Readability does not give a SMOG score.

Limitations of Readability Formulas:

- There is not a one-to-one correlation between the grade level of a specific document and a person's reading ability. For example, if you use the Flesch-Kincaid Readability Formula to analyze your informed consent document and you get a score of 10th grade, it does not mean that all adults reading at the 10th grade level will understand the text.
- Readability formulas do not measure many factors that affect reading ease, including the familiarity of vocabulary and concepts, clarity of writing, concept density, format and design, cultural relevance, believability, or the reader's readiness to learn.
- Because most readability formulas give you averages, they do not tell you which sections of text are hardest to read. You can select some of the potentially more difficult passages, such as paragraphs with drug names, complicated medical procedures, and very long sentences, when doing a manual SMOG analysis.

Additional Consent Form Language Requirements

Relating to Conflict of Interest

If required as part of the conflict-of-interest management plan, the following information may need to be disclosed in the consent form: sources of funding for the study, investigator conflicts of interest, and/or how to find out additional information. The following is recommended language to fulfill such requirements as required. Please know that the consent form templates include the below language.

Disclosing funding source

Investigators may be required to disclose the funding source(s) of the study or sponsors providing study drugs or equipment for the study. If the study is not being funded by an external sponsor, then the internal funding source may be identified, e.g., department funds, personal funds.

- Example language to identify the study sponsor: This study is being funded by the National Institutes of Health (NIH) [or Industry Sponsor or Private Foundation].
- Example language to identify the provider of the study drug if different than the sponsor: Commercial company name, the manufacturer of the investigational drug being used in this study, is providing the study drug [or device or assay] at no cost [or at cost] to the researcher or research participant.

Disclosing the nature of any financial or proprietary interests

When required, create a new section in the consent template entitled “Researcher Financial Interests in this Study” to disclose the nature of any financial or proprietary interests. This section should identify the researchers or research staff by name and study role.

- Example of language to indicate the interest in an entity or the product: Dr. Jane Doe, a researcher on the study team, has a financial interest in [name of company], [the company paying for this study; the company that will manufacture the study drug; the company that will sell the drug, and/or the company conducting part of this study].
- Example of language if the interest is other than a financial interest in an entity, e.g., in the product being tested: Dr. John Smith, the principal investigator for this study, has a financial interest in the [product, drug, device, name of company] being studied.
- Example of language to describe the interest:
 - [Name of company and relevance of company to study, e.g., sponsor] is paying Dr. Cohen [describe payment, e.g., consulting fee, salary].
 - Dr. Cohen is being paid to be a scientific advisor to [name of company and relevance of company to study].
 - Dr. Cohen is an unpaid member of the Scientific Advisory Board of [name of company and relevance of company to study].
 - Dr. Cohen is on the board of [name of company and relevance of company to the study].
 - Dr. Cohen is the [president; chief executive officer] of [name of company and relevance of company to study].
- Example of language to describe significant stock ownership in a publicly traded company, stock ownership in a non-publicly traded company, and/or holder of stock options:
 - Dr. Rodriguez owns stock in [name of company and relevance of company to study].
 - Dr. Rodriguez is a [founder or majority or minority shareholder] of [name of company and relevance of company to study].

- Dr. Rodriguez has a stock option from [name of company and relevance of company to study] and may receive income in the future.
- Example language for the inventor:
 - Dr. Chan invented the [drug, device] being studied and may benefit financially if it is marketed.
 - If possible, elaborate on the information provided. For example, “The consulting income Dr. Chan receives is in addition to her salary from the University.”

Explain why disclosures are being made and where participants can receive additional information

- Example language: This disclosure is [or, these disclosures are] made so that you may determine whether this relationship [or, these relationships] affect your willingness to participate in this study. If you have questions, please inform the study coordinator, and s/he will put you in touch with someone to talk to.

Special Considerations

Clinical and Medical Services During Clinical Research

Because Harvard does not have a teaching hospital, **providing clinical care** is outside the mission of the University (the exception being the teaching clinic at the Dental School). With no teaching hospital, Harvard lacks the administrative infrastructure that most hospitals have to comply with regulations that apply to clinical care – the treatment of patients. Clinical **research**, on the other hand, is supported across the University.

The Harvard University Office of the Vice Provost has created [guidance](#) that is intended to provide Harvard faculty who conduct clinical research and those who administer and oversee research projects uniform criteria for the conduct of research with a clinical care component.

The [guidance](#) is intended to clarify what clinical projects are appropriate to carry out at the University, and set out procedures for review and oversight of those projects. In addition to the guidance, there is a flow chart to describe the sequence of review of clinical research projects, and a set of scenarios to illustrate application of the Guidance principles in a variety of contexts, at different Schools.

Data Security

In social and behavioral research, breach of confidentiality is a serious risk posed to participants. Rigorous data security is a key element of protecting subject data from an accidental or malicious breach. Data security includes a plan to manage the physical documentation associated with the project, such as paper surveys, signed consent forms or documents that contain contact information for subjects, to ensure that those materials are not lost or accessed inadvertently by an unauthorized person. Increasingly important is the management of electronic data on desktops or servers as well as on mobile devices such as laptops and flash drives. See the Harvard University Research Data Security policy for information on how to protect your data - <http://vpr.harvard.edu/pages/harvard-research-data-security-policy>

International Studies

Research conducted outside the United States may create additional challenges for the researcher and the IRB. Cultural, economic, or political conditions of the host country may alter the risk for participants compared to the same research conducted within the U.S. Other countries and institutions within those countries may have Institutional Review Boards, Ethics Committees or other research oversight bodies which require review of the research before it can be conducted in that country. Conversely, some may have no mechanism for ethics review of social and behavioral research. Except for research, which is federally funded, and the international site is engaged, the regulatory authority of the Common Rule does not cover research outside the U.S.; therefore, the IRB must ensure that equivalent protections for human subjects participating in research are in place.

In its review of your application, the IRB will consider the following information:

- Description of where the research will be conducted (including geographic location and specific performance sites, where applicable). Note: In some areas, government–issue research visas are required.
- Information about the local research context, including the current economic, cultural, political, or religious conditions of the area that may affect the conduct of the research, and a description of the researcher’s personal experience conducting research (or studying or residing) in the region.

- The language(s) in which consent will be sought from participants and the research will be conducted, as well as whether the researcher is fluent in this language or whether an interpreter will be required. If an interpreter will be used, it should be clear what limitations or risks, if any, this might present for participants, as well as how these potential problems will be overcome or minimized.
- A description of the informed consent process as appropriate for the culture.
- Any benefits to the local community that will remain in the community once the research is complete.
- If compensation is being offered, a description of its appropriateness for the setting.
- Procedures for data security and storage in the local setting and for transfer of data and/or specimens to Harvard University.
- A copy of local IRB or equivalent ethics committee approval, where applicable. Depending on the location, this may take the form of a letter of approval from an IRB or research ethics committee, local university department sponsoring the research, institutional oversight committee, or an indigenous council. If the research is federally funded, check with the IRB for other regulatory requirements.

If you are traveling to an international setting for your research, submit your IRB application well in advance of your planned travel date. This is particularly crucial for projects that involve more than minimal risk to participants that will require full board review. See the CUHS website - (<http://cuhs.harvard.edu>) for meeting submission dates.

For those research studies that are determined to meet the criteria for expedited or full (convened) IRB review, it will also be necessary for the Office of the Vice Provost for Research (OVPR) to review the study. More information on this Provostial Review may be found on the OVPR website - <https://research.harvard.edu/2021/02/17/provost-criteria-for-review/>

Please also see the section in this manual on *Provostial Review*.

Research in Schools

Research conducted in primary and secondary schools, as well as in colleges and universities, receiving U.S. Department of Education funds may be subject to additional federal regulation. Schools that grant access to researchers may also impose requirements, such as district approvals or informed consent processes that would not be required by the IRB.

- **The Family Educational Rights and Privacy Act (FERPA) (34 CFR Part 99)**
<http://www.ed.gov/policy/gen/guid/fpco/ferpa/index.html>
FERPA applies to research involving student education records for any institution receiving U.S. Department of Education funding, meaning that it applies to most public and private K-12 schools as well as most public and private colleges and universities. Access to identifiable student records requires written permission from the parent (for minors) or from the adult student unless the research is being conducted by the researcher on behalf of the school.
- **The Protection of Pupil Rights Amendment (PPRA) (34 CFR Part 98)**
<http://www.ed.gov/policy/gen/guid/fpco/ppra/index.html>
The PPRA, created by the No Child Left Behind Act, applies to survey research conducted in elementary and secondary schools receiving funds under U.S. Department of Education programs. The provisions of the PPRA apply to surveys that involve specific sensitive survey topics. The PPRA includes requirements for parental permission as well as for making survey questions available for parental review prior to administration.

Secondary Data Analysis Projects

Projects that involve only the secondary analysis of data collected as part of a different research project do not require IRB review and approval if:

- the data set is publicly available; or
- the data set has been already de-identified, meaning that any data elements that could be used to identify an individual have been stripped.

Projects using Coded Private Information or Biological Specimens - If you will be using a data set provided by another researcher that has been coded for your use, your project may not require IRB oversight. Coded means that identifying information that would enable the researcher to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and a key (or crosswalk) to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Research using such a coded data set is not regulated by the IRB if the data were not collected for the proposed study and the researcher does not have access to the code linking to the identifiable information. More information regarding coded private information or biological specimens can be found at: <http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>.

Deception and Incomplete Disclosure Studies

Deception is the intentional misleading of a subject about the nature of the study. Withholding of full information is known as incomplete disclosure. Misleading or omitted information might include the purpose of the research, the role of the researcher, or what procedures in the study are experimental. Deception increases ethical concerns and should be used with discretion, because it interferes with the ability of the subject to give informed consent. The IRB recognizes that deception or incomplete disclosure may be necessary for certain types of behavioral research. Because people act differently depending on circumstances, full knowledge by the subject might bias the results in some cases.

Special requirements for deception or incomplete disclosure projects:

Waiver of Informed Consent

Because participants are not provided with all the details of the proposed research at the time consent is obtained, deception projects must meet the criteria for waiver of informed consent including that the project poses no more than minimal risk to the subjects.

Debriefing

In most circumstances, subjects have the right to full disclosure as soon as possible after participation in deception or incomplete disclosure research; a post-participation debriefing is usually required. The debriefing should disclose the full or true purpose of the research and allow the subject to indicate that their data not be used in the study. In exceptional circumstances, the full or true purpose of the research may not be revealed to the subjects until the data collection is complete. In such cases, subjects should not be exposed to undue stress or embarrassment and should have the right to full disclosure of the purpose of the study as soon as possible after the data have been collected.

There may be circumstances when debriefing is not appropriate. This may be when disclosure of the information may cause more distress to the subject than if not disclosed or when disclosure may bias the scientific integrity of the study.

Exempt Research

Know that if you are including deception or incomplete disclosure in certain studies that are determined to be exempt, a statement that the study involves deception or incomplete disclosure is required to be included in the exempt consent script. See TEMPLATE - HUA Exempt Human Research Consent Script (HRP-502c)

Use of Subject Pools

Some academic units at the University operate student subject pools that grant academic credit for participation in research. While the IRB has oversight for the research conducted in these pools, the administration of the pools is governed by the academic units.

- **Psychology Study Pool**
The Department of Psychology administers the Study Pool – an online pool of current research studies for volunteer subject participation. The Study Pool serves both to introduce students and members of the community to the process of psychological research and provide members of the department with subject participants for their research.
<http://studypool.psychology.fas.harvard.edu/>
- **Harvard Business School Computer Lab for Experimental Research**
The Computer Lab for Experimental Research (CLER) studies human behavior and decision-making by inviting participants from across the Boston area.
<http://www.hbs.edu/behave/Pages/default.aspx>
- **Harvard Digital Lab for the Social Sciences (DLABSS)**
The Harvard Digital Lab for the Social Sciences (DLABSS), or the Harvard Digital Lab, is an online experiments and survey community for social science research.
<http://dlabss.harvard.edu/>

Investigator Self-Experimentation

Harvard does not prohibit Investigator self-experimentation. However, as it would with any proposed research, the IRB will review each protocol and determine the appropriateness of the research. The IRB will consider as part of its review the level of self-experimentation and the potential risks and benefits to the Investigator as a research participant.

One of the main concerns of the IRB is that the enthusiasm for a novel concept may outweigh the Investigator's concern for his/her own welfare. For this reason, the IRB may require that a senior School official, Department Chair or even an IRB member obtain informed consent from the Investigator. The IRB also may institute additional safeguards for the research project, such as shorter review periods and monthly progress reports.

Policy on the Use of Harvard Names and Insignias

Harvard University has developed standards to regulate the use of the Harvard name by schools, units, and individuals within the University, and their use by individuals and institutions outside the University, as authorized.

The use regulated by the policy refers to the identification, statement, or display of Harvard's name in any way that may reasonably be interpreted as implying endorsement, approval or sponsorship by the University or one of its units. Nothing in the policy is intended to discourage fair use of Harvard's name to

comment on activities of the University or any of its units. More information on this policy may be found [here](#).

Lotteries and Raffles as a Form of Subject Compensation

According to Massachusetts State law, it is permissible to use a raffle or lottery as a method to compensate study subjects if the study subject does not pay to be in the raffle³ or lottery⁴.

³ *Raffles*: There are general Massachusetts statutes that restrict or prohibit the operation of a “raffle,” G.L. c. 271, § 7A, or a “lottery,” G.L. c. 271, § 7 (criminal statute), G. L. c. 137, § 1 (civil statute) defined as “an arrangement for raising money by the sale of tickets.” G.L. c. 271, § 7A. If a research study is using a raffle an incentive to participate rather than a means of fundraising, it is not a raffle under the statute. Guidelines published by the Attorney General’s Office also emphasize that charging money is what brings a raffle within the statute: “If no money is charged, anyone may legally operate a raffle, and businesses often do so for promotional purposes.” Frequently Asked Questions About Nonprofit Gaming Events, <https://www.mass.gov/service-details/frequently-asked-questions-about-nonprofit-gaming-events>.

⁴ *Lotteries*: A lottery has three elements: “payment of a price, a prize, and some element of chance.” *Mobil Oil Corp. v. Attorney General*, 361 Mass. 401, 406 (1972). Price must be “something of value” and requires more than “the formal or technical consideration, such as registering one’s name or attending at a certain place, which might be sufficient consideration to support a contract.” *Id.* (quoting *Commonwealth v. Heffner*, 304 Mass. 521, 523 (1939)). The emphasis in the case law on “price” as an element and the need for it to be “something of value” beyond consideration suggest that the price needs to be a monetary price. Certainly, the lottery cases in Massachusetts turn on the payment of money for a chance at a prize, and there is analogous support from the SJC in the context of identity fraud, where it held that the statutory term “anything of value” meant “that which can be exchanged for a financial payment” rather than “intangible things.” *Commonwealth v. Escobar*, 479 Mass. 225, 229 (2018). Therefore, if a research study does not charge the study subject to take part in the lottery, it is permissible.

Additional Resources for Data Management

Early in their project planning, investigators are encouraged to consider the lifecycle of their research data. Some specific tools prepared by the Harvard Catalyst Regulatory Foundations, Ethics, and Law Program are outlined below and additional resources are available [here](#).

Record Retention

Investigators must maintain Human Research records, including signed and dated consent documents, for at least seven years after closing the Human Research per Harvard University institutional requirements.

If the Human Research is sponsored, contact the sponsor before disposing of Human Research records as there may be specific policies related to record retention.

See the Harvard General Records Schedule here - <https://library.harvard.edu/services-tools/general-records-schedule>

Prompt Reporting Requirements

Report the information items that fall into one or more of the following categories to the IRB within 5 business days. Information that does not fall under any of the categories does not require reporting to the IRB. If unsure, contact [the IRB office](#).

1. Information that indicates a new or increased risk, or a new safety issue. For example:
 - a. New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk or uncovers a new risk that might adversely affect the safety of the participants or the conduct of the research.
 - b. An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk or describe a new risk.
 - c. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol.
 - d. Protocol violation that harmed participants or others or that indicates participants or others might be at increased risk of harm.
 - e. Complaint of a participant that indicates participants or others might be at increased risk of harm or at risk of a new harm.
 - f. Any changes significantly increasing the risk to participants and affecting the conduct of the research.
2. Harm experienced by a participant or other individual, which in the opinion of the investigator are **unexpected** and at least **possibly related** to the research procedures.
 - a. A harm is “**unexpected**” when its specificity or severity is inconsistent with risk information previously reviewed and approved by the IRB (via protocol, consent forms, etc.) in terms of nature, severity, frequency, and characteristics of the study population.
 - b. A harm is at least “**possibly related**” to the research procedures if in the opinion of the investigator, the research procedures more likely than not caused the event/harm.
3. Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.
4. Audit, inspection, or inquiry by a federal agency and any resulting reports (e.g., FDA Form 483.)
5. Written reports of study monitors.
6. Failure to follow the protocol due to the action or inaction of the investigator or research staff.
7. Breach of confidentiality.
 - a. Per Harvard Information Security policy, it is required that any researcher who experiences a security incident or breach involving research data levels 2-5 report the breach to the appropriate Harvard personnel. Detailed information about these reporting requirements can be [found on their website](#).
8. Change to the protocol without prior IRB review to eliminate an apparent immediate hazard to a participant.
9. Incarceration of a participant in a study not approved by the IRB to involve prisoners.
10. Complaint of a participant that cannot be resolved by the research team.
11. Premature suspension or termination of the protocol by the sponsor, investigator, or institution.
12. 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 participants.)

Additional Requirements for Studies Sponsored by a Common Rule Agency (45 CFR 46.116(h))

If the study is a clinical trial and supported by a Common Rule agency, one IRB-approved version of a consent form that has been used to enroll participants must be posted on a public federal website designated for posting such consent forms. The form must be posted after recruitment closes, and no later than 60 days after the last study visit. The consent form must have been used in enrolling participants to satisfy this provision.

At this time, two publicly available federal websites that will satisfy the consent form posting requirement, as required by the revised Common Rule, have been identified:

- ClinicalTrials.gov
- Docket folder on Regulations.gov (Docket ID: HHS-OPHS-2018-0021).

HHS and other Common Rule departments and agencies are developing instructions and other materials providing information to the regulated community about this posting requirement. More information may be found here - <https://www.hhs.gov/ohrp/regulations-and-policy/informed-consent-posting/index.html>

Additional federal websites that would satisfy the revised Common Rule's clinical trial consent form posting requirement might be identified in the future.

Additional Requirements: DHHS-Regulated Research¹

When a study subject withdraws from a study

- 1) When a participant decides to withdraw from a clinical trial, the investigator conducting the clinical trial should ask the participants to clarify whether the participant 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 participant previously gave consent may continue. The investigator should explain to the participant who wishes to withdraw the importance of obtaining follow-up safety data about the participant.
- 2) Investigators are allowed to retain and analyze already collected data relating to any participant who chooses to withdraw from a research study or whose participation is terminated by an investigator without regard to the participant'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 participant.
- 3) For research not subject to regulation and review by FDA, investigators, in consultation with the funding agency, can choose to honor a research participant's request that the investigator destroy the participant's data or that the investigator exclude the participant's data from any analysis.
- 4) When seeking the informed consent of participants, investigators should explain whether already collected data about the participants will be retained and analyzed even if the participants choose to withdraw from the research.
- 5) When research is covered by a certificate of confidentiality, researchers:
 - 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
 - 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.
 - May disclose information only when:
 - 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.
 - Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual.
 - Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
 - Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human participants in research.
 - Researchers must inform participants of the protections and limitations of certificates of confidentiality (see language in HRP-502 - TEMPLATE - HUA Adult Consent Form).
 - 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.

- If part of the study cohort was recruited prior to issuance of the Certificate, but are no longer actively 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.
- 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.

Single-IRB Studies

The Office for Human Research Protections expects that all sites located in the United States participating in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.

The following research is not subject to this provision:

- Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or
- Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the context.
- For research not subject to paragraph (b) of this section, an institution participating in a cooperative project may enter a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort.

¹ <http://www.hhs.gov/ohrp/policy/participantwithdrawal.html>

Additional Requirements: for FDA-Regulated Research

When a study subject withdraws from a study:²

- 1) The data collected on the participant to the point of withdrawal remains part of the study database and may not be removed.
- 2) An investigator may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection after their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant 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 participant's information.
- 3) If a participant 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 participant'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 if a participant 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 participant's medical record or other confidential records requiring the participant's consent.
- 4) An investigator may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

For FDA-regulated research involving investigational drugs:

- 1) Investigators must abide by FDA restrictions on promotion of investigational drugs:³
 - 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.
- 2) Follow FDA requirements for general responsibilities of investigators⁴
 - 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 participant 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 participant 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.
- 3) Follow FDA requirements for control of the investigational drug⁵
 - i) An investigator must administer the drug only to participants 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.
- a) Follow FDA requirements for investigator recordkeeping and record retention⁶

- (1) Disposition of drug: An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by participants.
- (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.
- b) Follow FDA requirements for investigator reports⁷
 - 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.
- c) Follow FDA requirements for assurance of IRB review⁸
 - 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 participants 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 participants.
- d) Follow FDA requirements for inspection of investigator's records and reports⁹
 - 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 participant 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.

- e) Follow FDA requirements for handling of controlled substances¹⁰
 - i) If the investigational drug is subject to the Controlled Substances Act, the investigator must take adequate precautions, including storage of the investigational 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.

For FDA-regulated research involving investigational devices:

- 1) General responsibilities of investigators.¹¹
 - a) 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 participants 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.
 - i) Specific responsibilities of investigators¹²
 - (a) Awaiting approval: An investigator may determine whether potential participants would be interested in participating in an investigation but must not request the written informed consent of any participant to participate, and must not allow any participant to participate before obtaining IRB and FDA approval.
 - (b) 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.
 - (c) Supervising device use: An investigator must permit an investigational device to be used only with participants under the investigator's supervision. An investigator must not supply an investigational device to any person not authorized to receive it.
 - (d) Financial disclosure:
 - (i) 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.
 - (ii) 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.
 - (e) 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.
 - (f) Maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:¹³
 - (i) All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
 - (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 participant'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. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each participant upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
 3. A record of the exposure of each participant 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.
- (g) Inspections¹⁴
 - (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.
 - (iii) Records identifying participants: An investigator must permit authorized FDA employees to inspect and copy records that identify participants, 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.
- (h) Prepare and submit the following complete, accurate, and timely reports¹⁵
 - (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 participant 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 participants, 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.

² <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf>

³ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.7>

⁴ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.60>

⁵ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61>

⁶ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62>

⁷ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64>

⁸ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.66>

⁹ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.68>

¹⁰ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.69>

¹¹ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.100>

¹² <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.110>

¹³ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.140>

¹⁴ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.145>

¹⁵ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.150>

Additional Requirements: Clinical Trials (ICH-GCP)

- 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 participants 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 Participants
 - 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 participant's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a participant when medical care is needed for inter-current illnesses of which the investigator becomes aware.
 - c) It is recommended that the investigator inform the participant's primary physician about the participant's participation in the trial if the participant has a primary physician and if the participant agrees to the primary physician being informed.
 - d) Although a participant 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 participant'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, participant recruitment procedures (e.g., advertisements), and any other written information to be provided to participants.

- 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 participant 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 hazard to trial participants, or when the changes involve 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 participants 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 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 participant, 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 participants. Investigators should maintain records that document adequately that the participants 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 participant and should check, at intervals appropriate for the trial, that each participant 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 Participants
- 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 participants.
 - b) The written informed consent form and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the participant's consent. Any revised written informed consent form, and written information should receive the IRB's approval opinion in advance of use. The participant or the participant's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant'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 participant 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 participant or the participant'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 participant or, if the participant is unable to provide informed consent, the participant'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 participant or the participant'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 participant or the participant's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether to participate in the trial. All questions about the trial should be answered to the satisfaction of the participant or the participant's legally acceptable representative.
 - h) Prior to a participant's participation in the trial, the written informed consent form should be signed and personally dated by the participant or by the participant's legally acceptable representative, and by the person who conducted the informed consent discussion.
 - i) If a participant 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 participants, is read and explained to the participant or the participant's legally acceptable representative, and after the participant or the participant's legally acceptable representative has orally consented to the participant'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 participant or the participant's legally acceptable representative, and that informed consent was freely given by the participant or the participant'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 participants 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 participant's responsibilities.
 - (vi) Those aspects of the trial that are experimental.
 - (vii) The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, fetus, or nursing infant.
 - (viii) The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
 - (ix) The alternative procedures or courses of treatment that may be available to the participant, and their important potential benefits and risks.
 - (x) The compensation and/or treatment available to the participant in the event of trial related injury.
 - (xi) The anticipated prorated payment, if any, to the participant for participating in the trial.
 - (xii) The anticipated expenses, if any, to the participant for participating in the trial.
 - (xiii) That the participant's participation in the trial is voluntary and that the participant may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the participant is otherwise entitled.
 - (xiv) That the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the participant's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the participant or the participant's legally acceptable representative is authorizing such access.
 - (xv) Those records identifying the participant 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 participant's identity will remain confidential.
 - (xvi) That the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the trial.
 - (xvii) The persons to contact for further information regarding the trial and the rights of trial participants, and whom to contact in the event of trial-related injury.
 - (xviii) The foreseeable circumstances and/or reasons under which the participant's participation in the trial may be terminated.

- (xix) The expected duration of the participant's participation in the trial.
 - (xx) The approximate number of participants involved in the trial.
 - k) Prior to participation in the trial, the participant or the participant'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 participants. During a participant's participation in the trial, the participant or the participant'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 participants.
 - l) When a clinical trial (therapeutic or non-therapeutic) includes participants who can only be enrolled in the trial with the consent of the participant's legally acceptable representative (e.g., minors, or patients with severe dementia), the participant should be informed about the trial to the extent compatible with the participant's understanding and, if capable, the participant 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 participant), should be conducted in participants who personally give consent and who sign and date the written informed consent form.
 - n) Non-therapeutic trials may be conducted in participants 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 participants who can give informed consent personally. b) The foreseeable risks to the participants are low. c) The negative impact on the participant'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 participants, 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. Participants 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 participant is not possible, the consent of the participant's legally acceptable representative, if present, should be requested. When prior consent of the participant is not possible, and the participant's legally acceptable representative is not available, enrolment of the participant 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 participant and to ensure compliance with applicable regulatory requirements. The participant or the participant'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 participants.

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 participants by unique code numbers assigned to the trial participants rather than by the participants' 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).

11) Premature Termination or Suspension of a Trial

- a) If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial participants, should assure appropriate therapy and follow-up for the participants, 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.
- 12) 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.

Additional Requirements: 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. Surveys performed on DOD personnel must be submitted, reviewed, and approved by the DOD Information Management Control Officer (IMCO) after the research protocol is reviewed and approved by the IRB. When a survey crosses DOD components, additional review is required. Consult with the Department of Defense funding component to coordinate this review.
10. 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
 - c. DoD Component security review
11. Data or information sent to a DOD component under a pledge of confidentiality for exclusively statistical purposes must be used exclusively for statistical purposes and may not be disclosed in identifiable form for any other purpose, except with the informed consent of the respondent.
12. When conducting multi-site research, a formal agreement between institutions is required to specify the roles and responsibilities of each party.
13. The following must be reported to the applicable DOD Component Office of Human Research Protections within 30 days:

- a. When significant changes to the research protocol are approved by the IRB or EC:
 - i. Changes to key investigators or institutions.
 - ii. Decreased benefit or increased risk to participants in greater than minimal risk research.
 - iii. Addition of vulnerable populations as participants.
 - iv. Addition of DOD-affiliated personnel as participants.
 - v. Change of reviewing IRB.
 - b. When the organization is notified by any federal body, state agency, official governing body of a Native American or Alaskan native tribe, other entity, or foreign government that any part of an HRPP is under investigation for cause involving a DOD-supported research protocol.
 - c. Any problems involving risks to participants or others, suspension or termination of IRB approval, or any serious or continuing noncompliance pertaining to DOD-supported human participant research.
 - d. The results of the IRB's continuing review, if required.
 - e. Change in status when a previously enrolled participant becomes pregnant, or when the researcher learns that a previously enrolled participant is pregnant, and the protocol was not reviewed and approved by the IRB in accordance with 45 CFR 46, Subpart B.
 - f. Change in status when a previously enrolled participant becomes a prisoner, and the protocol was not reviewed and approved by the IRB in accordance with 32 CFR 219, Subpart C.
 - g. Closure of a DOD-supported study.
14. For human participant research that would not otherwise be approved but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates, written approval from the DoD Office for Human Research Protections must be obtained through the DOD Component Office of Human Research Protections prior to research starting.
15. Other specific requirements of the Department of Defense research be found in the "Additional Requirements for Department of Defense (DOD) Research" section in the "WORKSHEET: Additional Federal Criteria (HRP-318)."

Additional Requirements: 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.

Additional Requirements: 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 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 "WORKSHEET: Additional Federal Criteria (HRP-318)."

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.
 - 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 "WORKSHEET: Additional Federal Criteria (HRP-318)."

Additional Requirements: 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 children¹⁶ involved in the research¹⁷ 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 “WORKSHEET: Additional Federal Criteria (HRP-318).”

¹⁶ 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.

¹⁷ 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.

Additional Requirements: 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 "WORKSHEET: Additional Federal Criteria (HRP-318)."

Additional Requirements: General Data Protection Requirements (GDPR)

1. Human Research involving personal data about individuals located in (but not necessarily citizens of) European Union member states, United Kingdom, Norway, Iceland, Liechtenstein, and Switzerland is subject to EU General Data Protection Regulations.
2. For all prospective Human Research subject to EU GDPR, contact your IRB of record who will consult with institutional legal counsel or your institution's 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 items 1 and 2 above.

Additional Requirements: NIH Funded Research, including Certificates of Confidentiality

As part of the NIH initiative to improve the quality and transparency of NIH supported research, a suite of initiatives has been launched. These initiatives include [dedicated funding opportunity announcements](#) for clinical trials, [Good Clinical Practice training](#), enhanced [registration and results reporting](#) on [ClinicalTrials.gov](#), and required use of [single IRBs for multi-site studies](#).

Definition of “Clinical Trial”

Determining whether these initiatives apply to your research largely depends on whether your research meets the NIH definition of a clinical trial. [The NIH definition of a clinical trial](#) is “a research study in which one or more human subjects are prospectively assigned to one or more [interventions](#) (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes”.

The NIH has also boiled down this definition to some basic questions researchers need to ask, and answer. These questions are:

1. Is your research funded by NIH?
2. Does the study involve human participants?
3. Are the participants prospectively assigned to an intervention?
4. Is the study designed to evaluate the effect of the intervention on the participants?
5. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?

If the answer to all five questions is yes, then NIH considers your research a clinical trial.

Good Clinical Practice (GCP) Training

All NIH-funded clinical investigators and clinical trial staff who are involved in the design, conduct, oversight, or management of clinical trials can learn about the requirement to be trained in Good Clinical Practice (GCP). Effective date: January 1, 2017.

The principles of Good Clinical Practice (GCP) help assure the safety, integrity, and quality of clinical trials by addressing elements related to the design, conduct, and reporting of clinical trials. GCP training describes the responsibilities of investigators, sponsors, monitors, and IRBs in the conduct of clinical trials.

GCP training aims to ensure that:

- The rights, safety, and well-being of human subjects are protected.
- Clinical trials are conducted in accordance with approved plans with rigor and integrity.
- Data derived from clinical trials are reliable.

Training in GCP may be achieved through the CITI online training module: GCP or the NIH online training module for social behavioral researchers. A paper based GCP training is also available to researchers who may not have access to the online version. The paper-based training may be found on the IRB [website](#).

Single IRB Policy for Multi-Site Research

Historically, in many multi-site studies, each site has its own IRB which conducts an independent review of studies involving human research participants. The use of a single IRB of record for multi-site studies that are conducting the same protocol will help streamline the IRB review process by eliminating the unnecessary repetition of those reviews across sites.

The goal of this policy is to enhance and streamline the IRB review process for multi-site research so that research can proceed as quickly as possible without compromising ethical principles and protections for human research participants.

Policy Guidelines & Implementation

For applications with due dates on or after January 25, 2018, and contract solicitations published on or after January 25, 2018, NIH expects that all sites participating in multi-site studies, which involve non-exempt human subjects research funded by the NIH, will use a single Institutional Review Board (sIRB) to conduct the ethical review required for the protection of human subjects.

This policy applies to the domestic sites of NIH-funded multi-site studies where each site will conduct the same protocol involving non-exempt human subjects research. It does not apply to career development, research training, or fellowship awards. Implementation of the NIH sIRB policy is expected to reduce unnecessary administrative burdens and systemic inefficiencies while maintaining appropriate human subjects protections.

Requirements for Registering & Reporting NIH-funded Clinical Trials in ClinicalTrials.gov

All NIH-funded clinical trials are expected to register and submit results information to [Clinicaltrials.gov](https://clinicaltrials.gov), as per the "[NIH Policy on Dissemination of NIH-Funded Clinical Trial Information](#)" for competing applications and contract proposals submitted on or after 1/18/2017. This *ClinicalTrials.gov* website provides resources for understanding and complying with this NIH policy and the federal regulations in Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) as implemented by 42 CFR Part 11 (Final Rule).

Policy for Issuing Certificates of Confidentiality (COCs)

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

CoCs are automatically granted, and the requirements of such must be complied with, whenever a NIH-funded activity falls within the scope of the policy. Investigators and institutions are responsible for determining when a NIH-funded activity falls within the scope of the policy.

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

- Human subjects research as defined in 45 CFR 46, including research determined to be exempt (except for exempt research when the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects),
- Research involving the collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request

for the biospecimen, and other available data sources could be used to deduce the identity of an individual,

- Research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, **regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained**, or
- Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual, as defined in subsection 301(d) of the Public Health Service Act.

Protections and Requirements

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

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

Additional Protections

1. Identifiable, sensitive information protected under a CoC, and all copies thereof, are immune from the legal process, and shall not, without the consent of the of the individual to whom the information pertains, be admissible as evidence or used in any action, suit, or other judicial, legislative, or administrative proceeding.
2. Identifiable, sensitive information that has been collected under a CoC, and all copies thereof, are protected for perpetuity.
3. Nothing in the rule (42 U.S.C. 241(d)) may be construed to limit the access of a subject to information about himself or herself collected during the research.
4. When consent is obtained, the consent should inform subjects that a CoC is in place and describe the protections and limitations.

NIH CoC Policy Determination

Office of Sponsored Programs (OSP) staff will, in consultation with the investigator(s) (or Program or Project Director, if applicable), determine if the NIH policy applies to any NIH-funded activity. The questions outlined in the NIH policy will be used to guide the analysis. When it has been determined that the NIH policy doesn't apply, investigators (or Program or Project Directors, if applicable) are responsible for consulting with OSP whenever they are proposing changes to the NIH- funded activity that may impact or change the analysis.

The NIH policy includes additional responsibilities and requirements for internal controls and for ensuring that recipients of identifiable, sensitive information protected by a CoC understand that they are also subject to the requirements of subsection 301(d) of the Public Health Service Act.

Application Procedures for non-NIH Research

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

If the research is conducting a sensitive research project that is covered by the Agency for Healthcare Research and Quality (AHRQ) confidentiality statute ([42 U.S.C. section 299c-3\(c\)](#)) or the Department of Justice (DoJ) confidentiality statute ([42 U.S.C. section 3789g](#)), then a CoC may not be needed.

If there is an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE), the sponsor can request a CoC from the FDA.

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

IRB Review

Investigators are responsible for clearly representing in the IRB submission that a CoC is in place (e.g., as terms and conditions of an NIH award), or that an application for CoC has been submitted. When the CoC application is in process or pending, the IRB may condition final approval upon its receipt.

For studies that are already underway, investigators must submit a Modification Request to the IRB, along with updated consent language (if applicable), when a CoC is applied for, or when automatically issued under the NIH policy. This includes NIH funded studies that were approved by the IRB prior to December 13, 2016, and for which a CoC was issued retroactively.

When reviewing research under a CoC, the IRB will evaluate whether the research protocol is consistent with the obligations to protect information and specimens under a CoC and whether the consent language, if applicable, discloses the CoC and appropriately describes the associated protections and limitations. Sample consent language is available in the informed consent template found in the ESTR library.

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

Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) required Congress to adopt a health information privacy law (the "Privacy Rule"), which was enacted in August 2002. The Privacy Rule, which became effective on April 14, 2003, is intended to protect the privacy of an individual's health care information when that information is held or handled, used, or disclosed, by an entity covered by HIPAA, which generally includes health care and social service providers, hospitals, nursing homes, insurance companies, managed care plans, and Medicare/Medicaid authorities, among others. The HIPAA Privacy Rule creates a federal "floor" of protection, with the understanding that states may create additional rights and protections. Massachusetts, among other states, has adopted more stringent rules in some areas, with which investigators should become familiar, depending on their areas of academic and research interest.

Effects of HIPAA on Research

HIPAA's definition of research is identical to that of the Common Rule: "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." Under HIPAA, "covered entities" must manage what is called "protected health information," or "PHI," in accordance with the Privacy Rule.

Harvard is a hybrid entity, meaning that only certain divisions (including the University Health Services and the Bureau of Study Counsel) must follow the HIPAA regulations. Thus, any research conducted by Harvard faculty and students and taking place at a "covered entity" and involving PHI, or drawing PHI from a "covered entity," must comply with the Privacy Rule.

Complying with HIPAA in Harvard Research

The HIPAA Privacy Rule's requirements must be respected by investigators in research protocols that involve handling PHI within, or drawing PHI from, an entity covered by HIPAA. For an investigator to handle PHI within, or draw Protected Health Information from, an entity covered by HIPAA, the investigator must do so under one of the following categories:

- A HIPAA authorization signed by the subject.
- A waiver of authorization granted by a Privacy Board, which may include, but is not limited to, the IRB of cognizant jurisdiction.
- Review preparatory to research, during which the investigator reviews PHI solely to assess the feasibility of a potential research protocol but does not retain any Protected Health Information from that review.
- Research on decedents' health information.
- A Limited Data Set.

De-Identified Information

The Privacy Rule does not apply to de-identified health information. Researchers therefore may access, use, and disclose de-identified information without any special permission or authorization under the HIPAA Privacy Rule.

De-identified information consists of information in one of two categories:

- a. A qualified statistician or expert has determined that the risk of re-identification is "very small" and must document the methods used to reach that conclusion; or

- b. Eighteen identifiers have been removed, and the covered entity does not have actual knowledge that the remaining information could be used to identify an individual. The eighteen identifiers of the individual, and of relatives, employers, or household members of the individual, that must be removed include:
- (1) Names,
 - (2) All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code in certain situations,
 - (3) All elements of date (except year) for dates directly related to an individual, including birth date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older,
 - (4) Telephone numbers,
 - (5) Fax numbers,
 - (6) Electronic mail addresses,
 - (7) Social security numbers,
 - (8) Medical record numbers,
 - (9) Health plan beneficiary numbers,
 - (10) Account numbers,
 - (11) Certificate/license numbers,
 - (12) Vehicle identifiers and serial numbers, including license plate numbers,
 - (13) Device identifiers and serial numbers,
 - (14) Web Universal Resource Locators (URLs),
 - (15) Internet Protocol (IP) address numbers,
 - (16) Biometric identifiers, including finger and voice prints,
 - (17) Full face photographic images and any comparable images, and
 - (18) Any other unique identifying number, characteristic, or code.

Using PHI in Human Subjects Research: Complying with HIPAA

When planning or reviewing a research protocol that involves identifiable information relating to an individual's health or mental health condition, or payment for treatment of that condition by a third party ("protected health information," or "PHI"), an investigator, IRB staff, or IRB member must consider whether any entity from which such information is drawn or in which it is handled is covered under the HIPAA Privacy Rule. If such an entity is covered by the HIPAA Privacy Rule, then the investigator may only handle PHI within the entity, or draw PHI from the entity, under (1) appropriate, signed subject authorizations, (2) a Limited Data Set, or (3) waiver of authorization granted by a Privacy Board. The research protocol must include, either as part of the informed consent form, or as a separate document to be signed by each subject, a HIPAA authorization, setting forth a description of the information to be used or disclosed, the parties to whom the information is to be disclosed and by whom it will be used, the purpose of the disclosure, the time period within which the authorization will be effective, which may be the duration of the research study itself, and the subject's right to revoke the authorization. See the section "Documenting HIPAA Authorization" for additional considerations.

Limited Data Sets

Without obtaining subject authorizations, the investigator may gain access to and use for research purposes a limited category of PHI, known as a Limited Data Set, from which all "direct" identifiers listed above must have been removed, except for dates and geographic information without street address.

To obtain access to a Limited Data Set, the investigator must assure that a Data Use Agreement (DUA) be agreed to between the investigator's institution(s) and the HIPAA-covered entity. A DUA describes the permitted uses and disclosures of the information received and prohibits any attempt to re-identify or contact the individuals.

A DUA must be reviewed and approved by the IRB, as part of the research protocol, the School Security Officer, and the Sponsored Programs Administrator of cognizant jurisdiction, before the DUA may be accepted and signed by the Office of Sponsored Programs. No researcher may enter in to or accept a DUA without such review and approval of their cognizant sponsored programs office.

Waiver by IRB or Privacy Board of HIPAA Authorization Requirement

Without obtaining subject authorizations or using a Limited Data Set, the investigator may gain access to and use for research purposes PHI by obtaining from a Privacy Board a waiver or alteration of the authorization requirement.

An IRB may serve as a Privacy Board, and any of the Harvard IRBs may serve in this capacity.

For the IRB to alter or waive authorization, the HIPAA Privacy Rule requires that the IRB find that:

- a) Disclosure of the PHI involves no more than minimal risk.
- b) The waiver will not adversely affect the privacy rights or welfare of the subject.
- c) The research could not practicably be carried out without the waiver.
- d) The research could not practicably be carried out without access to the PHI.
- e) The privacy risks are reasonable in relation to the information to be gained.
- f) There is an adequate plan to protect the identifiers from improper use and disclosure.
- g) There is an adequate plan to destroy the identifiers at the earliest opportunity.
- h) There is written assurance that the PHI will not be further disclosed, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted by the HIPAA Privacy Rule.

Compliance by Harvard Investigators with the Privacy Policies of Research Sites and Collaborating Institutions

Each Harvard Investigator is required to comply with all applicable privacy and security policies of the HIPAA-covered entity in which that investigator, as part of a research protocol, is handling PHI or from which the investigator is drawing PHI. It is the responsibility of each investigator when he or she is conducting research within, collaborating with, or seeking cooperation from, a HIPAA-covered entity to familiarize himself or herself with and to comply with the privacy policies of those entities. In general, should take care to ask about privacy policies and compliance rules when they deal with health care providers, social service agencies, mental health and substance abuse treatment facilities, counseling services, health insurers, managed care providers and government benefits offices, including those administering Medicare and Medicaid.

Massachusetts Law

Massachusetts Law Involving Fetuses in Research

Experimentation on human fetuses is also regulated under Massachusetts law, MGL Chapter 112C, § 12J(a), which states in part:

- I. No person shall use any live human fetus whether before or after expulsion from its mother's womb, for scientific, laboratory, research, or other kind of experimentation. This section shall not prohibit procedures incident to the study of a human fetus while it is in its mother's womb, provided that in the best medical judgment of the physician, made at the time of the study, said procedures do not substantially jeopardize the life or health of the fetus, and provided said fetus is not the subject of a planned abortion. This section shall not prohibit or regulate diagnostic or remedial procedures the purpose of which is to determine the life or health of the fetus involved or to preserve the life or health of the fetus involved or the mother involved.
- II. No experimentation may knowingly be performed upon a dead fetus unless the consent of the mother has first been obtained, provided, however, that such consent shall not be required in the case of a routine pathological study.
- III. No person shall perform or offer to perform an abortion where part or all of the consideration for said performance is that the fetal remains may be used for experimentation or other kind of research or study.
- IV. No person shall knowingly sell, transfer, distribute or give away any fetus for a use which is in violation of the provisions of this section.

For the purposes of this section, a fetus is a live fetus when, in the best medical judgment of a physician, it shows evidence of life as determined by the same medical standards as are used in determining evidence of life in a spontaneously aborted fetus at approximately the same stage of gestational development... [Also,] for the purposes of this section, "fetus" shall include a neonate and an embryo but shall exclude a pre-implantation embryo or parthenote as defined in section 2 of chapter 111L and obtained in accordance with said chapter 111L.

The Massachusetts statute includes criminal penalties, but states that those who have performed a procedure that allegedly violates the statute's provisions will not be held liable if: (i) the procedure received the written approval of a duly appointed IRB; and (ii) at the time the procedure was performed, there was not an outstanding court judgment that the procedure violated the statute. The IRB's written approval must state specifically that the procedure does not violate the provisions of the statute and must set forth a reasonable basis for this conclusion. The written approval must contain a detailed description of the procedure and must be maintained as a "permanent record" of the IRB or the institution for which it acts. A copy of the written approval must be filed with the office of the District Attorney for the county in which the IRB's institution is located and shall be available for public inspection at all times. MGL Chapter 112C, § 12J(a)(V-VII). IRB members are themselves immune from liability under the statute if they acted in good faith in concluding that the procedure was lawful. MGL Chapter 112C, § 12J(a)(VI).

Embryonic Stem Cell Research

Chapter 27 of the Acts of 2005, referred to hereinafter as the "MA Stem Cell Law" which, among other things, authorized with some restrictions the use of human Embryonic Stem Cells (hESCs) in research, also imposed certain IRB approval requirements on institutions conducting such research. Activities that the law specifically authorizes include "research and clinical applications involving the derivation and use of [hESCs], including somatic cell nuclear transfer, human adult stem cells from any source, umbilical cord cells, parthenotes and placental cells". The MA Stem Cell Law also specifically prohibits certain research activities, including those involving "human reproductive cloning," and those involving the creation of an

embryo by the means of fertilization “solely for the purpose of donating the embryo for research”. The law also requires that all research “involving the derivation of human embryonic stem cells” must be reviewed and approved by a duly constituted IRB, regardless of whether IRB approval may or may not also be required under federal law, and to report such projects to the Massachusetts Department of Public Health (DPH) on an annual basis. The statute describes the IRB’s required role as follows:

Research involving the derivation of human embryonic stem cells through the use of human genetic material, including somatic cell nuclear transfer, parthenogenesis and other asexual means . . . shall only be conducted upon the written approval of a duly authorized institutional review board. The written approval of the institutional review board shall include a detailed description of the research, experimentation, or study to be conducted and a detailed description of the research or a copy of the protocol, all of which shall be maintained as a permanent record by the board or by the hospital or institution for which the board acts.

Research involving the derivation of embryonic stem cells must be reviewed by the IRB. All research with embryonic stem cells must also be reviewed by the Embryonic Stem Cell Research Oversight (ESCRO) Committee.

Child Abuse Reporting/Mandated Reporter

Research proposals involving children ordinarily must include a plan for reporting suspected abuse of children to the Massachusetts Department of Children and Families (DCF, formerly the Department of Social Services). Additionally, consent and assent forms for children and parents ordinarily must include a statement that suspected child abuse or neglect may be reported to DCF.

Certain people, as a function of their professions or provisions, are deemed to be mandated reporters. Under Massachusetts law, (MGL Chapter 119, § 51A), mandated reporters include any: “physician, medical intern, hospital personnel engaged in the examination, care or treatment of persons, medical examiner, psychologist, emergency medical technician, dentist, nurse, chiropractor, podiatrist, optometrist, osteopath, public or private school teacher, educational administrator, guidance or family counselor, day care worker or any person paid to care for or work with a child in any public or private facility, or home or program funded by the commonwealth or licensed pursuant to the provisions of chapter 28 A, which provides day care or residential services to children or which provides the services of child care resource and referral agencies, voucher management agencies, family day care systems and child care food programs, probation officer, clerk/magistrate of the district courts, parole officer, social worker, foster parent, firefighter or policeman, licenser of the office of child care services or any successor agency, school attendance officer, allied mental health and human services professional as licensed pursuant to the provisions of section one hundred and sixty-five of chapter one hundred and twelve, drug and alcoholism counselor, psychiatrist, and clinical social worker, priest, rabbi, clergy member, ordained or licensed minister, leader of any church or religious body, accredited Christian Science practitioner, person performing official duties on behalf of a church or religious body that are recognized as the duties of a priest, rabbi, clergy, ordained or licensed minister, leader of any church or religious body, or accredited Christian Science practitioner, or person employed by a church or religious body to supervise, educate, coach, train or counsel a child on a regular basis.”

Reports must be made where the mandated reporter, in his or her professional capacity, has reasonable cause to believe that a child under the age of 18 is suffering physical or emotional injury resulting from abuse inflicted upon him or her which causes harm or substantial risk of harm to the child's health or welfare, including sexual abuse, or from neglect, including malnutrition, or who is determined to be physically dependent upon an addictive drug at birth. A mandated reporter must immediately make a verbal report to DCF and must make a written report within 48 hours.

Elder Abuse/Mandated Reporter

Analogous to the requirement for instances of child abuse, Massachusetts has a mandated report provision for elder abuse. Certain people, as a function of their professions or provisions, are deemed to be mandated reporters. Under Massachusetts law, ([MGL Chapter 19A, Section 15](#)), mandated reporters include any: “Any physician, physician assistant, medical intern, dentist, nurse, family counselor, probation officer, social worker, policeman, firefighter, emergency medical technician, animal control officer, licensed psychologist, coroner, registered physical therapist, registered occupational therapist, osteopath, podiatrist, director of a council on aging, outreach worker employed by a council on aging, executive director of a licensed home health agency or executive director of a homemaker service agency or manager of an assisted living residence who has reasonable cause to believe that an elderly person is suffering from or has died as a result of abuse, shall immediately make a verbal report of such information or cause a report to be made to the department or its designated agency and shall within forty-eight hours make a written report to the department or its designated agency.”

Confidential Birth Information

MGL Chapter 111, § 67E requires physicians to report diagnoses of congenital anomalies and birth defects to the Department of Public Health (DPH). 105 CMR § 302.070 provides a mechanism by which researchers may access and use this confidential birth information. Researchers must submit an application that includes: the purpose and design of the study, its public health benefits, its relationship to the DPH’s goal of reducing morbidity and mortality, the data requested, a justification for the data request, a description of the extent to which the study involves “contact with the data subjects,” a description of the extent to which informed consent will be obtained from the participants, information regarding IRB review and approval of the project, proposed measures to preserve the confidentiality of the data, and the names and titles of all persons who will access the data requested. Investigators also must submit to DPH copies of consent forms, questionnaires or telephone interview scripts, their filings with an IRB, the IRB’s written determinations, and their CVs (105 CMR § 302.070(B) and (C)). Investigators’ use of confidential birth information released by the DPH is subject to the terms and restrictions set forth in 105 CMR § 302.080. Thus, in addition to following IRB policies, investigators also must comply with DPH IRB requirements.

Massachusetts Department of Mental Health

Research outside the jurisdiction of the Massachusetts Department of Mental Health:

Research involving potential participants who are under the jurisdiction of the Massachusetts Department of Mental Health (DMH) is governed by state regulation as described below. Even where the DMH regulations do not apply, however, the IRB review process incorporates special protections when people who have a limited capacity to understand research or research concepts are potential research participants.

Research within the Jurisdiction of the DMH:

Under 104 C.M.R. § 31.00, et. seq., DMH has the jurisdiction to review and approve any human research “related to” the Department, its facilities, or programs in which its “clients” are proposed participants. Researchers whose research proposals fall within the DMH’s jurisdiction must submit them to the DMH IRB, the Central Office Research Review Committee (CORRC), for approval.

DMH regulations (104 CMR § 31.01 et seq.) describe information researchers must submit to the agency concerning such studies, and the standards governing review and approval of studies by the agency, which are very similar to the standards of review utilized by IRBs operating under the 45 CFR § 46. However, the regulations impose a few additional content requirements for informed consent forms for these studies, beyond those included in the 45 CFR § 46, such as: statements describing “the basis for selection of the subject”, and a statement indicating that participation in the study is not required of participants to obtain

continued access to DMH services. Please see DMH regulations (available through <http://www.mass.gov/dmh>) for specific information.

Principal Investigator Responsibilities and ESTR Assurance Statement

As the Principal Investigator of this research, I certify the following:

1. I will not start Human Research activities until I have obtained all other required institutional approvals, including local ethics committee review for international sites; and approvals of departments or divisions that require approval prior to commencing research that involves their resources.
2. I will ensure that there are adequate resources to carry out the research safely, e.g. sufficient investigator time, equipment, and spacing.
3. I will 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.
4. I will update the IRB office with any changes to the list of study personnel.
5. I will personally conduct or supervise the Human Research.
 - a. Conduct the Human Research in accordance with the relevant current protocol as approved by the IRB.
 - 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. Not modify the Human Research without prior IRB review and approval (when required) unless necessary to eliminate apparent immediate hazards to participants.
 - d. Protect the rights, safety, and welfare of participants involved in the research.
6. I will submit to the IRB in a timely manner:
 - a. Proposed modifications to the previously-approved Human Research, when applicable.
 - b. A continuing review application (to avoid a lapse in approval), when applicable.
 - c. A continuing review application when the Human Research is closed, when applicable.
7. I will submit to the IRB any reportable new information within five business days.
8. I will personally submit and ensure that Research Staff submit an updated Financial Interest Disclosure within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.
9. I will not accept or provide payments to professionals in exchange for referrals of potential participants ("finder's fees").
10. I will not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments").
11. I will comply with applicable federal and state regulations, ethical guidelines, and Harvard Institutional policies, including (but not limited to) the Institutional conflict of interest, DUA Policy and Guidance, and Harvard Research Data Security Policy.
 - a. To protect information, I must have a strong password for each of my Harvard accounts; including a log in for idle sessions and lock out screen for multiple failed log-in attempts. Log in information will not be shared.
 - b. Any system storing information qualifying as Level 2 or 'non-sensitive' by the IRB must have updated security patches and virus protection. These systems will only be accessed by those with a current and IRB approved research role.
12. I will maintain adequate and accurate records and make these records available to the IRB or QA/QI Program for review.
13. I will ensure that IRB-approved study documents, including recruitment materials, consent forms, and study tools, are accurately translated in a language understandable to study participants. If applicable, I will submit locally-approved versions of these materials to the IRB when they become available.

Provostial Review Process

The Provostial Review is a review of research proposals conducted by the Provost's Office at Harvard University. The Provostial Review process is designed to review projects that pose management challenges and/or reputational risks beyond those routinely covered by the IRB or other review committees. The Provostial Review process also considers the question of whether the proposed research project is within the research and academic mission of the University, as opposed to advocacy or consultancy.

There are ten criteria that can trigger a Provostial Review. These criteria are described under the "Criteria and Procedures for Provost's Review of New Projects or Grants" on the Office of the Vice Provost for Research (OVPR) website: <https://research.harvard.edu/2021/02/17/provost-criteria-for-review/>.

The Provostial Review is undertaken by a team comprised of staff from OVPR, the Office of Sponsored Programs (OSP), and the Office of the Vice Provost for International Affairs. The Provostial Review team relies on the IRB to address human subject protection risks (e.g., risks-benefits to the participants, adequacy of consent forms, protection of privacy, etc.) and focuses its review on other risks. In general, the Provostial Review team reviews the same documents submitted to the IRB (e.g., the protocol, Informed Consents, and Questionnaires). Therefore, the protocol should be complete and detailed, with a full explanation of the researcher's planned study design to assist with, and accelerate, both the IRB and the Provostial Review Process. The protocol should clearly describe the potential areas of risk in the planned project and provide plans to mitigate those risks.

The following provides a summary of the most common risks evaluated in the Provostial Review; researchers should carefully consider if their projects include any of these risks, and if so, provide details on their plans to manage those risk areas.

Note: While the next sections will be focused on international research projects, the risks below are not limited to locations outside the U.S. Researchers planning projects in the United States should also consider these risks and how to mitigate them.

1) Risk to the researcher

When planning an international research project, please consider the following:

- a) Check the GSS risk ratings site to determine if the region of interest is rated as high or elevated risk.
 - i) If the region of interest is rated as high-risk, researchers cannot conduct research there. The researcher must select another region for the project.
 - ii) For students, if the region is rated as elevated risk, they should follow the steps described under "Restricted Travel" on the Harvard College International Travel Policy website. When submitting their protocol and related materials to IRB, the researcher should include their correspondence from GSS allowing them to conduct research in the region.
- b) When preparing the protocol, the researcher should describe how they plan to protect their safety while working internationally. These plans could include checking in with the local U.S. embassy, working with local universities or non-governmental organizations (NGOs) to help navigate the cultural norms, and/or arranging safe meeting places when conducting interviews with research participants.

- c) Researchers should also provide details of their preparation for working in the area, including their fluency in the local language and any past travel or work that has helped them prepare for this project.

Example: A student plans to conduct a research project in a region designated as elevated risk by GSS. In their initial protocol, the student does not include any details on their preparation for the travel; there is no mention of any local connections the student has made, no information on the familiarity of the student with the country, or how the student would choose a safe location for interviews. This lack of information raises concerns that the student has not sufficiently considered the potential risks in the region, and how they would protect themselves. The review will certainly yield several key questions that would, at the minimum, delay the approval of the project.

How to Fix: The protocol should provide details about the student's efforts to prepare for this project, including discussions with GSS, contacting local NGOs, working with Harvard faculty who have experience in the region, and describing how they plan to setup a safe space for interviews. With this additional information, the Provostial Review team will be able to approve the work.

2) Reputational risks

The Provostial Review team assesses research projects not just about the research design, but also on the impact the project will have on the reputation of the participants, researchers, and the University. Generally, researchers should consider if anyone involved in the project, or the University itself, is at risk of reputational harm from the work. If there is a possibility of reputational risk, the researcher should explain why the risk is necessary, how they will mitigate that risk, and why other options for conducting the research are not feasible.

Example: A researcher's planned project includes the use of deception to get responses from political officials, with no plans to debrief the officials before the results are published. The results of the work could attract media attention and could potentially embarrass the officials and hurt their reputation in the community.

How to Fix: The Provostial Review team would request that a debriefing email be sent to the participating officials once data collection was complete, explaining the research project and notifying them that the results would be published. Including such details would assist with expediting the review process.

3) Risk to populations involved

When conducting research in an international location, the researcher should carefully consider the cultural and social norms in the region of interest. Research conducted with marginalized populations, or projects that ask questions about socially unacceptable or illegal behavior, could lead to negative consequences for the participants. In the research protocol, the researcher should explain how they will protect the participants, including plans to secure the data and to receive local IRB and/or community approvals in the region of interest. Additionally, if the research will be conducted in any places of business or in educational facilities, etc., the researcher should provide a letter from the business owner or principal, etc., confirming that they have gotten permission to conduct the project on the premises.

Example: A research project includes plans to interview sex workers in Uganda. Soliciting to sell sex is illegal in Uganda, so the participants could face risks associated with their participation.

How to Fix: In the protocol, the Principal Investigator (PI) should note if past research work has been conducted among sex workers in Uganda and provide plans to get approval from the local IRB and from

community leaders in the area to conduct the research. A data security plan should also be provided, to ensure the participants' responses remain confidential.

4) Aligned with the mission of the University

Research conducted through Harvard University must fall within Harvard's mission as a research university. Harvard University does not engage in advocacy, and while individual Harvard researchers may well be advocates for various causes, including those informed by their research, the aim of an academic research project must be to answer a research question objectively. Objectivity is lost if the aim of a research project is to produce a particular result or achieve a pre-determined policy outcome.

Example: A project is proposed to provide a voice for homeless youth in San Francisco, with a stated goal of getting a youth homeless shelter funded based on the results of the project. This proposed project doesn't include a research question, a systematic investigation, or a plan to contribute to the body of research, but instead is planned solely to advocate for the population of interest.

How to Fix: The researcher could propose a project that examines the age distribution among the homeless population in San Francisco, with plans to interview homeless youth in the city. The results would be published in academic journals or presented at conferences. This project may lead to greater attention paid to the plight of homeless youth, but it is not the primary goal of the work.

5) Is it research?

Harvard University researchers receive funding and support from a variety of sources, both within and outside the University. Sometimes, researchers at Harvard are offered funding to complete a project on behalf of a government entity, NGO, or corporation. In those cases, the researcher must consider if the project is still research, or if they are working as consultants, providing services to the organization or government providing the funding. If the Provostial Review team determines that the proposal is for a consulting project, then the researcher will need to redraft their protocol to fit within the research mission of Harvard University. For more information, please see the Harvard University policy on consulting or related service agreements: <http://osp.finance.harvard.edu/consulting-or-related-service-agreements>.

Example: A researcher at the Kennedy School of Government is provided funding by a foreign government to implement a new healthcare policy, with plans to provide a report back to the government funders on the success of the implementation.

How to Fix: The researcher could plan to systematically collect data regarding the implementation of the new policy and publish the results of that work in an academic journal. The results of this project could inform future work on how to best implement healthcare policies in the region of interest.

Resources:

- Office of the Vice Provost for Research (OVPR): <https://research.harvard.edu/>
 - Provost Review Criteria: <https://research.harvard.edu/2021/02/17/provost-criteria-for-review/>
 - OVPR Contact Information: <https://research.harvard.edu/about/>
- Global Support Services (GSS): <https://www.globalsupport.harvard.edu/>
 - GSS Risk Ratings: <https://www.globalsupport.harvard.edu/travel/risk-ratings>
 - Harvard College International Travel Policy: <https://www.globalsupport.harvard.edu/travel-tools/forms-policies/harvard-college>

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).

Tools and Resources for Developing Study-Specific Emergency/Disaster Risk Mitigation Plans for Ongoing Research

Review “HRP-108 - FLOWCHART - Study-Specific Emergency-Disaster Risk Mitigation Planning” and “HRP-351 - WORKSHEET - Protocol-Specific Emergency-Disaster Risk Mitigation Plan” for general guidance on developing study-specific risk mitigation plans.

Voluntary Holds on Human Research Activities

Investigators may voluntarily elect to place all recruitment, enrollment, and research procedures on temporary hold during emergency/disaster scenarios if doing so will better ensure the safety of research subjects and would not create any additional risks to the safety and welfare of research subjects. Such voluntary holds on research activity do not require IRB notification or review.

Submitting Study-Specific Emergency/Disaster Risk Mitigation Plans for IRB Review

If immediate modification of the research is necessary to eliminate an apparent immediate hazard to a subject, take action and notify the IRB within five business days following the standard pathway to submit reportable new information.

For all other study modifications made to ensure the ongoing safety of research subjects during emergency/disaster scenarios, submit a study modification and all relevant new or modified study materials to the IRB.

Other Reportable New Information Considerations During Emergency/ Disaster Scenarios

The IRB's list of reportable events includes two items for which additional clarification and guidance may be helpful during emergency/disaster scenarios:

- “Failure to follow the protocol due to the action or inaction of the investigator or research staff.”
Emphasis on action or inaction of the investigator or research staff has been added because this requirement does not include action or inaction of the research subject. For example, study teams may notice an increase in the number of subjects who do not arrive for scheduled research visits under emergency/disaster circumstances. Failure of a research participant to appear for a scheduled research visit is not noncompliance due to action or inaction by the investigator or research staff, and therefore does not require reporting to the IRB.
- “Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.” During emergency/disaster scenarios, there will be cases where there is sufficient time to receive IRB approval of any proposed modifications to previously approved research, and in such cases, researchers should follow standard IRB procedures for submitting modifications. However, there will be other cases where investigators must make more immediate changes to the protocol or investigational plan to minimize or eliminate immediate hazards or to protect the life and well-being of research participants. Such changes may be implemented without IRB approval but are required to be reported to the IRB within five business days afterward in accordance with IRB policies and procedures for submitting reportable new information.

Useful Resources

Harvard University

- Harvard University Area IRB office - <http://cuhs.harvard.edu>
- ESTR (Electronic Submission, Tracking, and Reporting) Support website <http://estrsupport.fss.harvard.edu/>
- Harvard Office for the Vice Provost of Research - <https://research.harvard.edu/>

Federal

- Department of Health and Human Services (HHS) - <http://www.hhs.gov>
- Centers for Disease Control and Prevention (CDC) - <http://www.cdc.gov>
 - *Human Participant Protection in CDC Research* - <https://www.cdc.gov/os/integrity/hrpo/index.htm>
- National Institutes of Health (NIH) - <http://grants.nih.gov/grants/policy/hs/index.htm> Certificate of Confidentiality Kiosk - <http://grants.nih.gov/grants/policy/coc/>
- Office of Civil Rights (HIPAA policy) - <http://www.hhs.gov/ocr/privacy/index.html>
- Office of Human Research Protection (OHRP) - <http://www.hhs.gov/ohrp/>
 - *Regulations* - <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>
 - *Decision Charts* - <http://www.hhs.gov/ohrp/policy/index.html#decision>
 - *Guidance and Policy* - <http://www.hhs.gov/ohrp/policy/>
 - *FAQs* - <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/index.html>
 - *International Research Policies* - <http://www.hhs.gov/ohrp/international/index.html#NatIPol>
- Food and Drug Administration (FDA) - <http://www.fda.gov/>
- Department of Education - <http://www.ed.gov/>
 - *Human Subjects Research* - <http://www.ed.gov/about/offices/list/ocfo/humansub.html>
 - *Family Policy and Compliance Office (FERPA and PPRA)*
<https://www.ed.gov/category/keyword/family-policy-compliance-office-fpco>
- National Science Foundation - <http://www.nsf.gov>
 - *FAQs on Interpreting the Common Rule for the Protection of Human Subjects for Social and Behavioral Research* - <http://www.nsf.gov/bfa/dias/policy/hsfaqs.jsp>
- National Science and Technology Council Report on Expedited Review of Social and Behavioral Research Activities - <http://www.ostp.gov/galleries/NSTC%20Reports/Expedited%20Review%20For%20Web.pdf>

Discipline-Specific Resources

- American Anthropological Association (AAA) - <http://www.aaanet.org>
- American Educational Research Association (AERA) - <http://www.aera.org>
- American Psychological Association (APA) – <https://www.apa.org/ethics/code>
- American Public Health Association (APHA) - <http://www.apha.org>
- American Sociologic Association (ASA) - <http://www.asanet.org>
- National Association of Social Workers – <https://www.socialworkers.org/About/Ethics>

IRB Submission Assistance

For IRB Submission Assistance and/or consultation, contact [the IRB office](#). They are available to answer questions regarding submission requirements and assist in completing forms, responding to IRB revisions and requests for additional information, and assist in drafting recruitment and consent materials.

If you are experiencing any technical problems with ESTR, contact the ESTR Help Desk at ESTRhelp@harvard.edu. ESTR-specific assistance, including job aid visuals and how-to instructions, can be found on the ESTR Support Website at <http://estrsupport.fss.harvard.edu/>.

Questions

This document and the policies and procedures for the Harvard University Area Research Protection Program are available on the [Harvard University Area IRB website](#).

If an investigator or member of the research team has any questions or concerns about the Human Research Protection Program, contact:

Jonathan M. Girard
Director, Human Research Protection Program
Smith Campus Center
1350 Massachusetts Ave, Suite 645
Cambridge, MA 02138
Office Phone: 617-496-2146
jonathan_girard@harvard.edu

If you have questions, concerns, complaints, allegations of undue influence, allegations or findings of non-compliance, or input regarding the Human Research Protection Program that cannot be addressed by contacting the HUA IRB office, follow the directions in the "HUMAN RESEARCH PROTECTION PROGRAM PLAN (HRP-101)" under "Reporting and Management of Concerns."