

INVESTIGATOR MANUAL

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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 Longwood Campus (HLC) Human Research Protection Program (HRPP), which serves the Harvard Longwood Medical Area (LMA) Schools (Harvard Medical School, Harvard School of Dental Medicine, and Harvard T.H. Chan School of Public Health). Additionally, this manual serves as a guide for the research community when preparing an IRB submission.

Key Definitions and Terms

ESTR

Electronic Submission, Tracking & Reporting (ESTR) is the IRB's online submission system, available at irb.harvard.edu. Users must have an active HUID/[HarvardKey](#) to access ESTR. ESTR-specific reference materials can be found on the [ESTR support website](#). A [Study Submission Guide](#) is available to guide investigators and study staff through the ESTR 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. The committee meets this mandate by reviewing and overseeing human research activities. The Harvard T.H. Chan School of Public Health Office of Regulatory Affairs and Research Compliance provides administrative support to the two IRB panels: Harvard Faculty of Medicine (HMS/HSDM) and Harvard T.H. Chan School of Public Health (Harvard Chan School). Collectively, these two panels are referred to as the Harvard Longwood Campus (HLC) IRBs.

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 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.

The HIPAA Privacy Rule establishes conditions under which covered entities can use or disclose PHI for many purposes, including for research. Specifically, the Rule establishes the right of an individual, such as a research subject, to authorize a covered entity to use and disclose his/her PHI for research purposes. This requirement is in addition to the informed consent to participate in research required under the [HHS Protection of Human Subjects Regulations](#) and other applicable Federal and State laws. See [Documenting HIPAA Authorization](#) for additional considerations.

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

A complete list of PHI, as defined by the HIPAA Privacy Rule §164.514(a)(2)(i), [here](#).

Human Research

The HLC IRBs follow the regulatory definitions of “Human Subjects Research,” which are described in the document “HUMAN RESEARCH PROTECTION PROGRAM PLAN.” To determine whether proposed activities constitute the DHHS or FDA definitions of Human Subjects Research, investigators can refer to “WORKSHEET: Human Research Determination” or [OHRP Decision Charts](#). If requested, the HLC 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 Longwood Campus Human Research Protection Program (HRPP) is a comprehensive system to ensure the protection of the rights and welfare of participants in Human Research. The HLC includes the Harvard Medical School, Harvard School of Dental Medicine, and Harvard T.H. Chan School of Public Health. The HRPP is comprised of institutional leadership; Office of Human Research Administration, which includes the Institutional Review Board (IRB) and Quality Improvement Program (QIP); investigators and their study staff; Department Chairs, and other relevant offices. The document “HUMAN RESEARCH PROTECTION PROGRAM PLAN” describes the 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

All Human Subjects Research must undergo review by the HLC IRB. Activities that do not meet the definition of Human Research do not require review and approval and do not need to be submitted to the IRB unless there is a question regarding whether the activity is Human Research. Refer to “WORKSHEET: Human Research Determination” or [OHRP Decision Charts](#) for guidance on whether the proposed activities constitute Human Research. Contact your [IRB Review Specialist](#) in cases where it is unclear whether an activity is Human Research.

To obtain a formal “Not Human Subjects Research” determination from the IRB, see [Submitting an Application in ESTR](#).

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 HLC IRB prior to implementation.. The IRB uses “WORKSHEET: Exemption” when determining whether a particular study meets one or more exempt criteria.

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, the Principal Investigator must obtain it before any Human Research activities are conducted locally. If assistance with applicable local requirements is needed, contact your [IRB Review Specialist](#).

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 “in-house”, rather than by the convened IRB. Refer to “WORKSHEET: Expedited Review” for information on applicable categories of research. Protocols eligible for review using the expedited procedure are reviewed on a rolling basis. Expedited Continuing Review applications should be submitted 21 days prior to the study’s expiration date.

Convened IRB Review (“Full Board”)

Non-exempt Human Research that does not qualify for expedited review must be reviewed by the convened IRB. The convened IRB meeting schedule and submission deadlines are available [here](#).

In general, investigators can expect to have the IRB associated with their primary appointment perform IRB review. Cross-panel review, however, may occur if the alternate IRB’s composition is better suited to review the proposed Human Research.

Applications and related study materials must be submitted by the posted “Submission Deadline” for consideration at the corresponding meeting. Your IRB Review Specialist will let you know as soon as possible if convened IRB review is required and provide a due date for when all pre-review questions/revisions must be resolved. Pre-review is conducted by the IRB Review Specialist to address any deferrable concerns prior to convened IRB review. Assignment to an agenda is not automatic and may vary depending on the quality and completeness of the submission, complexity of the project, required ancillary reviews, responsiveness of the PI to clarifications requested from the IRB Review Specialist, and attaining quorum at the monthly meeting. The PI may receive requests for additional information up until the day the meeting agenda is distributed (one week prior to the meeting). Once the agenda is sent, no additional agenda items can be added.

Determining when an IRB Application is Required

Harvard Longwood Campus IRBs are 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 LMA 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 HLC IRB review. Activities that do not meet the definition of “Human Subjects Research” do not fall under the [HHS Protection of Human Subjects Regulations](#). See [Not Human Subjects Research Determination](#) for additional guidance.

IRB Review Process

Once an application is submitted in ESTR, it will be reviewed by an [IRB Review Specialist](#) in the order it is received. If you have a time-sensitive submission, include a statement in your ESTR application (via a Comment, cover letter, etc) to inform the IRB at the outset of any deadlines or time constraints. Review and approval of a time-sensitive submission will be completed to the best of the IRB’s ability; however, it is not guaranteed and may vary depending on the quality and completeness of the submission, complexity of the project, required ancillary reviews, responsiveness of the PI to clarifications requested from the IRB Review Specialist, and attaining quorum at the monthly meeting.

After initial review, the IRB Review Specialist may request clarifications, revisions, and/or additional information in ESTR (“Clarifications Requested” or “Modifications Required to Secure Approval”). The Principal Investigator may “Submit Response” in ESTR to resolve these requests. Once responses are submitted, the IRB may request additional information following further review. When resolved, the IRB Review Specialist will either complete their review and issue a determination letter or assign the application to an IRB meeting for 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 your [IRB Review Specialist](#).

Note that human subjects research activities may not take place until all IRB requests are resolved and final IRB approval has been issued.

IRB Approval Criteria

The criteria for IRB approval of non-exempt Human Research can be found in “WORKSHEET: Criteria for Approval.” 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.”

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 consult these materials when writing the Research Protocol. Worksheets and Checklists can be found in the [ESTR Library](#).

IRB Review Turnaround Time

The below table reflects “target” review turnaround time for non-convened IRB reviews. Of note, these times may vary depending on the quality and completeness of the submission, complexity of the project, required ancillary reviews, and responsiveness of the PI to clarifications requested from the IRB Review Specialist.

Not Human Subjects Research Determination	1 week
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Exemption Determination	1 week
Expedited Initial and Continuing Applications	2-3 weeks
Expedited Modifications	1 week

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 institutional and/or local approvals have been secured. IRB approval may be non-expiring or granted for a limited period of time, not exceeding one year, which is noted in the approval notification letter.

For non-expiring studies that do not require continuing review, the PI remains responsible for submitting the following to the IRB, as applicable, in real time:

1. Any change or update to the research must be submitted in ESTR via a Modification prior to implementation.
2. Once the study is eligible for closure, a closure request must be submitted in ESTR via the Close Study activity.
3. All reports of new information must be submitted in ESTR via the Report New Information activity.

Requires Modification(s)

If the IRB requires modification(s) to secure approval, its 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.

Once a submission is reviewed and modifications are required, no new requests should be included in the response that are not related to the specific modifications requested. If brand new changes are submitted at that time, review time may be further delayed in order to review the existing modification requests and new modification requests in totality. In these cases, where additional changes are needed but are unrelated to the specific clarifications requested, the IRB recommends first securing approval for the original submission and then submitting a Modification at a later date to make further changes to the Human Research.

Deferral/Disapproval

If the IRB defers or disapproves the Human Research, it will provide a statement of the reasons for this decision. Deferral or Disapproval means that the Human Research, as proposed in the submission, cannot be approved and the IRB was unable to articulate specific modifications that, if made, would allow the Human Research to be approved.

In most cases, if the IRB's reasons for the deferral or disapproval can be addressed through revision(s) to the protocol, IRB approval can be achieved. In all cases, the Principal Investigator has the right to address his/her concerns to the IRB directly at an IRB meeting and/or in writing.

Responses to Deferral or Disapproval require review by the convened IRB. As such, forthcoming submissions should be submitted by the posted deadlines available [here](#).

Principal Investigator

Eligibility

A Principal Investigator (PI) for non-exempt Human Research must be a Harvard LMA School faculty member, e.g., professor, associate professor, assistant professor, instructor, lecturer, PI-eligible research scientist. This requirement does not preclude any non-faculty 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 [Appendix C](#).

Any Harvard affiliate, including faculty, staff, or student, may serve as a PI for Not Human Subjects Research and Exempt research.

Exception

The IRB may grant an exception to the PI eligibility requirement. If determined to be appropriate, such exceptions are made on a protocol-by-protocol basis. All exceptions granted are at-will; they are not guaranteed and can be revoked, revisited, or changed at any time. To request an exception, submit FORM: PI Exception Request in ESTR. To discuss one's candidacy as an Exception PI, contact your [IRB Review Specialist](#) or request a consult from the [Quality Improvement Program \(QIP\)](#).

Restrictions

If a Principal Investigator has a study that has fallen out of compliance (e.g. failure to submit a continuing review application by the submission deadline, lapsed IRB approval, failure to register a clinical trial and/or maintain a record, in good standing, in a Harvard LMA Schools clinicatrials.gov accounts), the PI may be restricted from submitting new Human Research application or Modifications until the issue has been resolved.

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 [Appendix C Principal Investigator Responsibilities and ESTR Assurance Statement](#).

For each application submitted to the IRB where a Harvard LMA School serves as the IRB of Record, the Principal Investigator is responsible for an additional set of obligations specific to serving as PI for a single IRB (sIRB) study. See [Appendix D Principal Investigator Responsibilities as Overall Site PI for sIRB Study](#).

For each human subjects research application submitted to the IRB, the Principal Investigator must have current human research training. See [Human Research Training](#) for additional information.

Human Research Training

New investigators and study staff are expected to review the [HUMAN RESEARCH PROTECTION PROGRAM PLAN](#) as part of their initial orientation.

Anyone that will have direct interaction with research participants and/or access to identifiable information/biospecimens 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. For assistance with the definition of identifiable information/biospecimens, refer to [Appendix J](#).

Harvard University and its Schools offer online human research training through the Collaborative Institutional Training Initiative (CITI) Program, which can be accessed via the [Harvard University CITI Single Sign-On page](#) (SSO). Of note, an HUID and PIN are required to access Harvard University’s CITI curriculum. If you do not have an HUID, you will need to have a Harvard affiliate/sponsor request one for you via the [Person of Interest \(POI\) Request Form](#) through [Identity Management Services](#). The HLC IRB does not sponsor researchers nor submit this on behalf of POIs.

To complete Harvard University CITI training, CITI Learners should log in with their HUID, affiliate with “Harvard University”, and select the “Human Research (Protection of Human Subjects)” course. (The following courses do not satisfy the requirement for human research training: Conflicts of Interest, Export Compliance, Good Clinical Practice Course, Information Privacy and Security, Responsible Conduct of Research, IRB Members, or IRB Chairs.) Within the “Human Research Protection of Human Subjects” course, CITI Learners should 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.

Human research training certification is valid for a three-year period from date of completion, regardless of which institution it was completed through. Basic training consists of 7 required modules and 3 electives. 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 by attending three QIP Education Series sessions during an academic year. CITI Refresher training includes 5 elective modules and is also valid for 3 years.

IRB approval may not be granted for proposed Human Research where any staff member’s human research training remains incomplete. To check the training status or obtain a copy of an individual’s training certificate, contact the ORARC Coordinator at 617-432-2157.

The Harvard Catalyst Community Engaged Research Subcommittee developed an alternative to CITI training for community partners for whom CITI might not be appropriate (e.g. individuals who can't access CITI online). This alternative to Harvard University's CITI curriculum is considered on a case-by-case basis. To determine whether this alternative training is appropriate, contact your [IRB Review Specialist](#).

Other Training & Requirements

Sponsors and/or funders may require investigators and study staff complete additional training.

The National Institutes of Health's (NIH) ["Policy on Good Clinical Practice Training for NIH Awardees Involved in NIH-funded Clinical Trials"](#) establishes the expectation that all NIH-funded researchers, investigators, and/or study staff who are involved in the conduct, oversight, or management of clinical trials should be trained in Good Clinical Practice (GCP). As such, Office of Regulatory Affairs and Research Compliance requires all researchers involved in the conduct, oversight, or management of an NIH-funded clinical trial to complete ICH-GCP training (e.g., [CITI "Good Clinical Practice" online course](#), [NIH GCP online modules for Social Behavioral Research](#), or Harvard's GCP for Social and Behavioral Research Field Guide). These courses are separate from the "Human Research (Protection of Human Subjects)" course. Completed ICH-GCP training certificates should be submitted to the IRB in the ESTR record.

Alternatively, social-behavioral researchers at Harvard can satisfy this by completing the "Good Clinical Practice (GCP) for Social and Behavioral Research FIELD GUIDE." To request a copy of this training guide and assessment questions, contact the ORARC Coordinator at 617-432-2157.

Reporting Financial Interests to the IRB

In order 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 disclose 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, research nurses, data coordinators, and other support staff possibly not captured within the ESTR SmartForm: Study Team Members Page.

To disclose, submit "FORM: Financial Interest Disclosure" at the time of initial review and throughout the life of the study. Investigators must report any change(s) to this disclosure to the IRB via Continuing Review, if required, or 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. (Harvard salary paid by a sponsor is excluded).
- 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 [Appendix F Additional Consent Form Language Requirements Relating to Conflict of Interest](#) for additional considerations.

Additional Policies:

- Harvard University: [Harvard University Policy and Individual Financial Conflicts of Interest for Persons Holding Faculty and Teaching Appointments](#)
- Harvard Faculty of Medicine: [Faculty of Medicine Policy on Conflicts of Interest and Commitment](#)
- Harvard T.H. Chan School of Public Health: [Harvard Chan School Implementation Plan for the Harvard University Policy on Individual Financial Conflicts of Interest for Persons Holding Faculty and Teaching Appointments and/or Conducting Work on School Sponsored Grants](#)

Conducting Research with Non-Harvard Collaborators

All Harvard LMA School investigators engaged in Human Research must secure IRB review. This applies when the Human Research is conducted at a Harvard LMA 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”). For more information, see [Cede Review \(Designating a single IRB\)](#) and [Requesting Cede Review/Submitting External IRB in ESTR](#).

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

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. To review the criteria for when a Harvard LMA School may rely on another institution for IRB review, refer to HUMAN RESEARCH PROTECTION PROGRAM PLAN. Activities that do not constitute human subjects research or are determined to be exempt are ineligible for reliance agreement/cede review; the HLC IRB requires in-house review of those projects.

For instructions on submitting a Cede/Reliance Request, see [Requesting Cede Review/Submitting External IRB in ESTR](#).

Requesting Cede Review/Submitting External IRB in ESTR

To request that HLC IRB serve as the IRB of record, follow instructions on [Submitting an Application in ESTR](#). An IRB application is required when an LMA School serves as the Institution of Record.

For each application submitted to the IRB where a Harvard LMA School serves as the Institution of Record, the Principal Investigator is responsible for an additional set of obligations specific to serving as PI for an single IRB (sIRB) study. See [Appendix D Principal Investigator Responsibilities as Overall Site PI for sIRB Study](#).

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

For each application submitted to the IRB where a Harvard LMA School relies on the IRB of another institution, the Principal Investigator listed on the External IRB application is responsible for an additional set of obligations specific to relying on an external IRB. See [Appendix E Principal Investigator Responsibilities When Relying on an External IRB](#).

ESTR Record Access

Principal Investigator

The Principal Investigator named in ESTR has full access to the corresponding record and all of the SmartForm Pages. The PI has the ability to make edits, create modifications and continuing review applications, and will receive all notifications generated via ESTR. To learn more about who can serve as Principal Investigator, see ‘[Principal Investigator Eligibility](#)’ section.

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. The Primary Contact cannot submit on behalf of the PI. 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 and the PI can change the Primary Contact any 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. Study Team Members and Guests do not receive system notifications.

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 and submit 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 require certain fields to be completed in order to proceed through the ESTR application, as identified by a red asterisk (*). You must attach a document to the Basic Information page before you can proceed any further with the application. In addition, the IRB requires all fields on the Basic Information page to be completed.

All funding for the study must be listed on the Funding Sources page. This page does not force a response for all applications because not all studies have funding, but it must be completed if the study has either sponsored or non-sponsored funding.

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 Review Specialist.

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. Consult your [IRB Review Specialist](#) in cases where it is unclear whether a proposed modification might alter the IRB’s original determination.

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

In the instance where one Modification proposes multiple changes, and any component of that Modification could require convened IRB review, your IRB Review Specialist/QIP may recommend dividing the Modification into two submissions for a more focused review and efficient turnaround time.

The IRB may request or require an investigator to complete an updated template version of a study document if, upon review, the IRB finds a very outdated version is being used that does not adequately enable to the IRB to assess the required regulatory criteria for approval.

When a Modification May Require A New Initial Application

If Modifications proposed to an existing study change the purpose/aims of the study, the study population, and/or the study procedures, your IRB Review Specialist/QIP may recommend or require that it is more appropriate for those changes to be submitted as a new application rather than a Modification to an existing study. Similarly, if a new study is submitted and has multiple non-overlapping aims, procedures, and/or participant groups, your IRB Review Specialist/QIP may recommend that it is more appropriate for you to submit multiple applications, rather than one, overly complex application. In both instances these recommendations are made in order to provide the most appropriate review; the IRB must review to the highest level of the regulations, which can increase clarifications requested, turnaround time, require convened IRB review, etc., and recommendations are made with this in mind.

Requesting Continuing Review

To request continuing review, [follow these instructions from the ESTR Support website](#). Complete the Continuing Review/Study Closure Information application, including all of the required responses to questions 1-4. Attach any documents that contribute to the review of the

submission (e.g. a summary of the study's progress on TEMPLATES: Summary of Study Progress Template, any sponsor progress reports, CITI refresher training, DSMB reports). 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 [“How to submit a modification?”](#)). 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 the continuing review application is not received by the [submission deadline](#), the PI may be restricted from submitting new Human Research until the completed application has been received (see [Principal Investigator Restrictions](#) for more information).

For studies that do not require continuing review, the PI remains responsible for submitting the following to the IRB, as applicable:

1. Any change or update to the research must be submitted in ESTR via a Modification.
2. Once the study is eligible for closure, a closure request must be submitted in ESTR via the Close Study activity.
3. All reports of new information must be submitted in ESTR via the Report New Information activity.

Reconciling a Lapse in IRB Approval

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. Continuation of Human Research procedures is a violation of federal regulations. If IRB approval of the Human Research expires, the PI must submit an RNI to report the lapse to the IRB. Such an RNI should include:

1. An explanation of how the lapse occurred.
2. A strong corrective action plan in place to avoid a future lapse.
3. The timeline for when the lapse will be resolved, with either a Continuing Review application or Study Closure.
4. Confirmation that no human subjects research activities took place while lapsed.
5. Confirmation that there are no outstanding RNIs, pending issues/Mods, participant complaints/concerns, etc.
6. A statement about whether there have been prior lapses for this project.
7. Verification that notification of lapse has been communicated to sponsor, local site/IRB, DSMB, etc., if/when applicable.

If it is necessary to continue Human Research activities to eliminate apparent immediate hazards to participants, prior notification is required. Contact the Assistant Director of IRB Operations at 617-432-7434 or your [IRB Review Specialist](#) 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 information and/or biospecimens and manuscript preparation can occur indefinitely. See [Appendix J](#) for the definition of identifiable information/specimens.

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

If the application for closing out a Human Research study is not received by the [submission deadline](#), the PI may be restricted from submitting new Human Research until the completed application has been received (see [Principal Investigator Restrictions](#) for more information).

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 study assigned a data security level 3 or higher requires IT review/approval prior to IRB approval.

Consent Considerations

Creating a Consent Script for Exempt Human Research

Exempt Human Research does not usually 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 required 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.

The IRB strongly recommends that investigators use “TEMPLATE: Exempt Human Research Consent Script” to create a consent script for Exempt Human Research. Upload the script to the Consent Forms and Recruitment Materials page in ESTR.

Creating Consent Forms for (non-exempt) Human Research

Consent documents must contain all of 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.

The IRB strongly recommends that investigators use IRB’s template consent documents. If an alternative format is preferred or required, i.e., by the Sponsor or local IRB, include justification in the Research Protocol, section 7. Note that use of a non-Harvard consent template does not absolve the researchers from including the required regulatory elements of consent. Should the

investigators wish to alter or waive such elements, refer to “CHECKLIST: Waiver or Alteration of Consent Process” for eligibility.

Note that “TEMPLATE: Short Form Consent Template” should only be used in the instance where consent is obtained from participants who do not speak English and oral presentation of informed consent information occurs in conjunction with this short form written consent. For guidance on consent requirements, refer to “SOP: Informed Consent Process for Research” and “SOP: Written Documentation of Consent.”

Refer to [Appendix G Additional Consent Form Considerations](#) when developing consent documents.

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.
- 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 signed and dated 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).

Documentation of consent should be captured with a signature, thumbprint, and/or equivalent mark made by the participant. It can be either written on paper or in an electronic format. A thumbprint or equivalent mark is appropriate in situations where participants are unable to sign their name or they belong to a cultural group/community in which signing forms is not the norm.

If the research team will not obtain signature and date, provide justification for requesting a waiver or alteration of documentation of consent (and/or parental permission). Should the investigators wish to waive consent documentation, refer to “CHECKLIST: Waiver of Written Documentation of Consent” for eligibility.

Obtaining HIPAA Authorization

Combine HIPAA authorization with the consent document, if applicable, using “TEMPLATE: Consent Template for HIPAA-covered entities.” (Refer to [HIPAA](#) for additional background). Use the signature block(s) approved by the IRB when obtaining combined informed consent and

HIPAA authorization. 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 customary requirements to document HIPAA authorization:

Required Elements:

- A description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion.
- The name or other specific identification of the person(s), or class of persons, authorized to make the requested use or disclosure.
- The name or other specific identification of the person(s), or class of persons, to whom the covered entity may make the requested use or disclosure.
- A description of each purpose of the requested use or disclosure.
- An expiration date or an expiration event that relates to the individual or the purpose of the use or disclosure. (The statement “end of the research study,” “none,” or similar language is sufficient if the authorization is for a use or disclosure of protected health information for research, including for the creation and maintenance of a research database or research repository.)
- Signature of the individual and date. If the authorization is signed by a personal representative of the individual, a description of such representative's authority to act for the individual must also be provided.
- The individual's right to revoke the authorization in writing.
- The authorization either:
 - Describes the exceptions to the right to revoke the authorization.
 - References the Notice for Privacy Practices for Protected Health Information which describes the exceptions to the right to revoke the authorization.
- The ability or inability to condition treatment, payment, enrollment or eligibility for benefits on the authorization, by stating either of the following:
 - The covered entity may not condition treatment, payment, enrollment or eligibility for benefits on whether the individual signs the authorization.
 - The consequences to the individual of a refusal to sign the authorization when the covered entity can condition treatment, enrollment in the health plan, or eligibility for benefits on failure to obtain such authorization.
- The potential for information disclosed pursuant to the authorization to be subject to re-disclosure by the recipient and no longer be protected by this authorization.

Other requirements associated with the HIPAA authorization document:

- The authorization is written in plain language.
- The individual will be provided with a copy of the signed authorization.
- If the marketing involves direct or indirect remuneration to the covered entity from a third party, the authorization must state that such remuneration is involved.
- The authorization is either a separate document or incorporated into the written consent document for research.
- No material information in the authorization is known to be false.

Should the investigators wish to waive obtaining HIPAA authorization, refer to “HIPAA Waiver of Authorization” for eligibility.

For assistance with the definition of identifiable information/biospecimens, refer to [Appendix J](#).

Additional Resources for Data Management

Early in their project panning, 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](#).

- **Investigators Guide to Research Data Management Practices** [\[PDF\]](#) Mapped along a Research Data Management Lifecycle, the Guide highlights key issues to consider and offers a roadmap for researchers to follow over the course of data collection, storage and use, dissemination, and final disposition/disposal.
- **Data Privacy and Security Planning Checklist** [\[PDF\]](#) A checklist for investigators preparing an IRB application. IRBs may use the checklist to supplement data security questions on their application forms.
- **Guidance for Researchers Using Internet Cloud Computing Services and Apps** [\[PDF\]](#) This document offers key points to consider when using cloud services, including how to mitigate risks and what to do in the event of data loss, breach, or unlawful or unethical use or disclosure.
- **Research Data Management at Harvard**
[<https://researchdatamanagement.harvard.edu/>] A university-wide initiative to coordinate research data management efforts across Harvard, including a reference guide with information and resources to help investigators manage their research data.

Record Retention

Investigators must maintain Human Research records and study documents, including signed and dated consent documents, for at least seven years after closing the Human Research.

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.

IRB Submission Assistance

To facilitate the IRB review and approval process, email or call your [IRB Review Specialist](#) with any questions.

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/>.

For IRB Submission Assistance and/or consultation, contact the Quality Improvement Program (QIP). They are available to answer questions regarding submission requirements and assist in completing forms, responding to IRB revisions and requests for additional information, and drafting recruitment and consent materials. To request assistance, submit a [Service Request Form](#).

Quality Improvement Program

The Quality Improvement Program (QIP) is available to Harvard LMA School affiliates seeking human research service support throughout the lifecycle of their proposed Human Research.

Some of the services offered by QIP are outlined below. To request QIP support, submit a [Service Request Form](#).

Routine On-site Review (not for cause audits)

QIP is available to conduct domestic and international routine onsite review of study conduct and regulatory documentation to ensure compliance including protocol adherence, accurate record keeping, appropriate informed consent process, and documentation of consent.

Education/Additional Training

- **In-Service.** QIP is available to conduct any size group in-service sessions addressing a variety of topics relating to research compliance; institutional policies/requirements; and best practice in human research.
- **New Investigator/Research Coordinator Orientation.** QIP is available to meet with new study staff (PIs, Coordinators, etc.) in order to familiarize them with ORARC policies and procedures, with a focus on the IRB review and approval process.
- **Monthly Education Series.** See the [QIP's webpage](#) for a schedule of the current offerings.
- **Student Education Sessions.** QIP offers education sessions for Harvard Chan School, HMS and HSDM students who will be conducting research for a class or dissertation during the academic year. See the [QIP's webpage](#) for a schedule of the current offerings.

Human Research Support

- QIP is available to provide a variety of support services designed to facilitate the IRB review and approval process. The following services are offered on a first-come, first-serve basis free of charge:
 - IRB submission assistance, which includes drafting and/or editing IRB submission materials; responding to the IRB, and submitting materials in ESTR.
 - Routine (not for cause) onsite monitoring of regulatory documentation, protocol adherence, consent process.
 - Review/edit the Human Subjects section of grants/proposals.
 - Short- or long-term temporary Research Coordinator/Project Manager support.
 - Study Management Tools designed to assist investigators and their study staff in maintaining and organizing essential study (regulatory) documents. These tools are available on [QIP's webpage](#).

Questions

This document and the policies and procedures for the Harvard Longwood Campus Human Research Protection Program are available on the [Office of Regulatory Affairs and Research Compliance's website](#).

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

Leslie Howes, MPH
Director, Office of Regulatory Affairs and Research Compliance
90 Smith Street, Room 338
Boston, MA 02120



SCHOOL OF PUBLIC HEALTH



HARVARD
School of Dental Medicine



HARVARD
MEDICAL SCHOOL

Office Phone: 617-432-2153
lhowes@hsph.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 ORARC, follow the directions in the “HUMAN RESEARCH PROTECTION PROGRAM PLAN” under “Reporting and Management of Concerns.”

Appendix A 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 your [IRB Review Specialist](#).

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/or sponsor, and any resulting reports (e.g. FDA Form 483.)
5. Written reports of study monitors and/or sponsor.
6. Failure to follow the protocol due to the action or inaction of the investigator or research staff.
7. Breach of confidentiality.

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. Complaint of a participant that cannot be resolved by the research team.

10. Premature suspension or termination of the protocol by the sponsor, investigator, or institution.
11. 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.)

Appendix B Additional Regulatory Requirements

DHHS-Regulated Research¹

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 participant's will be retained and analyzed even if the participants choose to withdraw from the research.

FDA-Regulated Research

1. When a participant withdraws from a study:²
 - a. The data collected on the participant to the point of withdrawal remains part of the study database and may not be removed.
 - b. An investigator may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the 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.
 - c. 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.

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

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

- d. 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.
 - e. 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.
2. For FDA-regulated research involving investigational drugs:
 - a. 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.
 - b. 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.
 - c. 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.
 - d. Follow FDA requirements for investigator recordkeeping and record retention⁶
 - i. Disposition of drug:

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>

1. 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.
- e. 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.
- f. Follow FDA requirements for assurance of IRB review⁸

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

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

- 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.
 - g. 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.
 - h. 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.
 3. For FDA-regulated research involving investigational devices:
 - a. General responsibilities of investigators.¹¹
 - i. An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of 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.
 - b. Specific responsibilities of investigators¹²
 - i. 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.
 - ii. Compliance: An investigator must conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

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>

- iii. 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.
- iv. Financial disclosure:
 - 1. A clinical investigator must disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under 21 CFR §54.
 - 2. The investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
- v. Disposing of device: Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator must return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
- c. Maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation: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.
 - 3. 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.

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

4. 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.
- d. 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.
- e. 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

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>

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.

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, including ICH-GCP training.
 - 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 hazards to trial participants, or when the changes involves only logistical or administrative aspects of the trial (e.g., change in monitors, change of telephone numbers).
 - c. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
 - d. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to trial 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 of the investigator's/institution's duties for investigational product accountability at the trial site to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.
 - c. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each 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 are 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 or not 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. That 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.
 - p. 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. Contact the study sponsor with any questions.
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).
 - d. Premature Termination or Suspension of a Trial If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial 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.

11. Final Reports by Investigator: Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the trial's outcome, and the regulatory authorities with any reports required.

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 participants 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 participants, the Department of Defense may evaluate this institution's education and training policies to ensure the personnel are qualified to perform the research.
8. When research involves U.S. military personnel, policies and procedures require limitations on dual compensation:
 - a. Prohibit an individual from receiving pay of compensation for research during duty hours.
 - b. An individual may be compensated for research if the participant is involved in the research when not on duty.
 - c. Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to \$50 for each blood draw.

- d. Non-Federal persons may be compensated for research participating other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.
9. When conducting multi-site research, a formal agreement between institutions is required to specify the roles and responsibilities of each party.
10. When conducting greater than minimal risk research, the IRB shall approve an independent research monitor by name.
11. Other specific requirements of the Department of Defense research be found in the “Additional Requirements for Department of Defense (DOD) Research” section in the IRB’s “WORKSHEET: Additional Federal Criteria (HRP-318).”

Department of Energy (DOE) Research

1. Research that involves one or more of the following is considered by DOE to be human subjects research and requires IRB review:
 - a. Intentional modification of the human environment
 - b. Study of human environments that use tracer chemicals, particles or other materials to characterize airflow.
 - c. Study in occupied homes or offices that:
 - i. Manipulate the environment to achieve research aims.
 - ii. Test new materials.
 - iii. 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.
2. The protocol must address the DOE requirements if your research includes Personally Identifiable Information (<http://science.energy.gov/ber/human-subjects/regulations-and-requirements/doe-special-requirements/#ProtectionOfData>).
3. You must report the following within 48 hours to the Department of Energy human subjects research program manager:
 - a. Any significant adverse events, unanticipated risks; and complaints about the research, with a description of any corrective actions taken or to be taken
 - b. Any suspension or termination of IRB approval of research
 - c. Any significant non-compliance with HRPP procedures or other requirements.
 - d. Any compromise of personally identifiable information must be reported immediately. (The time frame for “immediately” is defined as upon discovery.)
4. Requirements for human participant protections for classified research apply to all research conducted or supported by the DOE, including contracts, and including Human Terrain Mapping research.
5. Requirements for human participant protections and their accompanying Contractor Requirements Documents (CRDs) apply to all research conducted at DOE institutions regardless of funding source, or by DOE employees/contractor personnel regardless of funding source or location conducted, and whether done domestically or in an international environment, and including Human Terrain Mapping research. DOE workers are considered vulnerable subjects and shall be afforded additional protections as determined by the IRB.
6. Other specific requirements of the Department of Energy (DOE) research can be found in the “Additional Requirements for Department of Energy (DOE) Research” section in the IRB’s “WORKSHEET: Additional Federal Criteria (HRP-318).”

Department of Justice (DOJ) Research

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 participants.
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 participants 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 participants who are both: No longer in Bureau of Prisons custody. Participating in authorized research being conducted by Bureau employees or contractors.
8. A non-employee of the Bureau may receive records in a form not individually identifiable when advance adequate written assurance that the record will be used solely as a statistical research or reporting record is provided to the agency.
9. Except as noted in the consent statement to the participant, you must not provide research information that identifies a participant to any person without that participant'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 participants, 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 participant may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable).
 - d. A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law.

For example, an investigator may not guarantee confidentiality when the participant indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the participant 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 participant'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 participants (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 participants or a class of participants, 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).”

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 Participants 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 participant reports immediate harm to participants or others.
4. Under a privacy certificate, investigators and research staff do not have to report child abuse unless the participant 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.
6. Other specific requirements of the Department of Justice (DOJ) Research Funded by the National Institute of Justice can be found in the “Additional Requirements for Department of Justice (DOJ) Research” section in the IRB’s “WORKSHEET: Additional Federal Criteria (HRP-318).”

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.

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.

4. Other specific requirements of the Department of Education (ED) Research can be found in the “Additional Requirements for Department of Education (ED) Research” section in the IRB’s “WORKSHEET: Additional Federal Criteria (HRP-318).”

Environmental Protection Agency (EPA) Research

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

Research Subject to EU General Data Protection Regulations (GDPR)

1. Data collection involving personal data about individuals located in (but not necessarily citizens of) European Union member states, Norway, Iceland, Liechtenstein, and Switzerland is subject to EU General Data Protection Regulations.
2. For all prospective data collection activities subject to EU GDPR, contact 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. For all retrospective data collection activities subject to EU GDPR, submit data use agreements through the Agreements system 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.
4. 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 information and biospecimens associated with the research remain consistent with applicable sections above.

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).

Appendix C Principal Investigator Responsibilities and ESTR Assurance Statement

The Principal Investigator certifies the following is true for each application submitted:

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 throughout the lifecycle of 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 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:
 - Proposed modifications to the previously-approved Human Research.
 - A continuing review application (to avoid a lapse in approval).
 - A continuing review application when the Human Research is closed.
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 the Institutional conflict of interest and Harvard Research Data Security Policy.

- 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.
 - Any system storing level 2 information 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.

Appendix D Principal Investigator Responsibilities as Overall Site PI for sIRB Study

1. Coordinating with HRPP personnel 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.

Appendix E Principal Investigator Responsibilities When Relying on an External IRB

1. Obtain appropriate approvals from this institution 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.

Appendix F 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.

Disclosing funding source

In the consent template, section entitled *What is the purpose of this research?*, 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.

Appendix G Additional Consent Form Considerations

Purpose of the Research

- Describe the current therapies for their disease/condition and why they are not satisfactory.
- For non-therapeutic studies, explain the scientific problem. Describe how this research will attempt to solve the problem.
- Information about the drug/device, including current regulatory status, e.g., “The drug/device is/is not approved by the U.S. Food and Drug Administration (FDA) for the treatment of...”

Risk or Possible Discomforts

- In the case of participants who are patients, indicate procedures being performed as standard of care and which are part study procedures.
- Information about the study design, e.g., randomization, placebo, blinding.
- Special requirements, e.g., stopping current medications, fasting before tests.
- Reasons and procedures for early withdrawal from the study, e.g., tapering medications, final study visit.
- Sending data/specimens to research collaborators.
- Storage of data/specimens for future use.
- Sponsor use of identifiable study information for additional research. The sponsor may request to use identifiable study information for additional research related to the study.
- Unforeseeable risks that may result from study drugs, devices, procedures, e.g., “There may be other risks or side effects that are not known at this time.”
- Group the risks into those that are expected, occasional, or rare and describe them as such. List all expected and occasional side effects.
- If the research involves an investigational product or procedures whose risk profile is not well known, add: “In addition to these risks, this research may hurt you in ways that are unknown.”
- If the research involves pregnant women or women of child-bearing potential and procedures that involve risks to an embryo or fetus, add: “The procedures in this research are known to hurt a pregnancy or fetus in the following ways:...” If the research involves pregnant women or women of child-bearing potential and procedures whose risk profile in pregnancy is not well known, add: “The research may also hurt a pregnancy or fetus in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death. You should not be or become pregnant [include as applicable “or father a baby”] while on this research study.”

Benefits from being in the Research

- If the study is likely to lead to the development of a commercial product, then state this fact. You may also add, if true, that there are no plans to provide financial compensation to the participant in the event a commercial product is developed. See [Appendix D Additional Consent Form Language Requirements Relating to Conflict of Interest](#).
- For studies involving prisoners include the following statement: “Taking part in this research study will not improve your housing or correctional program assignments.”

Further, taking part in this research study will not improve your chance of parole or release.”

- Compensation should **not** be listed as a benefit. If remuneration will be provided, create a separate section.

Will I be compensated for participating in this research

- Describe money or other forms of compensation or reimbursement, e.g., gift certificate, meal voucher, parking voucher, and travel expenses. Include the method and timing of the compensation.
- Include how the amount of compensation is calculated if the participant does not complete the entire study for any reason, e.g., “If you do not complete all of the study visits, you will receive \$25 for each study visit you completed.”
- Refer to Harvard University Financial Policy on Human Subject Payment, which can be found at <http://policies.fad.harvard.edu/pages/human-subject-payments>

What will I have to pay for if I participate in this research

- Describe any costs the participant may incur. If participants will not incur any costs, please state so, e.g., “There will be no cost to you for participating in this research.” “The study drug and all of the tests and procedures that will be done only for the research will be paid for by study funds.”
- A statement indicating that the cost of research procedures that may be billed to the participant or his/her Health Insurance Company.
- A statement indicating that the cost of the participant’s routine medical care will be billed to the participant’s or his/her Health Insurance Company in the usual way, e.g., “The cost of your routine medical care will be billed to you or to your health insurance company in the usual way.”

What happens if I am injured as a result of participating in this research study?

- Include this section if the Human Research poses greater than minimal risk.

Can my taking part in the research end early?

- If there are no adverse consequences as a result of withdrawing, include “You may decide not to continue in the research at any time without it being held against you. The person in charge of the research [or the sponsor, if applicable] can remove you from the research at any time without your approval for any reason.” If appropriate, include: “Possible reasons for removal include (insert reasons, e.g., in the participant’s best interest(s) or participant doesn’t follow study directions).”
- If there are adverse consequences, include: “You may decide not to continue in the research at any time without it being held against you. If you decide to leave the research (describe adverse consequences). If you decide to leave the research, contact the investigator (describe the procedures for orderly termination by the subject).
- For FDA-regulated research, include: “If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care.” (Note: The consent document cannot give the subject the option of having data removed.) “If you agree, this data will be handled the same as research data.” (Note: 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 subject's consent. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.)

- For research that is not FDA-regulated, describe what will happen to data collected to the point of withdrawal. Describe whether participants will be asked to explain the extent of their withdrawal and whether they will be asked for permission to collect data through interaction or collection of private identifiable information. For example, a subject may wish to withdraw from the experimental procedure because of unacceptable side effects, but may agree to undergo follow-up procedures and data collection.)

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research

- Create this section when applicable

If I take part in this research, how will my privacy be protected? What happens to the information you collect?

- Describe confidentiality protections.
- If the identity of the participant is not known to investigators, you may say, "Your participation is anonymous, and your responses cannot be linked to your identity."
- If the identity of the participant is not known to investigators, you may say, "Your responses will be kept confidential," and then go on to describe measures, e.g.,
- Conducting interviews in a private place (if appropriate to minimize coercion, state "The person who gave me your name to contact you won't know whether you agreed to participate or not").
- Replacing names with a code and keeping the key in a secure location separate from the data.
- Using encrypted and password-protected electronic files; storing paper data in locked cabinets in locked offices.
- Destroying identifying raw data and erasing recordings at appropriate times
- Describing the publication protections, such as "I won't use your name or information that would identify you in any publications or presentations." Or, if you are requesting permission to identify and/or quote participants, say that instead.
- Indicate that the HLC IRB and/or Quality Improvement Program may review study records.
- If additional offices or agencies will collaborate on or oversee the research, indicate the possibility that information may be shared with these groups and describe how the data or samples will be transferred or transmitted.
- If data collection or storage includes technology maintained by a third party (e.g., cloud computing services, mobile health wearables and apps such as Fitbit, online survey tools, or social media platforms) you must disclose the extent to which that third party will protect the confidentiality of the research data.
- Refer to Harvard Catalyst [Sample Informed Consent Language Library](#) when developing consent documents to help participants understand how personal information will be used in research utilizing novel technologies (i.e., Google Glass, social media, mobile apps, smart devices, big data platforms, etc.)

Statement of Consent

- Indicate if the study involves the possibility of re-contacting the participant and provide a “yes/no” option for the participant to complete.
- Consider whether data or specimens will be stored for future use. And, if so, describe how the data or specimens will be stored (i.e., with identifiers), who will have access, and for how long. Provide a “yes/no” option for the participant to acknowledge and agree to this future use.

SIGNATURE

- There are multiple signature pages, appropriate for different types of studies. Create a separate consent document for each signature block type that will be used. Make any necessary alterations to the signature blocks, as instructed on the “TEMPLATE: CONSENT DOCUMENT”. If signature will not be obtained as part of the consent process, remove this section and provide justification in the Research Protocol.

Appendix H Preparing the Research Protocol General Requirements

A Research Protocol is required for any Human Research application (this includes application for an Exempt Human Research). A Research Protocol is not required when requesting a [Not Human Subjects Research Determination](#).

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 in ESTR.

The below sections correspond with the Research Protocol template. The Research Protocol template includes all basic instructions. Additional considerations are outlined below and applicable Worksheets/Checklists are referenced where applicable. Complete all sections, including check boxes, or indicate "N/A" when appropriate.

Additional Considerations for Exempt Research

The IRB strongly recommends that investigators use "TEMPLATE: HLC Exempt Human Research Consent Script Template" to create a consent script for Exempt Human Research. See the "Creating a Consent Script for Exempt Human Research" part of the Consent Considerations section of this manual for detailed instructions. For additional background, see section entitled [Creating a Consent Script for Exempt Human Research](#). The HLC exempt consent form template can be [found in the ESTR Library](#).

Additional Considerations for Secondary Analysis of Data and/or Biospecimen Research

For research projects that will utilize secondary data and/or biospecimens for analysis, the IRB recommends describing *only* the secondary use study procedures in the Research Protocol, rather than any specific details about the original, underlying, data and/or biospecimen collection. As a result, some sections of the Research Protocol may be not applicable and should be marked "N/A".

1. Specific Aims

Describe the specific aims, purpose, intent, and/or objectives of the Human Research. State the hypotheses to be tested, if applicable. Explain how the project meets the definition of research (a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge).

2. Background and Significance

Describe the relevant prior experience, gaps in current knowledge, and any relevant preliminary data.

3. Research Locations and Collaborating Sites

Research Locations refer to the geographic location that the research will take place, not to the people or institutions that you may be collaborating with. Knowing the location helps the IRB determine the local context of the research as well as if there are additional laws, regulations, and/or policies researchers need to adhere to. All Research Locations should be listed in ESTR on the Research Locations page.

Collaborating Sites refer to institutions or study staff that are also taking part in the research study. All Collaborating Sites should be listed in ESTR on the Sites page.

If conducting an online study, please indicate the location of the researcher who is conducting the study.)

Additional considerations for International Research: Provide the IRB with a description of the local research 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).
- 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.
- If a site doesn't have a local reviewing body, e.g. IRB/research ethics committee, the IRB may require Community Advisory Board (CAB) review. A CAB should include a minimum of 3 members who are independent of study staff to avoid any perceived or potential conflict of interest(s). The members should include one lay, non-scientist member, but otherwise include members with appropriate experience/expertise based on personal or professional qualifications, e.g., citizen of the country where the research will be conducted, investigator well-versed in proposed methodologies, etc. At a minimum, the CAB should review the recruitment/consent process and materials, study procedures, and dissemination of study results, if applicable.

The IRB recommends that any investigator conducting international research first consult the [OHRP International Compilation of Human Research Standards](#) to understand and comply with the applicable local human subjects protections laws, regulations, and guidelines in the country/countries where their research will take place.

4. Study Team

Describe the experience, resources, training, and qualifications for study team members who will conduct research activities on this study. Describe the time allocated to complete the study. Provide an anticipated date of study completion. Avoid naming specific individuals and, instead, use general titles or role names (e.g., program manager, site PI, research coordinator, etc.) to reduce the need for modifications.

5. Study Design

- Describe the study design.
- Describe the participants/participant group(s), the duration of their involvement, the total number to be screened and/or enrolled, and the inclusion/exclusion criteria.
- Study procedures:

- Provide a timeline of all procedures being performed, including follow-up visits and procedures being performed to monitor participants for safety or minimize risks.
- Describe procedures taken to lessen the probability or magnitude of risks.
- Describe what data will be collected, including long-term follow-up data.
- If study includes qualitative data collection, describe all procedures and information collected.
- Identify documents that will be used to collect data (e.g., questionnaires, surveys, interview guides) and upload to the Local Site Documents page in ESTR. Source documents, such as case report forms – prepared by a study sponsor for clinical trials, do not need to be submitted, but should be mentioned in the Research Protocol.
- Specify whether participants will be audio or video recorded, and outline plans for transcription and destruction, if applicable.
- Differentiate routine clinical/standard care from research procedures, if applicable.
- Differentiate procedures conducted by Harvard staff from those conducted by non-Harvard members of the research team.
- Describe primary and secondary study endpoints (i.e. events or outcomes that can be measured to determine effect of research intervention), as well as any primary and secondary safety endpoints (for qualitative research, study endpoint may include completion of 6-month survey).
- If proven beneficial, describe whether plans exist to make the intervention (e.g., investigational drug/biologic/device) available post-study (consider accessibility and cost to participants).
- Specify whether or not the research involves deception (i.e., providing participants with false information) or incomplete disclosure (i.e., withholding information from participants), and, if so, provide justification.
- Data and safety monitoring plan. Describe the plans to periodically evaluate the data collected regarding both harms and benefits to determine whether participants remain safe. Describe; 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.

6. Recruitment Methods

If a multi-center study in which participants are recruited by methods not under the control of the local site, e.g., call center or national advertisements, describe those methods.

The IRB must review and approve the content of all recruitment and advertisement materials, including oral communications, before implementation. For advertisements, submit the final version of printed advertisements. When advertisements are recorded for broadcast, provide the final audio/video recording. To avoid re-taping due to inappropriate wording, submit the proposed (draft) wording of the advertisement to the IRB. Otherwise, provide the final English

copy of these materials and include a version number and/or date within each document. For guidance on what to include in an advertisement, refer to “WORKSHEET: Advertisements”.

When community based participatory research is involved, define the term “community” as it relates to the protocol and describe provisions to engage this community in design and study conduct. Identify any community partners.

7. Consent Process

Describe the setting of the consent process; identify who will be responsible for obtaining consent, and how consent will be obtained, e.g., written or oral consent. Avoid naming specific individuals, but rather study roles, e.g., research coordinators or nurses vs. John Doe. Describe the time that will be devoted to the initial consent discussion. Describe any waiting periods between (a) informing the prospective participant and obtaining consent and (b) obtaining consent and carrying out the study procedures. Describe any steps that will be taken to minimize the possibility of coercion or undue influence.

Describe the process to ensure ongoing consent. Indicate that study staff will continue to ensure participants understand what the research is about and what their participation involves. Confirm that any new information which might influence a participant’s decision to continue participation will be provided to participants, including re-consent where applicable.

Indicate what language(s), if any, other than English are understood by prospective participants or their representatives. If non-English speaking participants will be enrolled, identify the languages consent will be conducted in and who will be responsible for translating. Describe the process to ensure that the information provided to those participants will be in that language understandable to the population. Provide an English copy of the consent document(s), as well as a copy of the local language translation when it becomes available. Include version number and/or version date within each document. Back-translations of foreign language consent forms are not required. For guidance on consent requirements, refer to “SOP: Informed Consent Process for Research” and “SOP: Written Documentation of Consent.”

If the Human Research involves any special population, describe 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”):

- i. Describe whether parental permission will be obtained from:
 1. 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.
 2. 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.
- ii. Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals’ authority to consent to each child’s general medical care.
- iii. Describe whether assent will be obtained from all, some, or none of the children, and if some children, which children population (e.g. age range) will be required to provide assent. Customarily, the IRB requires that investigators obtain assent from individuals

ages 7 years or older; however, if this is not appropriate for the specific target population, please describe.

- iv. When assent from children is obtained, describe whether and how it will be documented.
- v. Describe the procedures in place to obtain consent when, if any, children reach the local age of majority during the course of 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:

- i. If permission of a legally authorized representative will be obtained:
 1. List the individuals from whom permission will be obtained in order of priority, e.g., durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.
 2. Determine 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(i) or 21 CFR 50(1) to make this determination.
- ii. Describe the process for assent of the participants. Indicate whether:
 1. Assent will be required of all, some, or none of the participants. If some, indicated, which participants will be required to assent and which will not.
 2. If assent will not be obtained from some or all participants, include an explanation of why not.
 3. Describe whether assent of the participants will be documented and the process to document assent.
- iii. Describe how consent of the participant will be documented in writing and indicate that participants will be provided with a copy of their signed consent form. If there are extenuating circumstances that make it impossible or inappropriate to meet this requirement, please describe. 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” and address each of the following criteria for approval within this section:
 - (1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
 - (2) That the research presents no greater than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context

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” and address each of the following criteria for approval in this section.

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

If the research involves deception or incomplete disclosure, describe provisions in place to debrief participants after study procedures conclude.

- The debriefing process should include complete disclosure of all pertinent information relating to the protocol; an explanation of why deception and/or incomplete disclosure was necessary, and an opportunity for the participant to withdraw themselves (and all of their data) from the study. Use **TEMPLATE: Debriefing Statement**.
- Describe who will be responsible for carrying out the debriefing process. This should be a member of the study team who is knowledgeable about the research, the deception employed, and the debriefing process.
- Upload debriefing materials to the Local Site Documents page in ESTR for review and approval.

8. HIPAA Privacy Protections

Harvard University Health Services and Harvard School of Dental Medicine are covered entities. Harvard is otherwise not a HIPAA covered entity as defined by the HIPAA Privacy Rule. If protected health information (PHI) is derived from a covered entity (e.g. a hospital or community health center) for purposes of this protocol, describe plans to obtain authorization from the participant to access their protected health information or provide a rationale for requesting a waiver of authorization.

If requesting a waiver of HIPAA authorization, include the following in the Research Protocol:

1. Why it is not practical to obtain an authorization from the participant.
2. What PHI will be used and why the research cannot be conducted without obtaining or accessing that PHI.
3. An adequate plan to protect the PHI from improper use and disclosure.
4. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.
5. Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512.

Refer to “CHECKLIST: HIPAA Waiver of Authorization.” Note: standard Covered Entity Notice of Privacy Practices or Disclosure Statement documents are **not considered** authorization to access PHI for research purposes.

If HIPAA authorization will be obtained directly from the participant, the request must be specific to the proposed research. The IRB recommends making the request in conjunction with the consent process. Use “[TEMPLATE: HLMA Consent Template for HIPAA-covered entities](#),” which includes all of the required elements of HIPAA authorization.

See [‘What Is HIPAA?’](#) section for more information.

9. Research Subject to the European Union (EU) General Data Protection Regulation (GDPR)

GDPR applies to research involving the collection of “personal data” from research subjects who are located in the EEA. The EU/EEA includes the 28 states of the European Union (Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, & United Kingdom) and four additional countries: Iceland, Liechtenstein, Norway and Switzerland. Plans for collecting and/or obtaining “pseudonymized data” (e.g., coded data) and/or identifiable data and/or biospecimens from participants in the EEA should be described in this section.

10. Research Subject to the Family Educational Rights and Privacy Act (FERPA)

FERPA applies to research involving the collection of individually identifiable information from student records or personal education information from an education program (defined as: any program principally engaged in the provision of education, including, but not limited to, early childhood education, elementary and secondary education, postsecondary education, special education, job training, career and technical education, and adult education).

Plans for collecting and/or obtaining individually identifiable information from student records or personal education information from an education program should be described in this section.

11. Vulnerable Populations

Include information regarding participant populations likely to be included in the study that may be vulnerable to undue influence, coercion, or increased risk because of their belonging to that group. Vulnerable populations could include, but are not limited to, children; pregnant women, human fetuses, neonates; prisoners; elderly; economically disadvantaged; employees or students of the investigator or sponsor; undocumented individuals; refugees; racial and/or ethnic minorities; illiterate or low-literacy; military personnel; terminally ill; cognitively impaired or mentally ill; persons with a stigmatizing disease or condition, e.g. AIDS/HIV, etc. 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](#)” and address each of the criteria for approval.

- **Children.** If the Human Research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research (“children”), refer to “CHECKLIST: Children” and address each of the criteria for approval.
- **Neonates of Uncertain Viability.** If the Human Research involves neonates of uncertain viability, refer to “CHECKLIST: Neonates of Uncertain Viability” and address each of the criteria for approval.
- **Non-viable Neonates.** If the Human Research involves non-viable neonates, refer to “CHECKLIST: Non-viable Neonates” and address the criteria for approval in this section.
- **Pregnant Women.** If the Human Research involves pregnant women, refer to “CHECKLIST: Pregnant Women” and address each of the criteria for approval.
- **Prisoners.** If the Human Research involves prisoners, refer to “CHECKLIST: Prisoners” and address the criteria for approval in this section.

12. Risks

Describe the reasonably foreseeable risks, discomforts, and/or inconveniences to participants and/or the group/community to which they may belong. Indicate the probability, magnitude, and duration of each risk.

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. If so, indicate if there are mandatory legal reporting requirements associated with the disclosure of certain information during the course of the study (e.g. abuse, neglect, criminal activity, etc.).

Outline provisions in place to minimize or mitigate each risk.

13. Benefits

Describe the potential benefits to individual participants, as well as to society, if any. Note: compensation is not a benefit and should not be addressed in this section.

14. Participant Privacy

Describe the provisions implemented to protect participants’ privacy. 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. Describe steps that will be taken to reduce any sense of intrusiveness that may be caused by study questions or procedures. For assistance with the definition of identifiable information/biospecimens, refer to [Appendix J](#).

15. 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.

- Indicate the identifiability of the data. For assistance, refer to [Appendix J](#).
- Indicate if any identifiable data/specimens have been de-identified for use in the study.
- Describe plans for transmission, storage, management, and maintenance of study data/specimens.
- Describe the provisions implemented to limit dissemination of identifiable data.
- If future open access (i.e., free availability and unrestricted use) is planned, describe such plans. If data is subject to NIH [Genomic Data Sharing policy](#) or data will be voluntarily submitted to an NIH-designated repository, include 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 plans 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>. Refer to the [Harvard Data Classification Table and Data Security Requirements by Data Security Level](#) for additional information.

*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 level 3 or higher before beginning their research activities. Information Technology (IT) at Harvard is school-specific;. Your local IT Security Officer can assist with the IT-related services below and more, including cloud-based computing environments, Share Point, file backup services, high-performance computing and database platforms, etc. To find your local, school-specific IT Security Officer, [click here](#).

The recommended location for all research data, including electronic and digital files, is a secure Harvard file server. Harvard has school-specific, and sometimes department-specific, resources. Personal online/cloud computing solutions (e.g. Google Drive, Dropbox) should not be used to store or maintain research data. Contact your [local IT Security Officer](#) to confirm which secure server or storage service is available for your use.

Physical copies of research data (e.g. paper files, audio tapes, video tapes, etc.) should be stored in a locked file cabinet in a locked office. It is expected that for digital media, data will be securely erased by overwriting the information. Your [local IT Security Officer](#) can provide you with tools to do this.

Email should not be used to transmit any research data. If files need to be sent via email, please use the [Harvard University Accellion Secure File Transfer](#) server, the [Harvard Medical School Accellion Secure File Transfer](#) server, or the [Harvard Chan School Accellion Secure File Transfer](#) server.

Portable or handheld devices can only be used to store research data if they are configured and managed appropriately (i.e. password protected, up-to-date operating system, antivirus protection, active firewall, etc). This includes smart phones, tablets, wearables (e.g. Fitbit, Garmin), or any other tool that collects research data via mobile device application. Apple devices with a strong passcode are recommended. Mobile devices should be reset to factory defaults after being used for research purposes to securely remove the data. Consult your [local IT Security Officer](#) before using any of these kinds of devices.

USB/flash drives, CDs, or external hard drives should only be used if those devices are encrypted and preferably remote wipeable.

For online survey research it is recommended that Harvard affiliates use [Qualtrics](#) (level 1-3 data), [REDCap](#) (level 1-4 data), or [LimeSurvey](#) (level 1-4 data). No other survey tool vendors are approved by Harvard IT. Online surveys tools typically default to collect IP address, which is considered an identifier. The Research Protocol should describe whether or not IP address is collected and, if not, confirmation that this field will be deactivated in the survey tool. Instructions about turning off IP address collection can be found [here](#) for Qualtrics and [here](#) for LimeSurvey.

To request REDCap access, Harvard affiliates should contact their school-specific REDCap administrator. Harvard T.H. Chan School of Public Health affiliates can [request access here](#). Harvard Medical School/Harvard School of Dental Medicine can [request access here](#).

The use of Amazon Mechanical Turk for research purposes is permitted; however, it should not be used where there is an expectation of privacy, as there are no security controls or data use agreements in place to protect participant data.

To review all research data storage technologies/tools vetted by IT, please consult the following IT resources:

- [HMS/HSDM Collaboration Tools](#) ([also found in this FAQ](#) under “What technologies are approved for use with Harvard Data?”)
- [HSPH Collaboration Tools](#)

The IRB recommends that researchers consult the [OHRP/OCR Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Insurance Portability and Accountability Act \(HIPAA\) Privacy Rule](#) for a description of methods for de-identification of HIPAA covered research data. Additionally, Harvard affiliates can participate in the [Principles of Research Data Confidentiality course](#) within the [Harvard Training Portal](#) for an overview of data confidentiality protection, the risk of re-de-identification of data, and data management strategies for minimizing the risk of inadvertent disclosure.

16. Data/Statistical Analysis Plan

Describe plans for analysis (including the statistical method, if applicable) and sample size/power calculation, if applicable

17. Costs and Compensation

Refer to “WORKSHEET: Payments.”

Refer also to the [Harvard University Financial Policy on Human Subject Payments](#).

Describe the plan to securely transfer any financial paperwork to Accounts Payable for processing, if applicable.

18. Sharing Study Results

Describe the plan to share study results with individual participants and/or the participant group/community, if applicable

19. Research Related Injuries

Refer to the Research Protocol template for instructions.

20. Reportable Events

Indicate that reportable events will be reported to the IRB in accordance with IRB policies (refer to Appendix A for prompt reporting requirements and report categories), i.e., reporting to the IRB within 5 business days from the time the study team becomes aware of the information.

21. Regulatory Compliance

Explain the following: 1) who will be responsible for maintaining Regulatory Documents and Participant files (e.g., Study Manager, PI, Coordinator, etc.), 2) what is being maintained (e.g., keeping files in an electronic vs. hard copy Regulatory Binder, etc.), 3) how often will files be reviewed for compliance/completeness (e.g., quarterly, yearly, monthly, etc.) and using which method (e.g., Investigator Self-Assessment Checklist), and 4) the location where the documents will be kept (e.g., file cabinets in the PI's office, onsite at clinics, etc.).

Plans may include conducting internal checks using the Quality Improvement Program's "CHECKLIST: Investigator Quality Improvement Assessment." Submit a [Service Request](#) to the Quality Improvement Program for assistance in developing an appropriate plan to monitor and ensure regulatory compliance.

22. Data or Biospecimen Sharing

Describe the plan to send data/specimens to research collaborators outside of Harvard. Describe the plan to receive data/specimens from collaborators outside of Harvard. If you plan to establish a repository, do so by submitting a separate application using the [HLC Repository Protocol Template](#).

23. Clinical Trials

Refer to the following four guidance questions (or the [NIH determination tool](#)) to help determine whether a study meets the definition of a clinical trial:

1. Does the study involve human participants?
2. Are the participants prospectively assigned to an intervention?
3. Is the study designed to evaluate the effect of the intervention on the participants?
4. Is the effect being evaluated a health-related biomedical or behavioral outcome?

If the answer to all four questions is Yes, the study meets the definition of a clinical trial and this section of the Research Protocol should be completed.

Refer to the Research Protocol template for additional instructions.

See Appendix B for Additional Regulatory Requirements relating to clinical trials.

24. Device

Refer to “WORKSHEET: Devices” and “CHECKLIST: Non-Significant Risk Device.”

25. Drug/Biologic

Refer to WORKSHEET: Drugs.”

Appendix I Single IRB Studies

1. That National Institutes of Health expects that all sites participating in multi-site studies involving non-exempt human subjects research funded by the NIH will use a single Institutional Review Board (sIRB) to conduct the ethical review required by the Department of Health and Human Services regulations for the Protection of Human Subjects at 45 CFR Part 46.
 - a. 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, whether supported through grants, cooperative agreements, contracts, or the NIH Intramural Research Program. It does not apply to career development, research training or fellowship awards.
 - b. This policy applies to domestic awardees and participating domestic sites. Foreign sites participating in NIH-funded, multi-site studies will not be expected to follow this policy.
 - c. Exceptions to the NIH policy will be made where review by the proposed sIRB would be prohibited by a federal, tribal, or state law, regulation, or policy. Requests for exceptions that are not based on a legal, regulatory, or policy requirement will be considered if there is a compelling justification for the exception. The NIH will determine whether to grant an exception following an assessment of the need.

Appendix J Identifiable/Coded/De-Identified/Anonymous Data and/or Specimens

What the IRB Says	What the IRB Means	Examples
Anonymous	Participant data and/or specimens that were obtained and stored without the collection of any identification that may link to a specific individual. Anonymous samples may include population-level information (e.g., the samples may come from “patients with diabetes”).	A researcher surveys first-year students. She will not solicit nor record any identifiers, direct or indirect, as part of this research.
De-identified	Participant data and/or specimens that may have been acquired from identified participants, but all identifiers or codes have been removed and destroyed.	A researcher receives a data set that includes, along with other data, participant name, study ID, address, and medical record number. Upon receipt of the data set, she strips the data set of all of the above.
Coded	Participant data and/or specimens are labeled with a unique code (e.g., a number), rather than a person’s name or other direct identifier. The data provider retains a coding system/crosswalk, which links individual participants to their unique code. According to federal guidance, coded data is considered identifiable when an investigator has access to the coding system/crosswalk.	A researcher collects data and assigns a 6-digit ID number to each participant. The researcher maintains a coding system that captures participant ID and name.
Identifiable	Participant data and/or specimens are directly identified with participant name or other personal identifier (e.g., phone number, SSN, Address, email address, etc.)	A researcher surveys first-year students. She collects participant name, address, and telephone number on the survey.

Appendix K Guidance on Information and/or Biospecimen Repositories

I. Background

Databases, data banks, registries, and repositories all involve the collection and storage of information or biospecimens over time. Some are created and maintained primarily for diagnostic or clinical purposes. Others are created specifically for research. Many serve more than one purpose. Databases, data banks, clinical data registries, and registries are all considered “repositories” for regulatory purposes; all will be referred to as “repositories” throughout this guidance document.

Repositories constitute a vast resource that researchers can draw upon to address questions extending far beyond those envisioned when they were first created. Research use of these resources is governed by both the federal human subject protection regulations (Common Rule and DHHS regulations) at 45 CFR 46 and the federal privacy rule regulations (HIPAA) at 45 CFR 160 & 164. The Institutional Review Board (IRB) applies both regulations in their oversight of human subjects research. Specific requirements depend upon how and why the information and/or biospecimens in the repository are collected, stored, managed, used, and shared.

As a general rule, however, the research use or disclosure of individually identifiable private information and/or biospecimens by Harvard LMA School agents require the review, approval, and oversight of the Harvard Longwood Campus (HLC) IRB. Investigators whose activities may be subject to human subjects oversight and/or protection, or privacy rule requirements, should submit the appropriate materials to the IRB for an official determination.

II. IRB Applications for Research Repositories

An IRB application is required when an investigator plans on establishing and maintaining a new research repository, or converting an existing database, collection of specimens, or non-research repository into a research repository for which research is one or the sole purpose of the repository. As such, researchers wishing to establish a repository should submit the Repository Protocol Template with their application. This template can be [found in the ESTR Library](#). Of note, underlying information and/or biospecimen collection activities may also be subject to IRB review, and may need to be submitted separately from this application.

In addition to the information typically required in an IRB application, the following information is required:

A. Standard Operating Procedures (SOPs)

Standard operating procedures for the repository should be described in the IRB application or in an attached document. At minimum, the information should include:

- If there is an allocation and/or advisory committee for distribution of the information and/or biospecimens, and if so, a description.
- The conditions under which information and/or biospecimens will be released to recipient investigators, including confirmation that recipients will seek their home institution’s IRB approval before conducting human subjects research.
- If biospecimens are involved:

- Indication of whether the biospecimens would be collected as part of a research or a clinical procedure, or specifically for the repository.
- If the biospecimens are collected specifically for the repository, the number of collections per person.
- A Certificate of Confidentiality is recommended for sensitive genetic information stored in the repository.
- A copy of a Data Use Agreement and/or Material Transfer Agreement to be used when information and biospecimens are sent to another institution.
 - It might be helpful to consult with the Harvard University Office of Technology Development, local School Office of Sponsored Programs/Administration, and/or the Harvard University Office of the Vice Provost for Research for specific language to include.

B. Informed Consent Requirements

IRBs review the consent process and documentation for the initial collection of information and/or biospecimens for repositories, as well as the consent process and documentation for subsequent use of these materials. All research consent forms have required elements as set forth by the federal regulations that govern human subjects research. As such, the IRB recommends using the HLC consent form templates, which can be [found in the ESTR Library](#). In addition, unless waived by the IRB, the IRB will also require that the informed consent document used to establish a repository includes the following:

- A statement describing the future use of information and/or biospecimens. If the specific future use is currently unknown, this should be stated in the informed consent.
- Likely areas of research to be conducted with the collected information and/or biospecimens; e.g., “for health-related research, “at minimum.
- Indication of whether subjects will be informed of any incidental or other findings related to the research.
- Indication of whether subjects may be re-contacted in the future for prospective research.
- The procedures for protecting the privacy of subjects and maintaining the confidentiality of the collected biospecimens.
- Whether or not subjects may withdraw their information and/or biospecimens later and, if so, how they would indicate that wish.
- If human biological specimens are involved, a statement that the specimens may be used in research that may result in new discoveries and that the donor-subjects do not retain any property rights to their information and biospecimens. Thus, they would not receive any financial benefits from these discoveries.

III. Developing, Maintaining, and Using a Research Repository

Under a repository protocol, the IRB can approve relatively broad parameters for collecting, storing, managing, sharing, and using the repository’s information and/or biospecimens for research. If developed properly, the repository protocol will incorporate a series of research protections that permit multiple uses of repository information and/or biospecimens by multiple investigators and/or for multiple research projects with minimal additional review by the IRB.

The use and disclosure of information and/or biospecimens from a research repository are determined by (i) the IRB responsible for the review, approval, and oversight of the repository; and (ii) the IRB responsible for research at the site where the information and/or biospecimens are used.

HLC IRB is responsible for any research repository maintained by a Harvard LMA School agent. Information and/or biospecimens from these repositories may be accessed, used, shared, or disclosed in accordance with the IRB approved repository protocol and informed consent document, authorization, and any additional approval conditions stipulated by the IRB. Once provided to recipient-investigators outside Harvard LMA Schools, use and disclosure of the information and/or biospecimens must also comply with any additional requirements of the recipient institution and its IRB.