Human Research Protection Program (HRPP)

Investigator Guidance Manual

Version E

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About This Manual

Purpose of this Manual

This manual is designed to be an abbreviated guide to Sharp HealthCare (SHC) policies, procedures, guidances, and resources related to the conduct of human research at SHC. All human research related activities must be in full compliance with SHC Human Research Protection Program (HRPP), SHC Institutional Review Board (IRB) policies and guidances, and federal regulations to ensure the protection of human research participants.

Throughout this document, the term organization refers to SHC. Additionally, investigator and researcher, and subjects and participants are used interchangeably. To access the documents referenced in this manual, go to "Researcher Resources" in CREDIT/IRBANA (SHC's IRB management system; hereafter "IRBANA"), www.Sharp.com/Research, or research@sharp.com. Updates and revisions to HRPP documents will be posted on the main page of IRBANA and Sharp.com/Research. Researchers will be notified of substantive HRPP policy changes and updates through email notifications, with footnotes on IRB regulatory communications, and at HRPP education and training sessions.

Intended Audience

The intent of this manual is to provide support for investigators, study coordinators, and research team members involved in conducting human subjects' research at SHC. Physician principal investigators and sub-investigators are to be members of the SHC attending medical staff at the entity/ies where the research is being conducted.

Version History

Version	Date	Revision Description	Originator
A	01-OCT-2014	Initial Version	Director of Research
B	01-MAR-2015	Modifications from AAHRPP Step 1 Review	Director of Research
C	01-OCT-2017	Updated to Reflect Organizational Changes	Director of Research
D	01-SEP-2018	Updated after AAHROO Document Audit	Director of Research
E	21-Jan-2018	Updated to Reflect the Revised Common Rule	Director of Research

Human Research Basics

What is Human Research?

Human Research is defined in Department of Health and Human Services (DHHS) regulations 45 Code of Federal Reulations (CFR) §46.102(l) and 45 CFR §46.102(e) and in Food and Drug Administration (FDA) regulations 21 CFR §56.102(c), 21 CFR §56.102(e), and 21 CFR §812.3(p). An algorithm for determining whether an activity is human research can be found in WORKSHEET: Human Research Determination (HRP-310). This worksheet provides guidance in determining whether an activity meets either the DHHS or FDA definition of human research. In questionable cases, the IRB makes the ultimate determination as to whether an activity constitutes human research subject to IRB oversight.

The specific definitions of research, human subject, etc., are found in *GUIDANCE: Definitions (HRP-001)*.

Human research may not be conducted without prior IRB review and approval or prior to receipt of an IRB determination that the human research is exempt. For additional questions about whether an activity is human research, contact the SHC IRB Office at research@sharp.com.

What is a Clinical Trial?

A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

What is a Sponsor?

The sponsor is the organization or individual who initiates a clinical trial and is responsible for registering the clinical trial on clinicaltrials.gov, a clinical trial registry bank. There are organizational sponsors (e.g., pharmaceutical or device manufacturers or federal agencies, such as the National Institutes of Health [NIH]) and there are sponsor-investigators. A sponsor-investigator is an individual who both initiates and conducts an investigation, and under whose immediate direction, the investigational drug or device is administered, dispensed, or used.

Who is the Principal Investigator?

The principal investigator is the person responsible for the conduct of the clinical trial. If the clinical trial is conducted by a team of individuals, the principal investigator is the responsible leader of the team.

Human Research Protection at Sharp HealthCare

What is the SHC Center for Research (SCFR)?

The Sharp Center for Research (SCFR) is the coordinating office for the HRPP and IRB at SHC. It is located within the Clinical Effectiveness division. The Director of the SCFR reports to the Senior Vice President of Clinical Effectiveness, who in turn reports to the Executive Vice President. The Executive Vice President at SHC is the designated Institutional Official (IO) for research at SHC. The SHC IO is legally authorized to act for the institution, is responsible for ensuring that the HRPP functions effectively, and that the institution provides the resources and support necessary to comply with all requirements applicable to research involving human subjects.

What is the SHC Human Research Protection Program (HRPP)?

SHC's HRPP is a comprehensive system ensuring the protection of the rights and welfare of participants in human research. The HRPP is the organization's overall plan to protect subjects in human research and is responsible for:

- Determining the ethical principles that the organization follows governing the conduct of human research.
- Complying with applicable laws that govern human research.
- Determining when the organization becomes "engaged in human research" and when someone is acting as an agent of the organization conducting human research.
- Deciding the types of human research that may not be conducted.
- Defining the roles and responsibilities of individuals within the organization.
- Providing oversight of the SHC IRB.
- Providing researchers and research staff with answers to questions; allowing them to express concerns and convey suggestions regarding the HRPP. Researchers and research staff may contact the Director of Research at (858) 939-7196 with questions, concerns or to convey suggestions regarding the SHC HRPP.

The SHC HRPP's Assurance of Compliance for Human Subject Protection

The SHC HRPP maintains a Federalwide Assurance (FWA, 00000084) that obligates the organization to uphold ethical principles and is applicable whenever non-exempt research is conducted or supported by any United States federal department or agency that has adopted the Federal Policy for the Protection of Human Subjects (also known as the Common Rule).

What is the SHC Institutional Review Board (IRB)?

The SHC IRB is an interdisciplinary committee within SHC that has oversight responsibility to ensure the ethical conduct of research in the protection of human subjects and facilitate the optimum balance between valid and useful biomedical, social, and behavioral research.

The mission of the SHC IRB is to protect the rights, welfare, and privacy of human research participants.

The SHC IRB is guided by ethical principle mandates outlined in the Belmont Report (1979) and legal mandates outlined in the Code of Federal Regulations (CFR), Title 45 Part 46. To achieve these mandates, the SHC IRB will:

1. Review all submitted research protocols thoroughly to ensure research subject's rights and welfare are not violated.
2. Apply the highest level of ethical standards in reviewing research protocols.
3. Adhere to federal and local guidelines in human rights protection.
4. Require SHC IRB staff, board members, investigators and their research teams to complete periodic education in human subject protection.

See *POLICY: Human Research Protection Program (16500.99)* and *ADMINISTRATIVE: IRB HRPP Charter (HRP-110)* for further information.

What is the SHC System Administrative Review Committee (ARC)?

The SHC System Administrative Review Committee (ARC) is a standing advisory committee consisting of representatives from each of the SHC Service Lines, hospital entities, and the Sharp Rees-Stealy Medical Group research department. The following departments are represented on the ARC committee: administration, nursing, investigational pharmacy, lab, finance, legal, and supply chain. Other representatives, such as respiratory, pathology, radiation safety committee, etc., may be called upon to provide consultation to the ARC committee depending on the requirements of a specific research study. The purpose of this committee is to review and determine the appropriateness and feasibility of conducting a proposed research study (e.g., clinical trials, outcomes research, and nursing) at SHC based upon the organizational resource requirements of the proposed research and any potentially conflicting SHC initiatives.

The SHC IRB is responsible for providing the documents needed (protocol, informed consent, investigator brochure, etc.) for ARC review. If the ARC does not approve a proposed research study, the IRB will not conduct further review or action and the study will not obtain SHC or other IRB/Ethics Committee (EC) approval.

See *GUIDANCE: Review of Scientific Merit and Organizational Feasibility (HRP-045), DATABASE: System Administrative Review Committee (ARC) Monthly Spreadsheet Reviewer Assignments (HRP-601), PROCESS MAP: SHC System Administrative Review Committee (ARC) Process Map (HRP-701), DATABASE: System Administrative Review Committee (ARC) Monthly Spreadsheet Outcome (HRP-610) and TEMPLATE: Letter: System Administrative Review Committee (ARC) Outcome (HRP-526)* for additional information.

IRB Requirements

What Training is Required to Conduct Human Research?

Investigators and staff involved in the design, conduct, or reporting of research are required to complete training as identified below. IRB approval will not be granted for proposed research in which all members of the research team have not completed human research protections training, other required education, and yearly evaluation.

See *GUIDANCE: Education (HRP-002)* for further information.

	Investigator and Site Research Staff Training	
	Module	Timeline
Required Initial Training	Protecting Human Research Participants Tutorial[1]	Within 30 days of SHC engagement
	NIH Conflict of Interest Training required for investigators receiving grant funding from the PHS (e.g., NIH)[2]	Within 30 days of SHC engagement
	SHC Employees: HRPP Orientation	Within 30 days of SHC employment
	Non-SHC Employees/Medical Staff: Required Compliance/Safety Training	Within 30 days of SHC engagement
	HIPAA Training[3]	Within 30 days of SHC engagement
	Protocol-Specific Education	Sponsor Site Initiation Visit and/or Investigator Meeting (IM)
	Pharmacy	Sponsor Site Initiation Visit
	Good Clinical Practice Training	Within 90 days of SHC engagement, if required by site or sponsor
Required Continuing Training	Protecting Human Research Participants Tutorial (see footnote 1)	Every three years
	Good Clinical Practice Training	Every three years, if required by site or sponsor
	NIH Conflict of Interest Training required for investigators receiving grant funding from the PHS (e.g., NIH) (see footnote 2)	As required by funding agency
	SHC Employees: HRPP Orientation	Every three years
	Non-SHC Employees/Medical Staff: Required Compliance/Safety Training	Annually
	HIPAA Training (see footnote 3)	Annually
Ongoing Education	SHC-Sponsored Education Events	Quarterly
	Professional Organization-sponsored Education Events	When Available
Evaluation	Understanding of HRPP	Yearly

[1] The Protecting Human Research Participants Tutorial can be found at: https://sharp.cloud-cme.com/default.aspx?EID=10524&P=3000&CaseID=314%23. Contact CME@sharp.com for questions or problems.
[2] https://grants.nih.gov/grants/policy/coi/tutorial2018/story_html5.html
[3] HIPAA training must be completed before handling Protected Health Information (PHI) or within 30 days of appointment, and must be renewed according to institution requirements. (SHC POLICY: Compliance/Privacy Education and Training [01510]; SHC POLICY: Research and the HIPAA Privacy Rule [16508])

How does SHC protect the Privacy and Confidentiality of Research Participants?

The SHC IRB reviews research protocols and investigator plans for evidence that the study design adequately considers the privacy rights and expectations of subjects, and offers an adequate plan for maintaining the confidentiality of sensitive information related to the study subjects. See *GUIDANCE: Privacy and Confidentiality (HRP-008)*.

What are the Guidelines for Writing an Investigator Protocol?

As a starting point for drafting a new research protocol, use *TEMPLATE: Protocol (HRP-500)* and reference the instructions in italicized text for guidance on what information the IRB requires when reviewing research. All italicized comments are meant to be deleted prior to submission. Depending on the nature of the research, certain sections of the *TEMPLATE: Protocol (HRP-500)* may not be applicable to the research study. Indicate this as appropriate.

Investigators may request the use or disclosure of protected health information (PHI) solely to prepare a research protocol[4] or for similar purposes preparatory to research, provided that:

- Researcher(s) will not remove any PHI from the covered entity[5], and
- PHI for which access is sought is necessary for the research purpose.

This provision might be used, for example, to design a research study or to assess the feasibility of conducting a study. A completed *FORM: Request for Data Preparatory to Research (HRP-200)* is to be submitted and approved by the SHC IRB before such access PHI can begin. For more information, refer to 45 CFR 164.512(i)(1)(ii) and Section III.E. of *POLICY: Research and the HIPAA Privacy Rule (16508)*.

Regulations require that members of the following populations may not be involved as subjects in research unless additional required protections are delineated in the protocol:

- Adults unable to consent
- Individuals who are not yet adults (neonates/infants, children, teenagers)
- Pregnant women, fetuses
- Prisoners - Sharp HealthCare IRB does not review human research involving prisoners as subjects.

What is Required in an Informed Consent Document?

For guidance on creating an informed consent document for use in research, see *TEMPLATE: Informed Consent Document with California Bill of Rights (HRP-502)* or a short form of consent *TEMPLATE: Consent-Short Form (HRP-507)*. To create an assent document for children, use *TEMPLATE: Child Assent (ages 7-12) (HRP-503)* or *TEMPLATE: Adolescent Assent (Ages 13-17) (HRP-504), and also TEMPLATE: Parent Permission with California Bill of Rights (HRP-505).*

4 https://www.hhs.gov/hipaa/for-professionals/privacy/guidance/research/index.html
5 https://www.hhs.gov/hipaa/for-professionals/covered-entities/index.html

Long form consent documents and summaries for short form consent documents are to contain all required elements of informed consent. Review the IRB's *WORKSHEET: Criteria for Approval and Additional Considerations (HRP-314)* to ensure that these elements are addressed.

Consent documents are to include a version date to ensure the most recent IRB approved version is used.

In addition, the State of California requires language related to the Health Information Portability and Accountability Act (HIPAA) and PHI be in 14-point font. *TEMPLATE: PHI Authorization (HRP-509)* may be prepared as a stand-alone document or the elements required by HIPAA can be added to the end the consent document itself[6]. Review the IRB's *CHECKLIST: PHI Authorization Elements (HRP-422)* to ensure that these elements are addressed.

For additional information regarding consent documents, see *GUIDANCE: Legally Authorized Representatives (Surrogate Consent)(HRP-013), GUIDANCE: Child Assent, Parents or Guardians Permission, Waiver and Special Circumstances (HRP-014), GUIDANCE: Informed Consent Process for Research (HRP-090), GUIDANCE: Written Documentation of Consent (HRP-091), TEMPLATE: Informed Consent with CA Bill Of Rights and PHI Authorization (HRP-502), GUIDANCE: Waiver or Alteration to Consent and /or HIPPA Authorization (HRP-016),* and *WORKSHEET: Emergency Use (HRP 322*), as applicable.

What is the Process to Submit New Human Research to the SHC IRB?

To submit a new human research protocol to the IRB, complete *FORM: Initial IRB Review Application (HRP-211)* and submit electronically to the SHC IRB at research@sharp.com or via IRBANA with all applicable required supporting documentation (listed in the checklist on the last page of the application form).

What are the Processes for Relying on an External IRB to Oversee Human Subjects Research Instead of Sharp's IRB?

SHC has established processes for reliance on an external IRB, also known as a central IRB (CIRB) or single IRB (sIRB) review process. This enables a non-SHC IRB to serve as the IRB of Record for a single protocol or a portion of SHC's research portfolio. When SHC investigators consider participation in research that requires collaboration with an external Institution, it may be appropriate to rely on a qualified external IRB for review and approval of the research if such reliance benefits SHC, its investigators, and/or its research participants. When SHC relies on an external IRB for review and approval of human research, there must be a formal written agreement on record that clearly delineates the roles and responsibilities of each party. The SHC Institutional Official or his/her designee has the ultimate authority regarding whether or not to rely on an external IRB. The SHC IRB Office will conduct an administrative review to ensure that all institutional requirements are met. Research activities at SHC cannot begin until the investigator receives *TEMPLATE: Non-SHC IRB Reliance Permission to Proceed (HRP-558)* from the SHC IRB Office. In addition, investigators relying on an external IRB are still required to report certain items to the SHC IRB Office, per the specific reliance agreement with the external IRB.

See *GUIDANCE: SHC as Relying Organization or IRB of Record (HRP-009)* for further information.

What is Required by the SHC IRB when conducting Investigator-Initiated Research Internationally?

[6] California Code, Civil Code – CIV 56.11 requires that authorization for the release of medical information is clearly separate from any other language present on the same page, and is executed by a signature which serves no other purpose than to execute the authorization.

SHC investigators conducting investigator-initiated multi-center research involving international sites, follow *GUIDANCE: Reliance on External Review Boards (HRP-010).* Copies of the international IRB or Ethics Committee/s approval are to be provided to the SHC IRB prior to the initiation of the research at any SHC facility.

How Does SHC Manage Conflicts of Interest?

The principal investigator and other key study personnel (i.e., individuals who share responsibility for the design, conduct, or results reporting of a research project) are required to disclose all Financial Conflicts of Interest using *FORM: Financial Disclosure Statement (HRP-220)* when submitting *FORM: Initial IRB Review Application (HRP-211)*, and, if the conflict has changed, with *FORM: Continuation Request or Final Closure Report (HRP-212)*.

For the complete SHC IRB Financial Conflicts of Interest guidance, see *GUIDANCE: Financial Conflicts of Interest (HRP-055).*

What if an Unapproved Drug, Biologic, or Device is Needed and there is No Time for Prior IRB Review?

Emergency Use is defined by the FDA (21 CFR 56.102 [d]) as the use of an investigational drug, biologic, or device with a human patient in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval, see *GUIDANCE: Emergency Use Review (HRP-023), FORM: Emergency Use Notification (HRP-227), FORM: Exception from Informed Consent for Emergency Use (HRP-228),* and *WORKSHEET: Emergency Use (HRP-322).*

How Does the IRB Decide Whether to Approve Human Research?

The criteria for IRB approval can be found in *CHECKLIST: Exemption Determination (HRP-428)* for exempt human research and *WORKSHEET: Criteria for Approval and Additional Considerations (HRP-314)* for non-exempt human research. The latter worksheet references other checklists that might be relevant depending on the specifics of the study.

What Decisions does the IRB Make When Reviewing Proposed Research?

The IRB will make one of the following decisions when reviewing proposed research:

1. **Approval:** Made when all criteria for approval are met (see "How Does the IRB Decide Whether to Approve Human Research?" section below).
2. **Approval Pending Modifications (also known as Conditional Approval):** Made when IRB members require specific modifications to the research protocol or informed consent documents before approval can be finalized.
3. **Tabled:** Made when the IRB cannot approve the research at a meeting for reasons unrelated to the research, such as loss of quorum or the investigator did not appear to present their study at the scheduled IRB meeting. When taking this action, the IRB automatically schedules the research for review at the next meeting.
4. **Deferred***:* Made when the IRB determines that the committee is unable to approve the research and the IRB suggests modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB in person or in writing.

5. **Disapproval:** Made when the IRB determines that it is unable to approve the research and the IRB cannot describe modifications that might make the research approvable. When making this motion, the IRB provides its reasons for this decision to the investigator and gives the investigator an opportunity to respond to the IRB in person or in writing.

What are the Different Regulatory Classifications for Research Activities?

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

1. **Not Human Subjects Research (NHSR):** Activities must meet the DHHS or FDA definition of research involving human subjects for the activity to require IRB oversight. Activities that do not meet the definition of research involving human subjects are not subject to IRB oversight or review. Review *WORKSHEET: Human Research Determination (HRP-310*) for reference. When it is unclear whether a research activity meets the regulatory definition of human research, contact the SHC IRB at research@sharp.com.
2. **Exempt**: Certain categories of human research may be exempt from regulation, but require IRB review. The IRB, not the investigator, will determine whether human research is exempt from IRB oversight. Review *CHECKLIST: Exemption Determination (HRP-428)* for reference.
3. **Review Using the Expedited Procedure (also known as Expedited Review, or Non-Committee Review)**: Certain categories of non-exempt human research may qualify for review using the expedited procedure. The IRB, not the investigator, will determine whether the proposed research qualifies for expedited review. Review *CHECKLIST: Expedited Review Determination (HRP-429)* for reference.
4. **Review by the Convened IRB (also known as Full Board)**: Non-exempt human research that does not qualify for review using the expedited procedure must be reviewed by a convened IRB committee.

What is a Humanitarian Use Device (HUD)?

A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 8,000 individuals per year in the United States. FDA regulations (21 CFR 814.124) provide for the submission of a Humanitarian Device Exemption (HDE) in which the manufacturer is not required to provide the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose prior to marketing. This regulation was developed to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

A physician may use an HUD when agreeing to the following:

- The HUD will be used for treatment, diagnosis, or research in accordance with the labeling of the device, intended purpose, and in the designated population for which the FDA approved its use.
- The patient must be informed that: the HUD is a device authorized under Federal law for use; however, the effectiveness of the device for a specific indication has not been demonstrated.
- The informed consent of the patient or the patient's legally authorized representative will be obtained when the use of the HUD involves research and/or is required by the SHC IRB.

IRB Review of HUDs: An HUD requires prospective IRB review and approval. Use *FORM: Initial IRB Review Application (HRP-211)* for submitting an HUD for SHC IRB review. The use of an HUD does not constitute research unless the physician or health care provider and/or device manufacturer intends to collect and analyze data from its use.

Continuing Review Requirements for HUDs: The physician is responsible for fulfilling continuing review requirements of the SHC IRB at least annually (or more frequently if required by the SHC IRB). Use *FORM: Continuation Request or Final Closure Report (HRP-212)*.

Adverse Events and Unanticipated Problems: Adverse events and unanticipated problems that result from the use of an HUD are subject to the SHC IRB unanticipated problems reporting requirements. Use *FORM: Unanticipated Problem or Event Report (HRP-214)*. FDA regulations require that if a physician or health care provider receives or otherwise becomes aware of information, from any source, that reasonably suggests that an HUD has or may have caused or contributed to the death or serious injury of a patient, the physician or health care provider must report such findings to the FDA as soon as possible, but no later than 10 working days after the physician first learns of the effect or problem.

Modifications to the HUD: Modifications to the HUD or the clinical use of an HUD are to be reported to the SHC IRB using *FORM: Modification Request (HRP-213)*.

Emergency Use of an HUD: Use of an HUD in an emergency situation that cannot wait for SHC IRB review and approval may be handled using *GUIDANCE: Emergency Use Review (HRP-023)*. The HUD may only be used in an emergency situation if it meets the FDA criteria (21 CFR 56.104 [d]) and the HUD is not used outside its approved labeling.

For additional information, see *GUIDANCE: Humanitarian Use Devices (HUDs) (HRP-089), and the FDA's Information Sheet Guidance: Frequently Asked Questions About Medical Devices*.

What is Required for Recruitment Materials?

All recruitment materials must be submitted for review and approval by the IRB prior to distribution, posting, publishing, or broadcasting using *FORM: Update Recruitment Materials Request (HRP-222).* For inclusion of the SHC logo on recruitment materials, please check with entity marketing teams to ensure compliance with SHC logo usage. For SHC logo files, see http://sharpnet.sharp.com/marketing/creativeServices/System-Logos.cfm. No alteration of SHC logos is allowed. For additional information, see *GUIDANCE: Subject Selection, Recruitment, and Payments (HRP-006)*, and *TOOL: Media Guide (HRP-114).*

What is the Process for Requesting a Protocol Enrollment/Eligibility Exception?

To allow enrollment of a single individual who does not meet the protocol inclusion criteria of an IRB-approved protocol, the investigator may submit a written request for a one-time enrollment exception as a protocol modification request to the IRB. Obtaining prior sponsor and IRB approval for an enrollment (or eligibility) exception modification avoids a protocol violation. An enrollment exception request applies only to a single study subject. Such a request should be rare and justified in terms of serving the best interests of the potential study subject. The enrollment exception request will be referred to the appropriate SHC IRB chair or designee to evaluate the level of review required. Use *FORM: Modification Request (HRP-213)* and submit to research@sharp.com or via the "IRB: Revision Log" in IRBANA with the required supporting documentation identified on the form. Prior to submitting Form HRP-213, please contact the SHC IRB Office at research@sharp.com to discuss the specifics of the enrollment/eligibility exception request.

How is it Determined if an Adverse Event (AE) is an Unanticipated Problem that Needs to be Reported to the SHC IRB?

To aid investigators in determining whether an adverse event is an unanticipated problem that needs to be reported to the SHC IRB, the following is excerpted from *Guidance for Clinical Investigators, Sponsor, and IRBs*

– Adverse Event Reporting to IRBs – Improving Human Subject Protection. U.S. Department of Health and Human Services January 2009.

"An adverse event observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects and reported to the SHC IRB, ***only*** if it was unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent revision or change to the investigator's brochure). An individual AE occurrence ***ordinarily*** does not meet the criteria because, as an isolated event, its implications for the study cannot be understood.

Many types of AEs generally require an evaluation of their relevance and significance to the study, including an aggregate analysis of other occurrences of the same (or similar) event, before they can be determined to be an unanticipated problem involving risk to human subjects. For example, an aggregate analysis of a series of AEs that are commonly associated with the underlying disease process that the study intervention is intended to treat (e.g., deaths in a cancer trial), or that are otherwise common in the study population independent of drug exposure (e.g., cardiovascular events in an elderly population), may reveal that the event rate is higher in the drug treatment group compared to the control arm. In this case, the AE would be considered an unanticipated problem. In the absence of such a finding, the event is uninterpretable.

Because they have been previously observed with a drug, the AEs listed in the investigator's brochure would, by definition, not be considered unexpected and thus would not be unanticipated problems. Possible exceptions would include situations in which the specificity or severity of the event is not consistent with the description in the investigator's brochure, or it can be determined that the observed rate of occurrence for a serious, expected AE in the clinical trial represents a clinically important increase in the expected rate of occurrence.

Therefore, the FDA recommends that there be careful consideration of whether an AE is an unanticipated problem that must be reported to IRBs. In summary, the FDA believes that only the following AEs should be considered as *unanticipated problems* that must be reported to the IRB.

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g. tendon rupture, progressive multifocal leukoencephalopathy).
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control).
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to subjects.
- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison).

- Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects."

For SHC IRB reporting instructions, refer to *GUIDANCE: Non-Compliance and Other Reportable Unanticipated Problems Involving Risks to Subjects or Others (HRP-024)* and *FORM: Unanticipated Problem or Event Report (HRP-214)*.

What are the Responsibilities for Investigators who are the Lead Investigator on a Multi-Site Study?

For multi-center research where a SHC investigator is the lead investigator, the investigator is responsible for communicating to study sites any issues related to unanticipated problems, protocol modifications, and interim results. The investigator shall submit to the SHC IRB any documentation of such communication to sites. See *GUIDANCE: Activities that Require IRB Review (HRP-004).*

Effective for Federally funded research initially approved on or after January 21, 2019: For each clinical trial conducted or supported by a Federal department or agency, one IRB- approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms. Posting to ClinicalTrials.gov might be an appropriate choice as the website, applicable clinical trials will already have a record in the database making the burden of submission of the informed consent document substantially lower.

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

The informed consent form must be posted on the Federal Web site after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

At SHC, the Director of Research may assist investigators to ensure compliance with this requirement.

How is a Modification to a Study Submitted?

For protocol enrollment (or eligibility) exception requests, protocol changes, investigator's brochure or device manual updates, consent changes, subject material changes, target enrollment change, etc., complete *FORM: Modification Request (HRP-213)* and submit electronically via IRBANA with the required supporting documentation noted in the form.

For changes related to the sponsor, to the local research sites (i.e., addition, removal, address changes), complete *FORM: Update Site or Sponsor Information (HRP-223)* and submit electronically via IRBANA with the required supporting documentation noted on the form.

To add or remove investigators or research team members or to change the principal investigator of the study, complete *FORM: Research Team Updates (HRP-224)* and submit electronically via IRBANA with the required supporting documentation noted on the form.

NOTE: Modifications related to the conduct of the research may not be implemented until written IRB approval is issued.

What is the Process to Submit Sponsor Reports or New Regulatory Information to the IRB?

For Data Safety Monitoring Board (DSMB) reports, safety information from the sponsor, publications in literature (for both investigator-initiated research, and for multi-site trials when a local investigator is an author on the publication), annual reports for device studies, and notification of regulatory issues (e.g., Form FDA 483), complete *FORM: Alerts and Updates (HRP-226)* and submit electronically via IRBANA with the required supporting documentation identified on the form.

How is Enrollment for an Ongoing Study Closed or Re-Opened?

To close or re-open enrollment of an ongoing study, complete *FORM: Status Change Report (HRP-215)* and submit electronically via IRBANA with the required supporting documentation per the form. Prospective, written IRB approval is to be obtained before restarting enrollment, no matter who initiated the hold (i.e., site, sponsor/CRO, IRB, regulatory body, etc.).

What Process is used to Submit a Continuing Review?

To submit a study for continuation past the initial IRB approval period (not to exceed twelve months), complete *FORM: Continuation Request or Final Closure Report (HRP-212)* and submit electronically via IRBANA with required supporting documentation per the form.

All deviations must be submitted to the SHC IRB upon a research team member's awareness of the deviation. IRBANA's "Deviation Log" should be used for minor deviations that do not meet the criteria for reporting events as outlined in *FORM: Unanticipated Problem or Event Report (HRP-214)*.

Proposed modifications to previously approved research (e.g., amendments, updated investigator's brochures, revised informed consent documents, etc.), should not be submitted with continuation requests. See "How is a Modification to a Study Submitted?" section above.

The completed *FORM: Continuation Request or Final Closure Report (HRP-212)* and required supporting documentation must be received, and IRB review completed before the expiration date identified in the initial or continuing IRB approval letter. If the continuing review is not completed before the expiration date, the study will be suspended (expired). The research cannot re-start until all required items and/or IRB-requested changes have been received, and the IRB has issued an approval letter for study continuation.

If the approval of human research expires, all human research procedures related to the protocol must cease; including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection or analysis of private identifiable information. Continuing human research procedures in the absence of IRB approval is a violation of federal regulations. If current subjects will be harmed by stopping human research procedures and those procedures are available outside the human research context, provide the procedures on a clinical as-needed basis to protect the health and welfare of the subjects. If current subjects will be harmed by stopping human research procedures that are not available outside the human research context, immediately contact the SHC IRB and provide a written list of the currently enrolled subjects (by subject ID number only - do not include identifiable private information) and explain why they will be harmed by stopping human research procedures.

When is an Administrative Status Update Required?

Pre-2018 Requirements: Ongoing research studies initially approved prior to January 21, 2019 require continuing review, no less than annually.

Effective for Federally funded research initially approved on or after January 21, 2019: The SHC IRB requires an annual staus update for research that does not require continuing review as defined by the regulations.[7] The investigator or designee will submit a completed *FORM: Administrative Status Update (HRP-216)* to the "IRB: Initial, Continuing & Final Reviews" log in IRBANA (or electronically to research@sharp.com if instructed to do so by the IRB). Annual status updates are required until the research is no longer active at the local site(s) (i.e., for sponsored research, the site has undergone their study close-out visit; for non-sponsored research, data analysis is complete). All other requirements for review of research will remain in effect.

How is a Study Closed Out?

When all activities associated with the conduct of the study - including data analyses and sponsor close-out visits - are complete, submit *FORM: Continuation Request or Final Closure Report (HRP-212)* electronically via IRBANA with the required supporting documentation per the form.

How is a Previously Closed Study Re-Opened?

Once a study has been closed, no further activity can take place. Occasionally, however, there may be a request for study data after a study has closed. A closed study may be re-opened for one or more of the following reasons:

- Upcoming audit or quality assurance visit
- Query for data clarification involving data existing at the time of study closure
- Request for additional data analysis involving data existing at the time of study closure
- Query for new follow-up data related to events occurring since the study closure
- A need to notify subjects of their randomization status, study results or newly identified risk

Using identifiable private information for research may only occur with an IRB approved protocol in place, therefore access to data after a study has been closed requires the re-opening of a closed study. To re-open a closed study submit *FORM: Status Change Report (HRP-215) to the "IRB: Initial, Continuing & Final Reviews" log in IRBANA*. The request to re-open a closed study is not appropriate if the investigator is proposing to conduct new prospective data collection on subjects who participated in the closed study. If the investigator plans to conduct new prospective data collection or the study has been closed for one year or longer, re-opening the study using *FORM: Status Change Report (HRP-215)* is not permitted. Instead, submit as a new study, using *FORM: Initial IRB Review Application (HRP-211)*.

What Process is used when Disseminating Research Data and Findings Outside of SHC?

The SHC IRB is to be notified whenever data and findings from IRB approved research (for both investigator-initiated research, and for multi-site trials when a local investigator is an author on the publication) is to be disseminated outside of SHC using *FORM: Alerts and Updates (HRP-226)*. This notification requirement includes, but is not limited to, publication, poster presentation, abstract, classroom presentation, etc. If the research study is funded, follow the publication or dissemination requirements set forth by the sponsor.

[7] 45 CFR 46.109(f)(1)

What is Community Based Research (CBR)?

Community based research is research that is conducted in partnership with researchers and members of the community. There are multiple ways to define a community including but not limited to; individuals with a common issue or problem, individuals with a common interest, or individuals in a geographical area. A subset of CBR is Community-Based Participatory Research (CBPR), which is a partnership approach to research that equitably involves, for example, community members, organizational representatives, and researchers, in all aspects of the research process and in which all partners contribute expertise and share decision making and ownership. The aim of CBPR is to increase knowledge and understanding of a given phenomenon and integrate the knowledge gained with interventions and policy and social change to improve the health and quality of life of community members. When reviewing CBR or CBPR research, the SHC IRB will consider the following: (*CHECKLIST: Review of Community Based Research [HRP-425]*)

- Was the community involved in defining the need for the proposed research?
- Was the community involved in the design of the study protocol and informed consent?
- Is the recruitment plan sensitive and appropriate to the community proposed for the study and has the potential for coercion been minimized?
- Will the community be involved in conducting the research?
- What are the potential risks and benefits for the community with the proposed research?
- How will the outcomes of the research be disseminated within and outside the community?
- Is there a partnership agreement or memorandum of understanding between the researcher and the community partners?

What About Case Studies?

For case studies, see *GUIDANCE: Case Report Using Existing Data (HRP 094)* for further information.

Pre Enrollment Regulatory and SHC Institutional Requirements

Study Registration on Clinicaltrials.Gov

Before a SHC-initiated clinical trial is submitted to the IRB for review, the principal investigator is responsible for determining whether the study qualifies for registration with ClinicalTrials.gov, and if so, registering the trial and documenting registration information in the appropriate section of *FORM: Initial IRB Review Application (HRP-211)*. See *GUIDANCE: ClinicalTrials.gov Registration for SHC-Initiated Clinical Trials (HRP-048)* or https://clinicaltrials.gov/ct2/home for additional information.

Coverage Analysis

SHC requires all clinical trials and human subject research protocols in which there are medical procedures to have a Coverage Analysis completed prior to the initiation of the study. The Coverage Analysis is a systematic review of research-related documents to determine the Medicare billing status of both the study itself and the items and services provided. Medicare covers the routine costs of qualifying clinical trials, as well as reasonable and necessary items and services used to diagnose and treat complications arising from participation in all clinical trials subject to applicable Medicare Secondary Payer Rules, see *POLICY: Medicare Secondary Payer (MSP) (SHC 15631.99)* and *https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals*. Routine costs of a clinical trial include all items and services that are otherwise generally available to Medicare beneficiaries that are provided in either the experimental or the control arms of clinical trials except the investigational item or service itself, unless otherwise covered outside of the clinical trial. For more information, see *GUIDANCE: Medicare Coverage Analysis (HRP-049)*. *CHECKLIST: Coverage Analysis Required Documents (HRP-449)* is to be completed and submitted to SHC Center for Research at research@sharp.com. Changes to research documents may require a revision in the Coverage Analysis (see *HRP-449* for details). The coverage analysis and/or consistency review must be completed before the SHC IRB issues approval (for new studies or modifications affecting study procedures), or permission to proceed for studies reviewed by an external IRB. Contact the SHC Center for Research at research@sharp.com or call (858)939-7162 for assistance.

Budget Negotiations with Study Sponsors

When a clinical trial contract and budget is between the sponsor/contract research organization (CRO) and SHC, the SHC Contracts and Budgets Specialist will assist the research site to negotiate the budget with the sponsor/CRO. Contact the SHC Contracts and Budgets Specialist at (858)939-7194 or research@sharp.com for assistance in negotiating the budget with the clinical trial sponsor or CRO.

Service Agreements

A service agreement is to be completed for all clinical trials in which the SHC Investigational Pharmacy and/or other hospital ancillary services are to be used for purposes of the clinical trial and SHC does not hold the contract with the clinical trial sponsor. Use *TEMPLATE: Service Agreement (HRP-582)* and *WORKSHEET: Service Agreement Related to Research at Sharp HealthCare (HRP-332)*. Contact the SHC Contracts and Budgets Specialist at (858)939-7194 or research@sharp.com for assistance.

Contracts/Clinical Trial Agreements

All research contracts between SHC and sponsor/CRO and/or research site are to be reviewed by the SHC Contracts and Budgets Specialist in collaboration with SHC Legal Affairs department, prior to entity Chief Executive Officer or system Chief Financial Officer signing. Contact the SHC Contracts and Budgets Specialist for assistance at (858)939-7194 or research@sharp.com. See the following SHC research contract templates for guidance and required elements:

No.	Title
HRP-590	Template Contract: Clinical Trial Agreement Single Use
HRP-591	Template Contract: Master Clinical Trial Agreement
HRP-592	Template Contract: Clinical Trial Agreement Minimal Risk NO Sponsor
HRP-593	Template Contract: Clinical Trial Agreement Minimal Risk With Sponsor
HRP-594	Template Contract: Clinical Trial Agreement Sharp Employee
HRP-595	Template Contract: Clinical Trial Agreement Student
HRP-596	Template Contract: Nondisclosure Agreement
HRP-597	Template Contract: Indemnity Agreement
HRP-598	Template Contract: Facility Use Agreement

Clinical Trials Billing

The SHC Corporate Finance department is responsible for the management of clinical trials billing. For information regarding the general clinical trials billing process, see *PROCESS MAP: General Clinical Trials Billing Process Map (HRP-720)*. For billing information specific to the oncology clinical trials billing process, see *PROCESS MAP: Sharp System Oncology-Specific Clinical Trials Billing Process Map (HRP-721).* For billing information specific to clinical trials being conducted at Sharp Mesa Vista Hospital, see *PROCESS MAP: Sharp Mesa Vista Research Center-Specific Clinical Trials Billing Process Map (HRP-722).* For any additional questions regarding clinical trials billing, contact SHC Corporate Finance at clinicaltrials@sharp.com.

Investigators or their designees are responsible for providing the clinical trials billing representative with weekly enrollment logs for all open- to- enrollment studies. This requirement is effective regardless of whether there is new enrollment in that week. Investigators or their designees are also responsible for reviewing, completing and returning the Attestation Files provided by the clinical trials billing representative within five (5) business days of receipt. Investigators who fail to comply with these requirements may have their IRB approved studies suspended, or IRB approval of new studies may be withheld until these requirements are consistently met.

Subject Payment

Payment to research subjects for participation in studies is not considered a benefit. It is considered compensation for time and inconvenience, not a recruitment incentive. The amount and schedule of all payments should be described in the study protocol and informed consent at the time of initial IRB review, see *GUIDANCE: Subject Selection, Recruitment, and Payment (HRP-006*). Refer to *WORKSHEET: Subject Payments (HRP-316)* for information regarding prorating payments and subject withdrawal.

Investigational Drugs and Biologics

The research site must obtain written approval from the SHC IRB for a clinical trial prior to the sponsor's distribution to, and SHC's receipt of an investigational drug or biologic, except in the case of an emergency use. See *GUIDANCE: Emergency Use Review (HRP-023)*.

Investigational drugs being evaluated as part of a SHC IRB-approved clinical trial are to be stored at SHC hospital pharmacies. Investigational drugs will be stored under appropriate environmental control (temperature monitoring on a continual or daily basis) separate from routine drug stock in a secure pharmacy area in which access is limited to designated research pharmacy personnel. Storage facilities for investigational drugs or biologics must be in compliance with institutional, state, federal, and The Joint Commission requirements. If the investigational drug is subject to the Controlled Substances Act, the investigational drug will be stored in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure to which access is limited to designated research pharmacy personnel.

See *POLICY: Investigational Drugs (43019.01)* and *GUIDANCE: Investigational Drugs and Biologics (HRP-096)* for more information on the receipt, storage, handling, dispensing, accountability, transfer, return, and destruction of investigational drugs and biologics.

Investigational Devices

The research site must obtain written approval from the SHC IRB of a clinical trial prior to the sponsor distribution and SHC receipt of investigational devices, except in the case of an emergency use. See *GUIDANCE: Emergency Use Review (HRP-023)*.

Research protocols that the IRB has determined to involve a significant risk device cannot proceed without submission of an Investigational Device Exemption (IDE) application to the FDA and subsequent receipt of confirmation of the FDA decision on the application.

The investigator or designee is to maintain accurate, complete, and current records relating to the investigator's participation in an investigation and management of the investigational devices. See *WORKSHEET: Investigational Device Accountability Log (HRP-308).* When an investigational device is transported from one research site to a different site or entity, the courier ensures the device is accompanied by *WORKSHEET: Investigational Device Transport Log (HRP-319*).

See *POLICY: Investigational Devices (16509.00), GUIDANCE: Investigational Devices (HRP-095) and WORKSHEET: Study Device Workflow (HRP-795)* for more information about the management of investigational devices. For more information, refer to *WORKSHEET: Investigational Device Coverage in a Clinical Trial (HRP-309)*.

Record Retention

Human research records (including study records, training records, and communications), PHI authorizations, and consent documents that include PHI authorizations may need to be maintained for a period of up to fifteen years after completion of the research in an archived record binder or electronic file. Record where documents will be stored (off-site or on-site) and how they can be retrieved. The document storage location should be both fire and water safe. If the human research is sponsored, contact the sponsor before disposing of any human research records.

Third Party Access to SHC Data

Requests for research-related third party access to SHC clinical data are to be approved by the Director of Research or SHC research managers. Non-SHC employee or medical staff investigators will be given access to data limited to that associated with participants in protocols approved by the SHC IRB. Only researchers whose names appear as investigator, co-/sub-investigator, or study coordinator on Form FDA 1572 and/or *FORM: Initial IRB Review Application (HRP-211) and/*or *FORM: Research Team Updates (HRP-224)* will be provided access. Sponsor/Contract Research Organization (CRO) monitors and auditors and federal regulatory agency (e.g., FDA or Office of Human Research Protections [OHRP]) inspectors and auditors will be given access to data limited to that associated with participants in the clinical trials they are monitoring, auditing, or inspecting. Access to SHC computer systems will be granted as 'read only' and is for 'onsite use only.' See *GUIDANCE: Third Party Access to Data for Non-Sharp Staff (HRP-092)*.

Site Operational Guidelines

Investigator Obligations

1) Do not initiate human research activities, or changes to ongoing research, until after receipt of the IRB approval/determination letter, or permission to proceed letter.
2) Do not initiate human research activities until after the approval of entities, departments, or divisions whose resources will be used during the conduct of the research. See *GUIDANCE: Review of Scientific Merit and Organizational Feasibility (HRP-045)* for additional information. The SHC IRB typically does not issue approval or permission to proceed until confirmation that these additional scientific and administrative approvals have been granted.
3) Ensure 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.
4) Ensure that research staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials and, when relevant, privileges) to perform procedures assigned to them during the study.
   a) Maintain a list of appropriately qualified persons to whom significant clinical trial-related duties have been delegated.
5) Personally conduct or supervise the human research:
   a) Conduct the human research in accordance with the current IRB-approved version of the protocol.
   b) Ensure that current IRB-approved version of the consent is used to obtain informed consent, assent, or parental permission, as applicable.
   c) Do not modify the human research without prior IRB review and approval unless necessary to eliminate immediate hazards to subjects.
   d) Protect the rights, safety, and welfare of subjects involved in the research.
6) In accordance with IRB, FDA, DHHS, and other state or federal requirements, I will submit:
   a) Proposed modifications and other required information;
   b) Continuation Requests;
   c) Status Change Reports;
   d) Final Closure Report when the Human Research is closed; and
   e) Timely reports of noncompliance, unanticipated problems, or other reportable events.
7) Do not accept or provide payments to professionals in exchange for referrals of potential subjects (i.e., finder's fees).
8) Do not accept payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (i.e., bonus payments).

For additional requirements of various federal agencies, see Appendix B.

Pre-Screening and Screening

Pre-Screening

Pre-screening medical records to determine if a potential subject meets basic eligibility criteria for a clinical trial requires SHC IRB approvals for waiver of HIPAA authorization and waiver of informed consent. These waivers must be requested via *FORM: Initial IRB Review Application (HRP-211).* Once SHC IRB approval has been granted, an investigator, clinical research coordinator (CRC), or designee may begin to pre-screen prospective participants (subjects) to assess for clinical trial inclusion/exclusion criteria and may meet with

the potential participant and/or legally authorized representative. See *GUIDANCE: Legally Authorized Representatives (Surrogate Consent) (HRP-013)* for guidance on discussing the clinical trial and conducting the informed consent process with legally authorized representatives.

Screening

1. Informed Consent: The investigator, CRC, or designee will conduct the consenting process, or verify prior completion of the informed consent document including correct date and signatures, prior to performing any screening procedures, including holding or stopping therapy ("washout") for the purposes of participating in the clinical trial. Regardless of which written form of the consent, assent, or parent permission is used, a thorough written narrative of the informed consent process should be included in the participant's patient record or source document. See *GUIDANCE: Informed Consent Process for Research (HRP-090)* and *GUIDANCE: Written Documentation of Consent (HRP-091)* for additional information.
2. Clinical Evaluations: The investigator, CRC, or designee will perform the protocol-required clinical evaluations for the assigned protocol including, but not limited to, physical assessment; medical history and medication history review; and laboratory tests and/or procedures coordination.
3. Medications: The investigator, CRC or designee will obtain a medication history as directed by the protocol, and for inclusion/exclusion eligibility for all prospective subjects. Medications may be documented on the visit-specific flowsheet or on a subject-specific medication log. If the protocol requires documentation of concomitant medications, the medication start dates, dosage, route, and frequency must be documented. If the date is unknown, all attempts should be made to identify the year and estimate the start date as DD MMM YYYY. The principal investigator and research team will verify that no study exclusionary medications are being used by the research subject. If the subject is on an exclusionary medication, the investigator, CRC, or designee will query the participant's provider of the medication to inquire whether an allowable non-exclusionary substitution exists.
4. Procedures and Laboratory Analysis: The investigator, CRC, or designee will ensure that all necessary research procedures and laboratory analyses are obtained as outlined in the protocol after the subject has provided written informed consent. The investigator, CRC, or designee will coordinate with the receiving laboratories to ensure that the correct protocol procedures are used, the specimens are labeled and collected, and that either the local or central laboratory is available to receive and process the specimens. All clinical trial test results and procedures will be reviewed, signed, and dated by the investigator. Abnormal results will be evaluated and if clinically significant must be documented, including action taken.
5. Eligibility Criteria Checklist: The investigator, CRC, or designee will use an eligibility checklist to verify that all inclusion criteria are met and that no exclusion criteria exist. An eligibility criteria checklist may be provided by the study sponsor or created by the research site. Supportive documentation of all inclusion/exclusion criteria must be contained within the research record. The investigator and CRC, or designee will confirm each subject's eligibility prior to the research subject's randomization and study entry.
6. Scheduling Return Visits: The investigator, CRC, or designee will schedule next visits and verify that visits occur within the protocol specified timeframe. The investigator, CRC, or designee is responsible for notifying the study subject and research team, including data management, receiving laboratories, and investigational pharmacy (if applicable) of the anticipated randomization (study entry) date. The investigator, CRC or designee will keep a schedule of anticipated study visits. Missed visits must be followed up and documented.
7. Source Documentation: The CRC or designee will complete a protocol-specific flowsheet or other source documentation for the study visit. Source documents may be provided by the study sponsor or created by

the research site investigator, CRC or designee. If required by protocol and/or sponsor, the principal investigator will review source documentation and sign.

8. Case Report Forms (CRF): The investigator, CRC, or designee will complete CRFs as required by the protocol or sponsor CTA.
9. Investigational Pharmacy or Investigational Device: The investigator, CRC, or designee will verify communication with the investigational pharmacist when a randomization visit is scheduled for protocols that include investigational drugs. See *GUIDANCE: Investigational Drugs and Biologics (HRP-096)* for guidance on investigational drugs. See *GUIDANCE: Investigational Devices (HRP-095)* for guidance on investigational devices.

Randomization/Entry Visit

After eligibility has been confirmed by the principal investigator, the CRC or designee will schedule and implement the randomization (entry) visit within the protocol specific timeline and conduct the randomization visit as directed in the protocol.

1. Randomization: The investigator, CRC, or designee ensure that protocol specifications are followed. Per protocol specifications, randomization may occur prior to Day One/entry (see protocol for timeline/restrictions).
2. Clinical Evaluation: The investigator, CRC, or designee will perform the required randomization/entry evaluations for the assigned protocol including, but not limited to, physical assessment, signs/symptoms, diagnoses, medical and medication history review, and laboratory tests and/or procedures coordination.
3. Medications: The investigator, CRC, or designee will record all study and concomitant medications in the flowsheet or medication log as required by the protocol at the randomization/entry visit. If the investigator or CRC chooses to use a medication log, the visit flowsheet should document that a medication log is being used, and that it was reviewed and updated at this visit (e.g., "Medication log reviewed. No changes noted at today's visit." or "Medication log reviewed. Changes noted and documented on the medication log.").
4. Research Procedures and Laboratory Analysis: The investigator, CRC, or designee will coordinate with the receiving laboratories to ensure that the correct procedures and specimens are collected and laboratory staff are available to receive and process research specimens. All research tests and procedures will be reviewed, signed, and dated by the principal investigator. Abnormal results will be evaluated and, if clinically significant must be documented, including action taken. The research team will verify protocol required action and ensure compliance.
5. Pharmacy: The investigator, CRC, or designee will coordinate randomization requirements with the investigational pharmacist. The agent, route, dose, and frequency of all investigational medications (or changes) must be recorded in the source documents, flowsheet, record, drug accountability log, or study medication log. For additional information, see *GUIDANCE: Investigational Drugs and Biologics (HRP-096)*.
6. Return Visits: The investigator, CRC, or designee is responsible for notifying the study subject of the return date and keeping a schedule of anticipated study visit returns. Missed visits must be followed up and documented.
7. Source Documentation: The CRC or designee will complete a protocol-specific flowsheet or other source documentation (patient record) for the appropriate study visit, containing all protocol specified events during that visit. The CRC or designee will submit the source documentation/flow-sheet to the principal investigator for signature. All signed source documents must be filed in the research site record. Source documents to include a section for investigational medication where adherence, side effects, and dosing

are reviewed and documented. Hard copy lab or test results are also to be filed in the subject source binder. Lab or test results that include PHI are to be de-identified and code identifiers used.

8. Case Report Forms: The investigator, CRC, or designee will complete CRFs as required by the protocol or sponsor CTA.

Study Visits during Treatment Phase of Protocol/ Device Use

The investigator, CRC, or designee will implement the evaluations during the treatment phase as directed by the assigned protocol.

1. Clinical Evaluation: The investigator, CRC, or designee will perform the required follow-up evaluations for the assigned protocol including, but not limited to physical assessment (i.e., signs/symptoms, new diagnoses, hospitalizations); medication changes review; and investigational medications, laboratory tests and/or procedures adherence.
2. Medications: The investigator, CRC, or designee will record all study and concomitant medications in the flowsheet or medication log as required by the protocol at the randomization/entry visit. If the investigator or CRC chooses to use a medication log, the visit flowsheet should document that a medication log is being used, reviewed, and updated at this visit (e.g., "Medication log reviewed. No changes noted at today's visit." or "Medication log review. Changes noted and documented on the medication log."). Original entries and changes to the medication log should be reviewed, signed, and dated by the principal investigator.
3. Research Procedures and Laboratory Analysis: The investigator, CRC, or designee will coordinate with the receiving laboratories to ensure that the correct procedures and specimens are collected and laboratory staff are available to receive and process research specimens. All research tests and procedures will be reviewed, signed, and dated by the principal investigator. Abnormal results will be evaluated, and if clinically significant must be documented, including action taken. The research team will verify protocol required action and ensure compliance.
4. Pharmacy: The investigator, CRC, or designee will coordinate investigational medication dispensing requirements with the investigational pharmacist. The agent, route, dose, and frequency of all investigational medications (or changes) must be recorded in the source documents, flowsheet, record, drug accountability log, or study medication log.
5. Return Visits: The investigator, CRC, or designee is responsible for notifying the study subject of the return date and keeping a schedule of anticipated study visit returns. Missed visits must be followed up and documented.
6. Source Documentation: The CRC or designee will complete a protocol-specific flowsheet or other source documentation for the appropriate study visit, containing all protocol specified events during that visit. The CRC or designee will submit the source documentation/flowsheet to the principal investigator for signature. All signed source documents must be filed in the research site record/source documents. Source documents are to include a section for investigational medication where adherence, side effects, and dosing are reviewed and documented. Hard copy lab or test results are also to be filed in the subject source binder. Lab or test results that include PHI are to be de-identified and code identifiers used.
7. Case Report Forms: The investigator, CRC, or designee will complete CRFs as required by the protocol or CTA with sponsor.

On-Study/Off-Treatment or other Long-Term Follow-Up

For protocols using study medications, the protocol may require subjects who have stopped the investigational medication or completed the treatment phase of the protocol to be followed. Treatment evaluation must be followed as directed by the assigned protocol.

1. Clinical Evaluation: The investigator, CRC, or designee will perform the required follow-up evaluations for the assigned protocol including, but not limited to physical assessment (i.e., signs/symptoms, new diagnoses, hospitalizations); medication changes review; and investigational medications, laboratory tests and/or procedures adherence.
2. Medications: The investigator, CRC, or designee will record all study and concomitant medications in the flow-sheet or medication log as required by the protocol at the randomization/entry visit. If the investigator or CRC chooses to use a medication log, the visit flowsheet should document that a medication log is being used, and that it was reviewed and updated at this visit (e.g., "Medication log reviewed. No changes noted at today's visit." or "Medication log review. Changes noted and documented on the medication log."). Original entries and changes to the medication log should be reviewed, signed, and dated by the principal investigator.
3. Research Procedures and Laboratory Analysis: The investigator, CRC, or designee will coordinate with the receiving laboratories to ensure that the correct procedures and specimens are collected and laboratory staff are available to receive and process research specimens. All research tests and procedures will be reviewed, signed, and dated by the principal investigator. Abnormal results will be graded, and if clinically significant must be documented, including action taken. The research team will verify protocol required action and ensure compliance.
4. Pharmacy: The investigator, CRC, or designee will notify the investigational pharmacy of the subject's status as off-treatment.
5. Return Visits: The investigator, CRC or designee is responsible for notifying the study subject of the return date and keeping a schedule of anticipated study visit returns. Missed visits must be followed up and documented.
6. Source Documentation: The CRC, or designee will complete a protocol-specific flow-sheet or other source documentation for the appropriate study visit, containing all protocol specified events during that visit. The CRC or designee will submit the source documentation/flowsheet to the principal investigator for signature. All signed source documents must be filed in the research site record/source documents. Source documents to include a section for investigational medication where adherence, side effects, and dosing are reviewed and documented. Hard copy lab or test results are also to be filed in the subject source binder. Lab or test results that include PHI are to be de-identified and code identifiers used.
7. Case Report Forms: The investigator, CRC, or designee will complete CRFs as required by the protocol sponsor CTA.

Study Discontinuation Visit

In anticipation of study discontinuation, the investigator, CRC, or designee will notify the team of upcoming study discontinuation to aid in the transition to health management follow-up and marketed medication (if applicable). The investigator, CRC, or designee will implement the study discontinuation evaluation as directed by the assigned protocol.

1. Clinical Evaluation: The investigator, CRC, or designee will perform the required follow-up evaluations for the assigned protocol including, but not limited to physical assessment; signs/symptoms, new diagnoses, hospitalizations, medication changes review; and investigational medications and laboratory tests and/or procedures adherence.
2. Medications: For protocols requiring follow-up on concomitant medications, the investigator, CRC, or designee must record all study and concomitant medications in the source document flow-sheet, study/clinic note, or appropriate medication log.
3. Research Procedures and Laboratory Analysis: The investigator, CRC, or designee will coordinate with the receiving laboratories to ensure that the correct procedures and specimens are collected and laboratory staff are available to receive and process research specimens. All research tests and procedures will be reviewed, signed, and dated by the principal investigator. Abnormal results will be evaluated and, if clinically significant must be documented, including action taken. The research team will verify protocol required action and ensure compliance.
4. Discontinuation of Investigational Medication and Communication with PCP: The investigator, CRC, or designee will communicate with the investigational pharmacist regarding the discontinuation of investigational drug and collaborate with the subject's primary care provider for continued health care management.
5. Investigational Drug Return: For protocols using investigational agents (drugs or devices), the investigational pharmacist, investigator, CRC, or designee must record the return of all investigational study medications in the source document flowsheet, clinic/study visit note, or appropriate drug accountability log at the discontinuation visit. Documentation to include: agent, route, dose and frequency, stop date, return of all investigational product and packaging, and information about the subject's transition to marketed product (if applicable). The principal investigator will review, sign, and date any new entries or changes.

Follow-Up Visit(s)

Protocols using investigational drugs may require a follow-up visit four weeks after the investigational drug is discontinued. Additionally, subjects with ongoing adverse events (AE) with suspected study participation causality at study discontinuation may need to be followed under study until the event has resolved. The study protocol may allow for some of these follow-up visits to occur through telephone contact as long as no additional study or laboratory evaluations are required.

1. Clinical Evaluation: The investigator, CRC, or designee will perform and document the required follow-up evaluations for the assigned protocol, including, but not limited to physical assessments; signs and symptoms, new diagnoses, hospitalizations, serious adverse events, medication changes, and status of ongoing AEs review, and laboratory tests and/or procedures adherence.
2. Research Procedures and Laboratory Analysis: The investigator, CRC, or designee will ensure that all necessary research procedures and laboratory analysis are obtained as outlined in the protocol. The CRC or designee will coordinate with the receiving laboratories to ensure that the correct procedures and specimens are collected and laboratory staff are available to receive and process research specimens. All

research test results and procedures will be reviewed, signed, and dated by the principal investigator. Abnormal results will be evaluated and, if clinically significant must be documented, including action taken. The research team will verify protocol required action and ensure compliance.

3. Medications: The investigator, CRC, or designee will query and document any changes in the completion of the study medications. The principle investigator will review, sign, and date the entries.
4. Source Documentation: The CRC or designee will complete a source clinic note or protocol-specific flowsheet for the follow-up visit or telephone call and submit it to the principle investigator for review and signature. The signed source document will be filed in the patient's study file.
5. Case Report Forms: If the protocol includes a follow-up CRF, the investigator, CRC, or designee will complete the CRF as required by the assigned protocol.

Missed Study Visits

Study visits that are missed or out of the protocol-specified timeframe must be documented as missed study visits. The investigator, CRC or designee, together with the research team, will attempt to contact/locate the study participant and bring the study subject back into care. All attempts and action to locate and bring the study participant back into care or for study discontinuation must be documented and filed as source documentation.

If the study participant chooses to discontinue the study prematurely, then a discontinuation visit will be scheduled (see Study Discontinuation Visit section for details). Additionally, the study team, including investigational pharmacy and the sponsor, must be notified of the premature discontinuation visit. Subjects that choose to discontinue should be referred for primary health care management.

If the study participant missed two consecutive study visits and all attempts to locate the subject are unsuccessful, the study participant may be prematurely discontinued as lost to follow-up (refer to protocol for specifics on premature discontinuation). Subjects should not be discontinued as lost to follow-up until all efforts to locate and bring the subject back into care have been exhausted.

When a Subject Withdraws Consent

Although a participant is not obliged to give his or her reasons for withdrawing from a study prematurely, the investigator, CRC, or designee will make a reasonable effort to ascertain the reason, while fully respecting the participant's rights to withdraw from participation.

The data collected on the subject to the point of withdrawal remains part of the study database and may not be removed. However, an investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection after their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject is to clearly 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.

- If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information, the investigator is to 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 all informed consent documents is required.
- 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 may not access, for purposes

related to the study, the subject's medical record or other confidential records requiring the subject's consent.

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 statuses.

Adverse Events including Serious Adverse Events, Unexpected Adverse Drug Experiences, and Unanticipated Adverse Device Effects

Adverse Event Assessment and Recording

An Adverse Event (AE) may be a symptom (e.g., pruritus), a sign (e.g., rash), a lab result (e.g., ANC of 450), or a diagnosis (e.g., PCP). Each protocol or sponsor will specify requirements for recording AEs. The investigator, CRC, or designee will continuously screen for AEs on an ongoing basis using patient reported histories, physical assessment/exam, laboratory reports, chart review, and any other available data. When an AE is identified, the investigator, CRC, or designee will document the AE on a study flowsheet or an AE log sheet specific to the study participant. The principal investigator will review all AEs and assess causality and required course of action in accordance with the protocol and clinical trial's requirements. All AEs should be followed to resolution. When possible, the patient's primary care provider is to be kept informed of any adverse events requiring treatment interruption or changes, as well as any results that may confuse the clinical picture or complicate care.

Serious Adverse Event Assessment and Recording

The investigator, CRC, or designee will continuously screen for a Serious Adverse Events (SAE) on an ongoing basis using patient or family-reported events, home-base care reports, in-patient census, obituaries, or any other available data. The CRC or designee will immediately communicate SAE reports with the principal investigator (if not already aware). As soon as the site receives information of an SAE, an initial report must be made to the sponsor immediately. Any SAE that meets the definition of an unanticipated problem per *FORM: Unanticipated Problem or Event Report (HRP-214)* must be reported to SHC IRB per the following reporting timelines:

- Within two (2) working days of research team's awareness of any subject death determined Related, Possibly Related, or Probably Related to investigational drug/device/intervention.,
- Within ten (10) working days of research team's awareness, report any unanticipated problem involving risks to human subjects or others.

The investigator, CRC, or designees will supply the sponsor and the SHC IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).

Protocol Deviations, Protocol Violations or Protocol Eligibility Exceptions

Protocol Deviation/Violation

All deviations must be submitted to the SHC IRB, via the "IRB: Deviation Log." Minor deviations that do not meet the criteria for reporting events as outlined in *FORM: Unanticipated Problem or Event Report (HRP-214)*, and eligibility / enrollment exceptions implemented without prospective sponsor and IRB approval (per *FORM: Modification Request (HRP-213)*), are to be submitted via the "IRB: Deviation Log" in IRBANA, upon the research team's awareness of the deviation.

The SHC IRB will monitor all deviations for failure to follow federal regulations, institutional policies governing human subject research, and requirements or determinations of the IRB and will apply the requirements of *GUIDANCE: Non-Compliance and Other Reportable Unanticipated Problems Involving Risks to Subjects or others (HRP-024)*, when applicable.

Protocol Exceptions

An exception to the currently approved protocol is a planned temporary variance that must have received sponsor and IRB approval prior to its initiation (e.g., enrollment of subject who does not meet eligibility criteria or accommodation of a subject who moves out of the area for the remainder of his/her participation in research). See "What is the Process for Requesting a Protocol Enrollment/Eligibility Exception" on page 14 of this MANUAL for additional information on protocol exceptions. To submit a request for review of a protocol exception, use *FORM: Modification Request (HRP-213).*

Monitoring, Auditing, and Inspection Preparation

General Guidelines

It is recommended that investigators, CRCs, and other research site staff are prepared for sponsor monitoring and auditing, IRB audits, and federal agency (FDA and OHRP) inspection visits at all times. To be prepared:

1. Know and observe applicable federal regulations, state law, and SHC's guidance and/or policies and good clinical practices.
2. Have a basic understanding of the therapeutic area and indication for studies conducted in the department/clinic.
3. Know and observe SHC's policies, guidance, and procedures for research study-related activities.
4. Know and follow the reviewing IRB-approved protocol.
5. Know the study-related roles and responsibilities of the principal investigator and other research team members.
6. Differentiate between the study-related and health care provider roles and responsibilities.
7. Review the protocol with the research team members and identify and discuss any concerns or questions regarding conduct of the study.
8. Maintain open communications with other research team members and investigators, the principal investigator, sponsor, and the reviewing IRB.
9. Ensure that each research team member has access to the most current documents, including but not limited to, the informed consent document, protocol, and case report forms.
10. Create and use tools (source documents) to assist in the compliant conduct of the study (worksheets, data collection forms, logs, checklists, etc.).
11. Develop and maintain an effective system for data collection and secure storage.
12. Ensure the study is conducted in accordance with the SHC IRB-approved protocol, SHC policy, and required regulations.
13. If the study includes the use of electronically captured data, see *GUIDANCE: Third Party Access to Data for Non-Sharp Staff (HRP-092)* and *GUIDANCE: Badge and Credentialing for Non-Sharp Staff (HRP-093)* for review of electronically captured data by outside personnel. Be prepared to provide hard copies of the electronically captured data for the auditor's use.

See *CHECKLIST: Investigator Monitoring, Auditing and Inspection Preparedness (HRP-430)* for guidance on the documents needed during monitoring, auditing, and inspections.

Additional Tips for an FDA Inspection

The following provide investigators and designated staff with tips for a successful FDA inspection:

FDA Arrival

1. Identify who is to be notified at the time inspection commences.
2. Identify who is authorized to receive and accompany FDA inspector.
3. Develop a plan for managing oral inquiries and requests for documents.
4. Greet the FDA inspector and request identification and FDA Form 482.
5. Confirm the purpose of FDA inspection.
6. Provide the inspector with a work area that affords privacy.
7. Ensure phone/internet/power is available.
8. Keep conversation polite and professional.
9. Extend common courtesy.

During Inspection

1. Accompany FDA inspector(s) at all times other than when they are in the designated room reviewing documents. FDA inspectors should not be allowed to enter patient care areas or research staff work areas unescorted at any point during the inspection.
2. Keep an accurate written record of the following:
   a. Areas of the site visited and to whom FDA inspector spoke.
   b. Accurate and complete record of all comments and suggestions made by inspector, unanswered questions, and site commitments.
   c. Any commitments made to the FDA by the investigator or designee.
3. Schedule a daily summation with FDA, and separately with site staff.
4. If additional inspection days are required, prepare an agenda for next day(s) with FDA.
5. Prepare daily report to management, if applicable.
6. Maintain a list of the study subjects reviewed by the inspector and their corresponding study numbers.
7. If the FDA inspector asks for the identities and demographics of the study subjects because of some concern, comply with the request.

Document Marking and Duplication

1. Do not permit marking of documents by FDA inspector.
2. When an inspector requests a copy of a document, retain a second copy for the site's records.
3. Mark as "confidential" documents containing trade secret or confidential information before providing to the FDA inspector.
4. If confidential information is conveyed orally, establish these facts to FDA.

What the FDA inspector/s will be reviewing during the inspection:

Subject Records

1. Did the principal investigator maintain records that are supportive of each entry in CRFs for each subject?
2. Were all CRFs completed in a timely fashion?
3. Reporting of Study Progress
4. Did principal investigator terminate or discontinue the study before completion?
5. Were reports of Serious Adverse Events to Sponsor and IRB handled properly?
6. Did principal investigator maintain copies of all reports submitted to sponsor and IRB?
7. Did the site enroll subjects who did not meet the inclusion/exclusion criteria (screen failure of subjects)?
8. Did the site make any changes in the protocol in dosage, frequency, time of dosing, or method of dosing of the 'test article'?
9. Did the site fail to report serious adverse events promptly to the SHC IRB and the sponsor?
10. Did the site fail to document illnesses, hospitalizations, and other significant problems concurrent with the study?
11. Did the site fail to perform critical tests, examinations, or assessments at the protocol-specific time or visit?
12. Was there any administration of concomitant therapy that could compromise the study results?
13. Did the site fail to record or report all concomitant therapy?
14. Did the site enroll more subjects into the study than originally approved by the SHC IRB or the sponsor?
15. Did the sponsor maintain accounting procedures for the test article?
16. Were all unused supplies returned to sponsor or disposed of properly?
17. Did the investigator, pharmacist/s, or designees limit test article access and distribution?
18. Was the route of administration and proper use of the investigational product maintained?
19. See *CHECKLIST: Investigator Monitoring, Auditing, and Inspection Preparedness (HRP-430)* for guidance on the documents needed during an FDA inspection.
20. Medical/Clinical Laboratory Facilities
21. Are the facilities adequate and proper diagnostic equipment available to fulfill protocol requirements?
22. Is the equipment in good working order?
23. Does the equipment require calibration and are there records documenting the required equipment calibration?
24. Is the laboratory accreditation/license documentation current?
25. Is there proper documentation and storage of trial samples?
26. Safety Information on Serious Adverse Events
27. How does the sponsor ensure that the principal investigator notifies the sponsor and SHC IRB promptly of SAEs?

28. Is the monitor involved in reporting?
29. Is the timeframe for reporting SAEs consistent with regulations?
30. Do source data support the SAEs?
31. Were there any deaths or dropouts due to SAEs?
32. IRB Communication
33. Did the site obtain proper IRB approval and documentation for protocol and informed consent?
34. Does the site have documentation of the IRB qualifications?
35. Has the site maintained all communication/correspondence between principal investigator and the IRB?
36. Have all required continuing reviews been submitted and approved within the timeline required by the IRB?

Exit Interview

1. The FDA inspector will discuss their findings with the designated site management and principal investigator.
2. This is an opportunity for the site to correct any misunderstandings; identify incorrect deficiencies.
3. The FDA may also prepare an affidavit about the inspection/audit findings. A signature on this affidavit constitutes an acknowledgment of the contents. SHC does not authorize SHC research personnel to sign FDA Inspection/Audit Affidavits. If the FDA inspector requires signature on the affidavit, forward to the Director of Research at research@sharp.com for review. The Director of Research will review with SHC Legal Affairs Office and if appropriate will have the SHC Institutional Official sign. A copy of the FDA affidavit is to be sent to the SHC IRB.
4. If a FDA Form 483 is issued, each observation should be reviewed with the inspector and understood.
5. Begin plan to correct deficiencies; however, it is best to document those plans in the response to the Form FDA 483 (see below) and not during the exit interview.
6. Provide the inspector with a timetable for future actions to correct the identified deficiencies (answer will be recorded by FDA).

If you Receive an FDA Form 483

1. The principal investigator should consult with the Director of Research and/or SHC Legal Affairs Office and sponsor for guidance on how to respond.
2. A copy of the FDA Form 483 is to be forwarded to the Director of Research and the SHC IRB.
3. The principal investigator is to discuss the findings with the Director of Research and other organizational offices as necessary or determined by the findings.
4. The principal investigator will prepare a written response to the FDA Form 483. SHC internal research sites will seek guidance and input from Director of Research, the SHC Legal Office and any other appropriate persons to any observations noted in the FDA Form 483 and send the response to the FDA within the time specified by FDA, typically within 15 days. The written response is to:
    - Address each observation and explain what steps have been implemented or will be implemented to remedy the observation and prevent future occurrences of similar observations, and
    - Be factual and the tone should be respectful, professional, and cooperative.

5. The principal investigator or designee may attempt to obtain a copy of the official FDA investigator's field audit report (i.e., Establishment Inspection Report [EIR]) under the Freedom of Information Act. This request can be made at the conclusion of the FDA Form 483 response. The principal investigator can make this request separately and the SHC Legal Affairs Office may assist. Typically, FDA will not respond to an EIR request until the matter is formally closed.

Appendix A: Prisoners

A Prisoner is an individual involuntarily confined or detained in a penal institution, including individuals:

- Sentenced under a criminal, civil, or military statute;
- Detained in other facilities (e.g., for drug detoxification or treatment of alcoholism) by virtue of statutes or commitment procedures, which provide alternatives to criminal prosecution or incarceration in a penal institution; and
- Detained pending arraignment, trial, or sentencing.

The SHC IRB does not review research involving prisoners. However, if a participant in a SCH IRB-approved research study becomes a prisoner, the principal investigator is responsible for promptly notifying the SHC IRB of the participant's incarceration. All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-participant must be suspended immediately, except as noted below:

In special circumstances in which the investigator asserts that it is in the best interests of the participant to remain in the research study while incarcerated, the subject may continue to participate in the research. The SHC IRB chairperson (or designee) will include on the agenda of the next convened IRB meeting a discussion of the research with the incarcerated participant. A prisoner representative is to be present and included in the IRB meeting discussion.

NOTE: In these narrow circumstances, the finding required under 45 CFR 46.305 (a)(4) regarding the selection of subjects within the prison is not applicable since the subject was recruited outside of an incarcerated context. The SHC IRB will document these findings of non-applicability in the IRB meeting minutes.

Appendix B: International Conference on Harmonization - Good Clinical Practice (ICH-GCP) Requirements

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of the ICH GCP guidance is to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guidance was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization (WHO).

This guidance should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The evaluation of the available nonclinical and clinical information on an investigational product is to be adequate to support a proposed clinical trial.

The principles established in the guidance may also be applied to other clinical investigations. For consolidated guidance on International Conference on Harmonization – Good Clinical Practice (ICH-GCP), go to https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

Appendix D: Other Resources

- International Conference on Harmonization – Good Clinical Practice (ICH-GCP) Requirements
- 45 CFR 46 - Human Subjects
- WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects
- Nuremberg Code
- The Belmont Report
- Categories of Research That May Be Reviewed by the IRB Through an Expedited Review Procedure
- Decision Charts and Checklists
- OHRP Home
- OHRP Compliance Oversight
- OHRP Policy & Guidance
- OHRP Newsroom & LISTSERV Sign-up
- Food and Drug Administration (FDA)
- FDA Information Sheets
- 21 CFR 50- Protection of Human Subjects
- 21 CFR 54- Financial Disclosure by Clinical Investigators
- 21 CFR 56 - Institutional Review Boards
- 21 CFR 312 - Investigational New Drug (IND) Applications
- 21 CFR 812 - Investigational Device Exemptions (IDE)
- FDA Center for Devices and Radiological Health
- FDA Forms - Devices & Drugs
- International Conference on Harmonisation (ICH) Guidance Documents
- ICH Guidance for Industry - E6 Good Clinical Practice: Consolidated Guidance
- Health Insurance Portability and Accountability Act (HIPAA)
- SHC SharpNet - HIPAA Privacy and Security
- HIPAA Privacy Rule Booklet for Research
- National Institutes of Health (NIH)
- Office of Extramural Research
- AAMC Medical Research Initiatives
- American Society of Bioethics and Humanities

- ClinicalTrials.gov
- ClinicalTrials.gov registration requirements fact sheet (PDF)
- First Clinical Research
- IRB Forum
- Office of Research Integrity (ORI)
- Public Responsibility in Medicine and Research (PRIM&R)