

HRP-103 | 7/2/2024 | Author: N. Harneja | Approver: D. Aziz

Investigator Manualⁱ

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Scope

Throughout this document “institution” refers to The University of Texas M.D. Anderson Cancer Center (MD Anderson).

What is the purpose of this manual?

This document, HRP-103 - INVESTIGATOR MANUAL, is designed to guide you through policies and procedures related to the conduct of Human Research that are specific to MD Anderson.

General information regarding Human Research protections and relevant federal regulations and guidance is incorporated into the required human protections training. For additional information see below: [“What training does my staff and I need in order to conduct Human Research?”](#)

What is Human Research?

HRP-101 - HUMAN RESEARCH PROTECTION PROGRAM PLAN defines the activities that this institution considers to be “Human Research.” An algorithm for determining whether an activity is Human Research can be found in HRP-310 - WORKSHEET - Human Research Determination, located in OneIRB in the HRPP Toolkit Documents link. Use this document for guidance as to whether an activity meets either the DHHS or FDA definition of Human Research, keeping in mind that the IRB makes the ultimate determination in questionable cases as to whether an activity constitutes Human Research subject to IRB oversight.

You are not to conduct Human Research without prior IRB review and approval (or an institutional review and determination of exempt Human Research). If you are unsure if an activity is Human Research, submit a request for review of the activity in OneIRB (the electronic IRB submission and review system).

What is the Human Research Protection Program?

HRP-101 - HUMAN RESEARCH PROTECTION PROGRAM PLAN describes this institution’s overall plan to protect subjects in Human Research.

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

- The roles and responsibilities of individuals within the institution.

What training does my staff and I need to conduct Human Research?

MD Anderson has training requirements for individuals who conduct Human Research. All individuals who are involved in the design, conduct and reporting of the research must have Human Subjects Protections Training and ICH GCP training. You may also have additional training imposed by other federal, state, or institutional policies. Please refer to Clinical Research Services for specific training requirements:

<https://mdandersonorg.sharepoint.com/sites/protocol-support-management/SitePages/research-education.aspx>

Can I be the Principal Investigator on a human research study?

A principal investigator (PI) is an MD Anderson employee determined to have the appropriate level of authority and responsibility for the proper conduct of research.

Qualifications

PI status is granted using the following guidelines:

The following individuals are eligible to be PI based on titles, provided the individual is a salaried, regular faculty member.

- Professor; Associate Professor; Assistant Professor

Persons holding the following non-academic titles may request and be granted principal investigator status for exempt projects **directly related to the mission and responsibility of their office**:

- Vice President; Associate Vice President; Director; Associate Director; Assistant Director, Clinical Pharmacist

Persons holding the titles listed below are **not eligible** for PI (or co-I) status, unless a formal request is made in writing and an exception granted by the Vice Presidents of Research and/or Clinical Research as applicable.

- Lecturer; Instructor
- Emeritus Professor
- Adjunct Professor; Adjunct Associate Professor; Adjunct Assistant Professor; Adjunct Instructor
- Senior Research Associate; Research Associate; Research Assistant
- Research Scientist
- Postdoctoral Researchers or doctoral students

What financial interests do my staff and I need to disclose to conduct Human Research?

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

All individuals involved in the design, conduct, or reporting of research are required to disclose their financial interests in the Initial Submission Form in OneIRB and in the following scenarios:

- On submission of an initial review.
- At least annually as part of continuing review (when applicable).
- Within 30 days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.

Individuals with 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 are required to disclose the purpose of the trip, the identity of the sponsor or organizer, the destination, and the duration of the travel.

Identification of any financial interests related to a particular research study is in addition to the MD Anderson annual conflict of interest reporting requirements.

Additional details can be found at

<https://mdandersonorg.sharepoint.com/sites/compliance/SitePages/Conflicts-of-Interest.aspx> for the following MD Anderson policies:

- “Institutional Conflict of Interest Policy for the University of Texas Cancer Center and its Institutional Decision Makers (ADM1273)”;
- “Conflicts of Interest and Conflicts of Commitment Policy for Faculty Members, Investigators, Institutional Decision Makers, and Trainees (ACA0001)”;
- “Conflict of Interest and Conflict of Commitment Policy (ADM0255)”.

How do I submit new Human Research to the IRB?

Complete the Initial Submission xForm in OneIRB and attach all requested documents, and have the xForm submitted by the PI. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Before submitting the research for initial review, you must:

- Obtain the financial interest status (“yes” or “no”) of each research staff.
- Obtain the agreement of research staff to their role in the research.

What if I will be doing a quality improvement project? Do I need to submit to the IRB?

The Quality Improvement Assessment Board (QIAB) is established by Institutional Policy, Quality Assessment Improvement Board Policy (ADM1080) and reviews all MDACC Quality Improvement (QI) projects to: assure patient safety; optimize the potential benefits being sought; and discern which projects may be more appropriately designed or categorized as research studies IRB oversight. Please refer to the QIAB for additional information: <https://mdandersonorg.sharepoint.com/sites/quality-education/SitePages/Quality-Improvement-Assessment-Board.aspx>

Can I hold the Investigational New Drug (IND) or Investigational Device Exemption (IDE) for an investigational drug or device study?

The University of Texas MD Anderson Cancer Center has worked to initiate an institutional program to provide investigators with support, while at the same time ensuring compliance with sponsor federal regulatory requirements. As a result, MD Anderson takes the obligations of IND and IDE sponsorship off the investigator and assumes this responsibility at a centralized level.

MD Anderson is the sponsor of record for all investigator-initiated studies that are conducted under an IND or IDE and are not sponsored by another entity. The Vice President for Clinical Research is the Official Sponsor representative, and the FDA Submission Group serves to represent the sponsor on a day-to-day basis. For additional information, please contact the FDA Submission Group at: IND_PM@mdanderson.org

How do I submit a request to use a Humanitarian Use Device (HUD) for clinical use?

MD Anderson utilizes the IRB to review and approve the use of a HUD before it can be used at a facility for clinical care. You can refer to HRP-323 - WORKSHEET - Criteria for Approval HUD for additional information regarding the criteria that the IRB uses to review and approve HUD uses. The clinical use of a HUD is not considered Human Research but must still be submitted for review and approval by the IRB prior to clinical use (with the exception of emergency use). An informed consent form is not required by the IRB for HUD use as the IRB expects that the HUD patient brochure will be used to inform the patient about the HUD and expected use. However, if the information in the patient brochure is not adequate, the IRB may request an informed consent form be used.

Complete the Initial Submission xForm in OneIRB and attach all requested documents. Attach the Patient Information Brochure (or equivalent) in lieu of an informed consent form. Have the xForm submitted by the PI. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Before submitting the research for initial review, you must:

- Obtain the financial interest status (“yes” or “no”) of each research staff.
- Obtain the agreement of other staff to his/her role on the project.

How do I request to rely on an external IRB?

Please refer to HRP-832 - WORKSHEET - Considerations for Ceding IRB Review for the criteria that are used to determine if MD Anderson can rely on an External IRB for review. Complete the Initial Submission xForm in OneIRB, and indicate that an External IRB will serve as the IRB of Record and attach all requested documents. When choosing the External IRB, if the IRB is not on the list, please contact the OHSP at OHSPReliance@mdanderson.org. The OHSP will then work with you to make sure that reliance criteria are met and that an appropriate reliance agreement is in place with the External IRB.

Have the xForm submitted by the PI. Personnel modifications are required to be submitted in OneIRB.

How do I request that this IRB serve as the IRB of record (sIRB) for my collaborative or multi-site research study?

Please refer to HRP-833 - WORKSHEET - Considerations for Serving as the sIRB for the criteria that are used to determine if MD Anderson can serve as the sIRB. On the Initial Submission xForm in OneIRB, indicate that the study is a multi-site or collaborative research study, then select “Yes” to the question “Will your IRB act as the single IRB of record for other participating sites?” Complete the rest of the submission form and attach all available documents.

Please refer to HRP-103p - INVESTIGATOR MANUAL – pSite for detailed information regarding the process for when MD Anderson will be serving as the sIRB.

What if I’m a student conducting Human Research?

Students may only participate in a research project where an MD Anderson faculty member or employee is serving as the student’s Mentor. When serving as a Mentor, the MD Anderson faculty or employee is responsible for providing supervision and guidance to the student by:

- Serving as the PI for the protocol;
- Overseeing the design and conduct of the protocol;
- Ensuring that the student assuming research duties is well-trained and competent;
- Ensuring that the student has taken the required institutional human subjects and privacy training courses;
- Protection of the rights and welfare of participants, including obtaining informed consent and maintaining privacy and confidentiality of data;
- Reviewing the Initial Submission application in OneIRB prior to submission to the IRB;
- Providing guidance in the protection of research participants;
- Assuring proper application and reporting to the IRB;
- Working with the student to identify modifications warranted by unanticipated problems or circumstances involving risks to participants or others.

MD Anderson employees who are students, and whose human research will fulfill an educational requirement, may be asked by their educational institution to have MD Anderson

serve as the sIRB. Please contact the OHSP for further assistance at OHSPReliance@mdanderson.org.

What do I need to submit to the IRB if I have a sponsor/multi-site protocol that I'm using?

If you will be using a sponsor/multi-site protocol for the conduct of a study, attach that protocol in OneIRB. You will also need to complete HRP-508 - TEMPLATE SITE SUPPLEMENT TO SPONSOR PROTOCOL to capture MD Anderson specific items related to the conduct of the protocol. Also attach the Site Supplement in OneIRB along with the sponsor protocol.

Does the IRB need to review advertisements that I will use for the study?

Yes, advertising or soliciting for study participants is the start of the informed consent process and participant selection process. Advertisements must be reviewed and approved by the IRB during the initial review of the study. Following initial review, if you decide to advertise for participants or change the advertisement, a study modification should be submitted for IRB approval. Refer to HRP-315 - WORKSHEET – Advertisements for guidelines.

IRB review and approval is generally not required for the following:

1. Communications intended to be seen or heard by health professionals, such as “dear doctor” letters and doctor-to-doctor letters.
2. News stories without recruitment material.
3. Publicity intended for other audiences, such as financial page advertisements directed toward prospective investors.
4. Clinical trial listing services as outlined below:
 - a. National Cancer Institute’s Cancer Clinical Trial Listing (PDQ)
 - b. AIDS Clinical Trials Information Service (ACTIS)
 - c. National Institutes of Health clinicaltrials.gov
 - d. MD Anderson Cancer Center clinicaltrials.org

These sites only contain basic necessary information about a clinical study (e.g. title, purpose, study summary, eligibility, study sites, contact information) and therefore IRB review of listings on these sites is not required.

What documents do not need to be submitted to the IRB, as IRB will not be reviewing and approving?

The following is a list of documents that do not need to be submitted to the IRB as long as they contain information that is consistent with the protocol or other IRB reviewed documents and do not include new information that would affect subjects’ willingness to take part in the study.

- Pharmacy Manuals
- Lab Manuals
- Dear Doctor Letters
- Case Report Forms
- Pill Diaries (electronic or paper)

- Manual of procedures
- Appointment Reminders
- Pregnant Partner ICDs for sponsored initiated trials
- Validated, widely recognized/accepted questionnaires, if indicated and described in the protocol

What do I need to take into consideration when initiating contact for the first time with potential participants?

If you do not have a pre-existing relationship with the potential participant (e.g. s/he is your patient), care should be taken to ensure that the potential participant understands how you acquired private information about them and that it was obtained in a legitimate manner. For example, if the potential participant was referred to you by the person's physician or other treating health care professional, you can cite that reason for the contact.

If you identify potential participants through chart reviews, an initial "cold contact" to a potential participant may cause concern regarding how you accessed personal information and could lead a complaint to the Privacy Office if misconstrued as illegal use of PHI. You may want to consider first sending a letter to potential participants and providing a telephone number or other means that the potential participant can use to verify that the study is MD Anderson research.

What guidelines should I follow if I want to pay participants in my study?

You can refer to HRP-316 - WORKSHEET – Payments for information regarding the criteria that the IRB uses to review and approve payment to participants. The amount of payment should be based on the incremental time, inconvenience and discomfort associated with participation in the research (compared with not participating) or the actual out-of-pocket expenses. It is appropriate to provide participants with higher payments for larger amounts of time, more inconvenience (e.g., strategies that require participant responses throughout the day, or requiring travel to distant study sites), and more discomfort (e.g., blood draw vs. bronchoscopy).

Payment to physicians or staff in exchange for referral of potential participants and payment tied to the rate or timing of enrollment (e.g., a bonus payment) is prohibited.

Based on the principle of equity, lotteries or drawings are discouraged. It is preferred that payment be distributed evenly among all participants. In the case where a lottery is critical to the success of the study, the plan must comply with applicable state laws.

Distribution of payments must be documented in the permanent study records. Procedures for distribution and documentation of payments must be clearly described in the protocol or appendices.

Can I enroll pediatric patients in Phase 1 adult studies?

Yes, pediatric patients under the age of 18 can be enrolled in Phase 1 studies if permitted in the inclusion/exclusion criteria of the study. Please refer to HRP-416 - CHECKLIST - Children for additional requirements.

Does my study need a Certificate of Confidentiality?

A Certificate of Confidentiality (CoC) protects the privacy of research participants by prohibiting disclosure of identifiable, sensitive research information to anyone not connected to the research except when the participant consents or in a few other specific situations. Please refer to HRP-333 - WORKSHEET - Certificate of Confidentiality for the criteria that are used to determine if you need/are automatically issued a Certificate of Confidentiality for your study.

How do I involve the community in the design and conduct of my Human Research?

The Community Scientist Program is designed to provide researchers with rapid feedback from trained community members to ensure their research projects are culturally appropriate and relevant to the community. Our Community Scientists are a diverse group of community members who provide valuable insights to researchers by sharing lived experiences with cancer or chronic illness.

This free program allows researchers to use Community Scientists as consultants on aspects of their proposals or active studies. As community/patient engagement increasingly becomes a requirement among funding agencies like the NIH and FDA, feedback sessions with the program can help with overall research outcomes.

Community Scientists:

- Serve as a sounding board to ensure research addresses local patient and community member interests;
- Provide advice on the development of culturally appropriate studies and recruitment strategies; and
- Provide input on research questions, study designs, and recruitment and retention barriers.
- For additional information contact:

CommunityScientistProgram@mdanderson.org

How do I create a consent document?

Please contact the consent editor team at consenteditors@mdanderson.org if you need help with creating an informed consent document (ICD). There are multiple consent templates available which can be found in the HRPP Toolkit Documents.

You should use the biomedical ICD template whenever the study involves an investigational agent (e.g. drug, device); the study is FDA regulated; or the study involves any medical procedures (e.g. blood draws, scans).

You should use the psychosocial ICD template whenever the study primarily involves procedures such as questionnaires, surveys, diaries or focus groups to evaluate the primary objective; quality of life studies; or studies that primarily involve behavioral interventions (e.g. therapy).

Note that all ICDs (and study summaries when using the short form VTPS process) must contain all of the required and all additional appropriate elements of informed consent disclosure. Review the “Long Form of Consent Documentation” section in HRP-314 - WORKSHEET - Criteria for Approval, to ensure that these elements are addressed.

If your research study meets the requirements for an exemption and there are interactions with participants, you may use an abbreviated process for obtaining consent. Consent can be verbal, but you must provide the following information to participants through an information sheet or written script:

The participant is being asked to participate in a research study;

A description of the procedure(s) the participant will be asked to complete;

Participation is voluntary; and

The investigator’s name and contact information.

We recommend that you date the revisions of your consent documents to ensure that you use the most recent version approved by the IRB.

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

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

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

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

What if I expect to enroll non-English speaking participants in my study?

You should identify in the protocol or HRP-508 - TEMPLATE SITE SUPPLEMENT TO SPONSOR PROTOCOL that non-English speakers can be enrolled in the study. If you know the language(s) of potential participants, the consent form must be translated into the language understandable to the non-English speaking participants expected to enroll in your study. You may use the services of MD Anderson Language Assistance department or another certified translation service to prepare the requisite translation of the English consent form. When the translation is not provided by the MD Anderson Language Assistance department, you must

upload into OneIRB (under “Other Attachments”) the documentation to show that the translated consent form has been certified as an accurate and complete translation of the English ICD.

If your study allows for non-English speakers to be enrolled in the study, but do not have a full translation of the consent in the patient’s primary language, you may provide the participant a Verbal Translation Preparative Sheet (VTPS) (also known as the consent short form) in the primary language of the participant. The VTPS informs the participant of the type of information they should receive during the informed consent process with the interpreter. An unexpected encounter using the VTPS should only occur twice for a single protocol. Following the second occurrence, you should have the consent document translated into that language if there are at least 5 accrual spots at MD Anderson remaining.

What are the different regulatory classifications that research activities may fall under?

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

- Not “Human Research”: Activities must meet the institutional definition of “Human Research” to fall under IRB oversight. Activities that do not meet this definition of are not subject to IRB oversight or review. Review HRP-310 - WORKSHEET - Human Research Determination for reference. Contact the IRB Office in cases where it is unclear whether an activity is Human Research.
- Exempt: Certain categories of Human Research may be exempt from regulation but require IRB review. It is the responsibility of the institution, not the investigator, to determine whether Human Research is exempt from IRB review. Review HRP-312 - WORKSHEET - Exemption Determination for reference on the categories of research that may be exempt.
- Review Using the Expedited Procedure: Certain categories of non-exempt Human Research may qualify for review using the expedited procedure, meaning that the project may be approved by a single designated IRB reviewer, rather than the convened board. Review HRP-313 - WORKSHEET - Expedited Review for reference on the categories of research that may be reviewed using the expedited procedure.
- Review by the Convened IRB: Non-Exempt Human Research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB.

What are the decisions the IRB can make when reviewing proposed research?

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

- Approval: Made when all criteria for approval are met. See “[How does the IRB decide whether to approve Human Research?](#)” below.

- Modifications Required to Secure Approval: Made when IRB members require specific modifications to the research before approval can be finalized.
- Tabled: Made when the IRB cannot approve the research at a meeting for reasons unrelated to the research, such as loss of quorum. When taking this action, the IRB automatically schedules the research for review at the next meeting.
- Deferred: Made when the IRB determines that the board is unable to approve research and the IRB suggests modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB in writing.
- Disapproval: Made when the IRB determines that it is unable to approve research and the IRB cannot describe modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision and gives the investigator an opportunity to respond to the IRB in person or in writing.

How does the IRB decide whether to approve Human Research?

The criteria for IRB approval can be found in HRP-312 - WORKSHEET - Exemption Determination for exempt Human Research and HRP-314 - WORKSHEET - Criteria for Approval for non-exempt Human Research. The latter worksheet references other checklists that might be relevant. All checklists and worksheets can be found in the HRPP Toolkit Documents.

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

What will happen after IRB review?

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

- If the IRB has approved the Human Research: The Human Research may commence once all other institutional approvals have been met. IRB approval is only good for a limited period of time which is noted in the approval letter.
- If the IRB requires modifications to secure approval and you accept the modifications: Make the requested modifications and submit them to the IRB. If all requested modifications are made, the IRB will issue a final approval. Research cannot commence until this final approval is received. If you do not accept the modifications, write up your response and submit it to the IRB.
- If the IRB defers the Human Research: The IRB will provide a statement of the reasons for deferral and suggestions to make the study approvable and give you an opportunity

to respond in writing. In most cases if the IRB's reasons for the deferral are addressed in a modification, the Human Research can be approved.

- If the IRB disapproves the Human Research: The IRB will provide a statement of the reasons for disapproval and give you an opportunity to respond in writing.

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

What are my obligations after IRB approval?

- 1) Do not start Human Research activities until:
 - a) You have obtained all other required institutional approvals, including approvals of departments or divisions that require approval prior to commencing research that involves their resources.
 - b) You have the final IRB approval letter and have activated the protocol in OnCore.
- 2) Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.
- 3) Ensure that Research Staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties assigned to them during the study.
- 4) Update the OHSP with any changes to the list of study personnel.
- 5) Personally conduct or supervise the Human Research. Recognize that the investigator is accountable for the failures of any study team member.
 - a) Conduct the Human Research in accordance with the relevant current protocol as approved by the IRB, and in accordance with applicable federal regulations and local laws.
 - b) When required by the IRB ensure that consent or permission is obtained in accordance with the relevant current protocol as approved by the IRB.
 - c) Do not modify the Human Research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to subjects.
 - d) Protect the rights, safety, and welfare of subjects involved in the research.
- 6) Submit to the IRB:
 - a) Proposed modifications as described in this manual. (See "[How do I submit a modification?](#)")
 - b) A continuing review application as requested in the approval letter. (See "[How do I submit continuing review?](#)")
 - c) A continuing review application when the Human Research is closed. (See "[How Do I Close Out a Study?](#)")
- 7) Complete the Report New Information xForm in OneIRB within five business days for any of the following information items:
 - a) Information that indicates a new or increased risk, or a new safety issue. For example:
 - i) 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.

- ii) 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.
- iii) Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol.
- iv) Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm.
- v) Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm.
- vi) Any changes significantly affecting the conduct of the research.
- b) Harm experienced by a subject or other individual, which in the opinion of the investigator are **unexpected** and **probably related** to the research procedures.
 - i) A harm is “unexpected” when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.
 - ii) A harm is “probably related” to the research procedures if in the opinion of the investigator, the research procedures more likely than not caused the harm.
- c) 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.
- d) Audit, inspection, or inquiry by a federal agency and any resulting reports (e.g. FDA Form 483.)
- e) Written reports of study monitors that indicate non-compliance with federal regulations or failure to follow the protocol due to the action or inaction of the investigator or research staff that potentially impacts subject safety or integrity of the study.
- f) Failure to follow the protocol due to the action or inaction of the investigator or research staff that potentially impacts subject safety or integrity of the study.
- g) Breach of confidentiality.
- h) Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
- i) Incarceration of a subject in a study not approved by the IRB to involve prisoners.
- j) Complaint of a subject that cannot be resolved by the research team.
- k) Premature suspension or termination of the protocol by the sponsor, investigator, or institution.
- l) Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects).
- 8) Submit an updated disclosure of financial interests to the Conflict of Interest (COI) Office within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.

- 9) Do not accept or provide payments to professionals in exchange for referrals of potential subjects (“finder’s fees.”)
- 10) Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment (“bonus payments.”)
- 11) See additional requirements of various federal agencies in [Appendix A](#). These represent additional requirements and do not override the baseline requirements of this section.
- 12) 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. Please contact the study sponsor with any questions.
 - a) If certain information should not be made publicly available on a Federal website (e.g. confidential commercial information), the supporting Federal department or agency may permit or require redactions to the information posted. Contact the Federal department or agency supporting the clinical trial for a formal determination.
 - b) Contact the supporting Federal department or agency sponsor with any other questions regarding consent form posting obligations.
- 13) Keep data confidential. MD Anderson has guidelines for best practices for maintaining confidentiality found at:
<https://mdandersonorg.sharepoint.com/sites/compliance/SitePages/Privacy-and-Information-Security.aspx>

What are my obligations as investigator when relying on an external IRB?

- 1) Obtain appropriate approvals from OHSP prior to seeking reliance on an external IRB (except for NCI CIRB).
- 2) Submit the external IRB study in OneIRB for review and reliance confirmation.
- 3) Ensure that local study team members satisfy training requirements.
- 4) Comply with determinations and requirements of the external IRB.
- 5) Provide the external IRB with requested information about local requirements or local research context issues relevant to the IRB’s determination prior to IRB review.
- 6) Notify the external IRB when local policies that impact IRB review are updated.
- 7) Cooperate in the external IRB’s responsibility for initial and continuing review, record keeping and reporting and providing all information requested by the external IRB in a timely manner.
- 8) Disclose conflicts of interest as required by the external IRB and complying with management plans that may result.
- 9) Promptly report to the external 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.
- 10) When enrolling participants, obtain, document and maintain records of consent for each participant or each participant's legally authorized representative.

- 11) Promptly report to the external IRB any unanticipated problems involving risks to participants or others according to the requirements specified in the reliance agreement.
- 12) Provide the external IRB with data safety monitoring reports in accordance with the external IRB's reporting policy.
- 13) Report non-compliance, participant complaints, protocol deviations or other events according to the requirements specified in the reliance agreement.
- 14) Submit external IRB determinations of Serious Non-Compliance; Continuing Non-Compliance; Suspension of IRB Approval; Termination of IRB Approval; or Unanticipated Problems Involving Risks to Subjects or Others for an event that occurred locally at MD Anderson as Reportable New Information in OneIRB.
- 15) Specify 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 external IRB.
- 16) Update the OneIRB study record when the following are issued by the external IRB:
 - a. Closure of the study at MD Anderson
- 17) Update local study members and any study team changes in OneIRB for those who require access to the OneIRB external IRB study record.
- 18) Manage any MD Anderson ancillary reviews required for modifications to external IRB studies.

How do I document consent?

Please refer to SOP 04_Informed Consent Process which can be found at:

<https://mdandersonorg.sharepoint.com/sites/clinical-research-administration/SitePages/Policies-and-Procedures.aspx> for detailed information about how to obtain and document consent.

Use the consent forms approved by the IRB. Complete all items in the signature block, including dates.

The following are the requirements for ICDs:

- The participant or representative signs and dates the consent document.
- The individual obtaining consent signs and dates the consent document.
- Whenever the IRB or the sponsor require a witness to the oral presentation, the witness signs and dates the consent document.
- For 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 subject.

The following are the requirements when using the VTPS (short form consent):

- The participant or representative signs and dates the VTPS.
- The individual obtaining consent signs and dates the summary (which is the English version of the ICD).
- The witness to the oral presentation signs and dates the VTPS and the English version of the ICD.

- Copies of the signed and dated VTPS and English ICD are provided to the person(s) signing those documents.

How do I submit a modification?

Complete the Modification xForm in OneIRB and attach all requested documents, have the xForm submitted by the PI or PI Proxy. Tracked changes versions of documents should be submitted, along with a summary of changes, when applicable, so the IRB can focus on the changes. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Please note that research must continue to be conducted without inclusion of the modification until IRB approval is received.

Do I need to submit every Investigator Brochure update to MD Anderson's IRB for review?

No. The MD Anderson IRB only requires the submission of IB updates that include a change in risk OR that result in a change to the protocol or the informed consent document. Updates to drug or device information should be submitted in OneIRB as a modification (MOD) to Other Parts of the Study and the applicable document(s) should be updated. Regardless of submission to the IRB, study teams should keep documentation of all IB updates in regulatory files.

How do I submit a request for Single Subject Exception?

(previously also called a PI override or prospective protocol deviation)

A single subject exception can only be submitted for industry sponsored studies (the Office of Clinical Research is no longer allowing single subject exceptions for investigator initiated studies). These should be submitted to the MD Anderson IRB in OneIRB as a modification.

If you are relying on an external IRB, please refer to that specific IRB's policies and procedures for how to submit requests for single subject exceptions.

How do I submit continuing review?

OneIRB will send you a reminder 90, 60, 30 and 7-days before the IRB approval end date of your study. Complete the Continuing Review xForm in OneIRB, attach all requested supplements, and have the xForm submitted by the PI or PI proxy. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

If the continuing review application is not received by the date requested in the approval letter, you will be restricted from submitting new Human Research until the completed application has been received and approved.

If the approval of Human Research expires, the study record status in OneIRB will transition to "Lapsed." If this occurs, there are two applicable scenarios described below; please be sure to correctly identify which scenario is applicable to your situation:

- 1) If no continuing review (CR) was submitted to the IRB prior to lapse, or the CR was submitted late (<60 days to expiration) and there was not time to schedule IRB review prior to lapse, then all Human Research procedures related to the protocol under review must cease, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection or analysis of private identifiable information. Continuing Human Research procedures is a violation of institutional policy. If current participants will be harmed by stopping Human Research procedures that are available outside the Human Research context, provide these on a clinical basis as needed to protect current participants. If current participants will be harmed by stopping Human Research procedures that are not available outside the Human Research context, immediately contact the OHSP staff at IRB_Help@mdanderson.org and provide the number of enrolled participants, how many are on active protocol therapy, and why they will be harmed by stopping Human Research procedures. The request will be forwarded to the IRB Chair for review and approval.
- 2) If the study team did submit a continuing review (CR) prior to lapse, and on-time (≥60 days prior to expiration), AND your continuing review application is reviewed prior to the IRB approval end date AND the IRB requires modifications to secure approval BUT you have either not submitted the requested modifications or the IRB has not approved the submitted modifications prior to the IRB approval end date, the status of the study in OneIRB will still transition to “Lapsed.” During this time (between the IRB approval end date and when the modifications required to secure approval are approved by the IRB), you cannot enroll new participants in the study but may continue study-related procedures for currently enrolled participants.

In either scenario described above, if participants are enrolled on a study and the study lapses, the IRB will review the lapse to determine if it constitutes an incident of serious and/or continuing non-compliance. A Corrective Action Plan should be submitted with the Continuing Review to describe how future lapses will be avoided.

How do I close out a study?

Complete the Study Closure xForm in OneIRB, attach all requested documents, and have the xForm submitted by the PI or PI Proxy. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

Please note that the following activities can still be carried out after a study is closed with the IRB (and the study does not need to be kept open with the IRB for these to occur):

- Invoicing the sponsor for research-related items and services.
- Receipt of final payment from a sponsor.
- Return of destruction of unused investigational drug(s).

- Preparation of a final research report provided the report does not involve the use or disclosure of protected health information/individually identifiable information of participants.
- Resolution of data queries from the sponsor or corrections that are required as a result of FDA or other regulatory body inspections after the research has been closed with the IRB, provided resolution does not involve the use or disclosure of protected health information/individually identifiable information of participants.
- Data analysis required to respond to queries from journal editors, manuscript reviewers or readers, provided such analysis does not involve the use or disclosure of protected health information/individually identifiable information of participants.

How long do I keep records?

Maintain your Human Research records, including signed and dated consent documents for at least three years after completion of the research. Maintain signed and dated HIPAA authorizations and consent documents that include HIPAA authorizations for at least six years after completion of the research.

If your Human Research is sponsored, contact the sponsor before disposing of Human Research records.

What if I need to use an unapproved drug, biologic, or device and there is no time for IRB review?

Contact the OHSP immediately to discuss the situation. If there is no time to make this contact, see HRP-322 - WORKSHEET - Emergency Use for the regulatory criteria allowing such a use and make sure these are followed. Use HRP-506 – TEMPLATE CONSENT DOCUMENT - Emergency Use ICD to prepare your consent document. You will need to submit a report of the emergency use to the IRB within five working days of the use. You should submit the request for emergency use or 5-day report of the emergency use in OneIRB and complete the Application for Emergency Use of Test Article xForm.

Emergency use of an unapproved drug or biologic in a life-threatening situation without prior IRB review is “research” as defined by the FDA, and the individual receiving the test article is a “subject” as defined by the FDA, and therefore is governed by FDA regulations for IRB review and informed consent. Emergency use of an unapproved device without prior IRB review is not “research” as defined by the FDA and the individual receiving the test article is not a “subject” as defined by the FDA. However, FDA guidance recommends following similar rules as for emergency use of an unapproved drug or biologic.

Individuals receiving an unapproved drug, biologic, or device without prior IRB review cannot be considered a “subject” as defined by DHHS and their results cannot be included in prospective “research” as that term is defined by DHHS.

What if I have an expanded access use/request for an unapproved drug, biologic or device?

Expanded access is a specific pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available. Please visit FDA's website for detailed information:

<https://www.fda.gov/news-events/public-health-focus/expanded-access>

There are 3 different types of expanded access:

1. Expanded access for individual patients (referred to at MD Anderson as "SPIND"), including for emergency use
2. Expanded access for intermediate-size patient groups
3. Expanded access for widespread treatment use

For emergency use, please refer to [What if I need to use an unapproved drug, biologic, or device and there is no time for IRB review?](#)

For any non-emergency use expanded access request, you will need to create and Initial Submission Form in OneIRB and complete the xForm. Refer to [How do I submit new Human Research to the IRB?](#)

- For individual patient expanded access (SPIND) requests:
 - If you checked "Request for Authorization to Use Alternative IRB Review Procedures" on FDA Form 3926 (field 10.b.) or have a separate waiver request included with FDA Form 1571 for the purpose of obtaining concurrence from an IRB Chair or designee, include that information in the application.
 - Attach the proposed treatment plan for the patient in lieu of a research protocol.
 - Use HRP-506 – TEMPLATE CONSENT DOCUMENT - Emergency Use to prepare your consent document.

For individual patient expanded access requests (SPIND) please contact:
IND_PM@mdanderson.org

How do I get additional information and answers to questions?

This document and the policies and procedures for the IRB are available in the HRPP Toolkit Documents. You can also view our FAQs found on our storefront on SharePoint.

If you have any questions or concerns, about the Human Research Protection Program, contact the OHSP at:

Hallie Kassan, MS, CIP

Director, Human Subjects Protection
7007 Bertner Ave., Unit 1637
Houston, TX 77030
Email: IRB_Help@mdanderson.org
(713) 792-6477

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

Appendix A-1 ***Additional Requirements for DHHS-Regulated Researchⁱⁱ***

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

- ii. Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;
 - iii. Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
 - iv. Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human participants in research.
- d. Researchers must inform participants of the protections and limitations of certificates of confidentiality (see language in HRP-502 - TEMPLATE CONSENT DOCUMENT).
 - i. For studies that were previously issued a Certificate and notified participants of the protections provided by that Certificate, NIH does not expect participants to be notified that the protections afforded by the Certificate have changed, although IRBs may determine whether it is appropriate to inform participants.
 - ii. If part of the study cohort was recruited prior to issuance of the Certificate, but are no longer actively participating in the study, NIH does not expect participants consented prior to the change in authority, or prior to the issuance of a Certificate, to be notified that the protections afforded by the Certificate have changed, or that participants who were previously consented to be re-contacted to be informed of the Certificate, although the IRB may determine whether it is appropriate to inform participants.
- e. Researchers conducting research covered by a certificate of confidentiality, even if the research is not federally funded, must ensure that if identifiable, sensitive information is provided to other researchers or organizations, the other researcher or organization must comply with applicable requirements when research is covered by a certificate of confidentiality.

Appendix A-2 ***Additional Requirements for FDA-Regulated Research***

1. When a subject withdraws from a study:ⁱⁱⁱ
 - a. The data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.
 - b. An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.
 - c. If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). IRB approval of informed consent documents is required.
 - d. If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent.
 - e. An investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.
2. For FDA-regulated research involving investigational products please refer to SOP07 Control and Accountability of Investigational Products.

Appendix A-3 ***Additional Requirements for Department of Defense (DOD) research***

1. When appropriate, research protocols must be reviewed and approved by the IRB prior to the Department of Defense approval. Consult with the Department of Defense funding component to see whether this is a requirement.
2. Civilian researchers attempting to access military volunteers should seek collaboration with a military researcher familiar with service-specific requirements.
3. Employees of the Department of Defense (including temporary, part-time, and intermittent appointments) may not be able to legally accept payments to participate in research and should check with their supervisor before accepting such payments. Employees of the Department of Defense cannot be paid for conducting research while on active duty.
4. Service members must follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty or off-duty.
5. Components of the Department of Defense might have stricter requirements for research-related injury than the DHHS regulations.
6. There may be specific educational requirements or certification required.
7. When assessing whether to support or collaborate with this institution for research involving human subjects, the Department of Defense may evaluate this institution's education and training policies to ensure the personnel are qualified to perform the research.
8. When research involves U.S. military personnel, policies and procedures require limitations on dual compensation:
 - a. Prohibit an individual from receiving pay of compensation for research during duty hours.
 - b. An individual may be compensated for research if the participant is involved in the research when not on duty.
 - c. Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to \$50 for each blood draw.
 - d. Non-Federal persons may be compensated for research participating other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.
9. Surveys performed on DOD personnel must be submitted, reviewed, and approved by the DOD Information Management Control Officer (IMCO) after the research protocol is reviewed and approved by the IRB. When a survey crosses DOD components, additional review is required. Consult with the Department of Defense funding component to coordinate this review.
10. When research involves large scale genomic data (LSGD) collected on DOD-affiliated personnel, additional protections are required:
 - a. Additional administrative, technical, and physical safeguards to prevent disclosure of DoD-affiliated personnel's genomic data commensurate with risk (including secondary use or sharing of de-identified data or specimens)
 - b. Research will apply an HHS Certificate of ConfidentialityDoD Component security review
11. Data or information sent to a DOD component under a pledge of confidentiality for exclusively statistical purposes must be used exclusively for statistical purposes and may not be disclosed in identifiable form for any other purpose, except with the informed consent of the respondent.

12. When conducting multi-site research, a formal agreement between institutions is required to specify the roles and responsibilities of each party.
13. The following must be reported to the applicable DOD Component Office of Human Research Protections within 30 days:
 - a. When significant changes to the research protocol are approved by the IRB or EC:
 - i.Changes to key investigators or institutions.
 - ii.Decreased benefit or increased risk to participants in greater than minimal risk research.
 - iii.Addition of vulnerable populations as participants.
 - iv.Addition of DOD-affiliated personnel as participants.
 - v.Change of reviewing IRB.
 - b. When the organization is notified by any federal body, state agency, official governing body of a Native American or Alaskan native tribe, other entity, or foreign government that any part of an HRPP is under investigation for cause involving a DOD-supported research protocol.
 - c. Any problems involving risks to participants or others, suspension or termination of IRB approval, or any serious or continuing noncompliance pertaining to DOD-supported human participant research.
 - d. The results of the IRB's continuing review, if required.
 - e. Change in status when a previously enrolled participant becomes pregnant, or when the researcher learns that a previously enrolled participant is pregnant, and the protocol was not reviewed and approved by the IRB in accordance with 45 CFR 46, Subpart B.
 - f. Change in status when a previously enrolled participant becomes a prisoner, and the protocol was not reviewed and approved by the IRB in accordance with 32 CFR 219, Subpart C.
 - g. Closure of a DOD-supported study.
14. For human participant research that would not otherwise be approved but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates, written approval from the DOD Office for Human Research Protections must be obtained through the DOD Component Office of Human Research Protections prior to research starting.
15. Other specific requirements of the Department of Defense research be found in the "Additional Requirements for Department of Defense (DOD) Research" section in the IRB's HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

Appendix A-4 ***Additional Requirements for Department of Education (ED) Research***

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

Appendix A-5 ***Additional Requirements for Clinical Trials (ICH-GCP)***

1. Investigator's Qualifications and Agreements

- a. The clinical trial should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice and the applicable regulatory requirements.
- b. The investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirements, and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authorities.
- c. The investigator should be thoroughly familiar with the appropriate use of the investigational product, as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.
- d. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
- e. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authorities.
- f. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

2. Adequate Resources

- a. The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.
- b. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
- c. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- d. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product, and their trial-related duties and functions.

3. Medical Care of Trial Subjects

- a. A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
- b. During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illnesses of which the investigator becomes aware.

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

accountability at the trial site to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

- c. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product received from the sponsor.
 - d. The investigational product should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.
 - e. The investigator should ensure that the investigational product is used only in accordance with the approved protocol.
 - f. The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.
 - g. Randomization Procedures and Unblinding: The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product.
7. Informed Consent of Trial Subjects
- a. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB's written approval opinion of the written informed consent form and any other written information to be provided to subjects.
 - b. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB's approval opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.
 - c. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

- d. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.
- e. The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval opinion by the IRB.
- f. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.
- g. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.
- h. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.
- i. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.
- j. Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:
 - i. That the trial involves research.
 - ii. The purpose of the trial.
 - iii. The trial treatments and the probability for random assignment to each treatment.

- iv. The trial procedures to be followed, including all invasive procedures.
- v. The subject's responsibilities.
- vi. Those aspects of the trial that are experimental.
- vii. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- viii. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- ix. The alternative procedures or courses of treatment that may be available to the subject, and their important potential benefits and risks.
- x. The compensation and/or treatment available to the subject in the event of trial related injury.
- xi. The anticipated prorated payment, if any, to the subject for participating in the trial.
- xii. The anticipated expenses, if any, to the subject for participating in the trial.
- xiii. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- xiv. That the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- xv. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- xvi. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- xvii. The persons to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- xviii. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- xix. The expected duration of the subject's participation in the trial.
- xx. The approximate number of subjects involved in the trial.
- k. Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable

representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

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

Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

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

reporting requirements and within the time periods specified by the sponsor in the protocol.

- c. For reported deaths, the investigator should supply the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).
 - d. **Premature Termination or Suspension of a Trial** If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirements, should inform the regulatory authorities. In addition:
 - i. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB, and should provide the sponsor and the IRB a detailed written explanation of the termination or suspension.
 - ii. If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.
 - iii. If the IRB terminates or suspends its approval opinion of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.
11. **Final Reports by Investigator:** Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the trial's outcome, and the regulatory authorities with any reports required.

Appendix A-6 ***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.
2. The Office for Human Research Protections expects that all sites located in the United States participating in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.

The following research is not subject to this provision:

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

Appendix A-7 ***Additional Requirements for Research Subject to EU General Data Protection Regulations (GDPR)***

This information applies to Human Research involving personal data about individuals located in (but not necessarily citizens of) European Union member states, Norway, Iceland, Liechtenstein, and Switzerland is subject to EU General Data Protection Regulations.

1. For all prospective Human Research 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.
2. Where FDA or DHHS regulations apply in addition to EU GDPR regulations, ensure that procedures related to withdrawal from the research, as well as procedures for managing data and biospecimens associated with the research remain consistent with Appendices A-1 and A-2 above.

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

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

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

^{iv} 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.

^v 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.