Human Research Protection Program (HRPP)

Investigator Guidance Manual

Version 1

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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 SharpNET/IRB, Sharp.com/Research, or research@sharp.com. Updates, and revisions to HRPP documents will be posted on the main page of SharpNET/IRB 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 site personnel 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

Human Research Basics

What is Human Research?

Human Research is defined in DHHS regulations 45 CFR §46.102(d) and 45 CFR §46.102(f) and in 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)* and in Appendix A of this manual.

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 biomedical or behavioral research study of human subjects designed to answer specific questions about diagnostic procedures or therapeutic interventions (i.e., drugs, treatments, devices, or new ways of using known drugs, treatments or devices). Clinical trials are used to determine whether new diagnostic procedures or therapeutic interventions are safe, efficacious, and effective.

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 Investigator?

The 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 (CFR)?

The Center for Research (CFR) is the coordinating office for the HRPP and IRB at SHC. It is located within the Clinical Effectiveness division. The Director of the SHC CFR 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 for research at SHC.

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) 499-4875 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, unless exempt, obligates the organization to uphold ethical principles and is applicable whenever research is conducted or supported by any United States federal department or agency that has adopted the 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 IRB is guided by ethical principle mandates outlined in the Belmont Report (1979) and legal mandates outlined in the Code of Federal Regulations, Title 45 Part 46. To achieve these mandates, the 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 IRB staff, board members, and investigators 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, 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 IRB approval.

See *GUIDANCE: Review of Scientific Merit, Organizational Feasibility and Antibiotic Oversight (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.

What is the SHC System Antibiotic Review Committee (SARC)?

The SHC System Antibiotic Review Committee (SARC) is a standing system advisory committee consisting of representatives from the following departments: infectious disease, infection control, microbiology, laboratory, and pharmacists representing all SHC inpatient facilities. The purpose of this committee is to review and determine the appropriateness of a proposed investigational antimicrobial clinical trial protocol to ensure that the trial is appropriate for the intended indication(s), provides useful scientific information, and is balanced against minimizing potentially increased pressure for antibiotic resistance emergence. Clinical trials, whether investigating or using as comparators antimicrobial medications, must be submitted to the SARC committee for review concurrently or prior to submission to the SHC IRB. The outcome of the SHC SARC review is provided to the SHC IRB prior to IRB study approval.

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 Research Site Staff Training	
	Module	**Timeline**
Required Initial Training	National Institute of Health (NIH) * Human Subjects Tutorial	Within 30 days of SHC engagement
	SHC Employees: HRPP Orientation for New CFR Staff	Within 30 days of SHC employment
	Non-SHC Employees/Medical Staff: Required Compliance Training	Within 30 days of SHC engagement
	HIPAA Training	Within 30 days of SHC engagement
	Protocol-Specific Education	Site Initiation Visit and/or Investigator Meeting
	Pharmacy	Site Initiation Visit
Required Continuing Training	National Institute of Health (NIH) Human Subjects Tutorial*	Every two years
	SHC Employees: HRPP Orientation for New CFR Staff	Every two years
	Non-SHC Employees/Medical Staff: Required Compliance Training	Every two years
	HIPAA Training	Annually
Ongoing Education	SHC-Sponsored Education Events	Quarterly
	Professional Organization-sponsored Education Events	When available
Evaluation	Understanding of HRPP	Yearly

*The NIH site can be accessed at http://phrp.nihtraining.com/users/login.php.

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[1] or for similar purposes preparatory to research, provided that:

- Researcher(s) will not remove any PHI from the covered entity2, 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 a consent document for children, use *TEMPLATE: Child Assent (ages 7-12) (HRP-503)* or *TEMPLATE: Adolescent Assent (Ages 13-17) (HRP-504).*

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 embedded in the consent document itself.

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), 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.

1 http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/research.html
2 http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/

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 with all applicable required supporting documentation (listed in the checklist on the last page of the application form).

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 an IRB application, Continuation Review, and Final Closure Report.

For 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.

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:** 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 the 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 Research:** 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. It is the responsibility of the IRB, not the investigator, to determine whether human research is exempt from IRB review. For reference on the categories of research that may be exempt, review *CHECKLIST: Exemption Determination (HRP-428)*.
3. **Review Using the Expedited Procedure**: 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. For reference on the categories of research that may be reviewed using the expedited procedure, see *CHECKLIST: Expedited Review Determination (HRP-429)*.
4. **Review by the Convened IRB**: 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 4,000 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 a 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 a HUD for SHC IRB review. The use of a HUD does not constitute research unless the physician or health care provider intends to collect 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 a 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 a 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 a HUD are to be reported to the SHC IRB using *FORM: Modification Request (HRP-213).*

Emergency Use of a HUD: Off-label use of a 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)*.

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).*

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 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 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 Sharp HealthCare 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 Sharp IRB any documentation of such communication to sites. See *GUIDANCE: Activities that Require IRB Review (HRP-004).*

How is a Modification to a Study Submitted?

For protocol enrollment (or eligibility) exceptions, protocol changes, investigator's brochure or device manual updates, consent changes, 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 personnel or to change the principal investigator of the study, complete *FORM: Update Site Personnel Request (HRP-224)* and submit electronically via IRBANA with the required supporting documentation noted on the form.

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

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

For Data Safety Monitoring Board (DSMB) reports, safety alerts, publications in literature, 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 and written IRB approval is to be obtained before restarting enrollment, no matter who initiated the hold (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. If the sponsor requires the site to submit all minor or administrative deviations to the IRB, complete *FORM: Deviation Summary Sheet (HRP-225)* and include with the Continuation Request or Final Closure Report. The Deviation Summary Sheet is only to 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).*

If the continuing review involves modifications to previously approved research, submit those modifications separately using a completed *FORM: Modification Request (HRP-213)*.

If the continuation request is not received by the date identified in the initial or continuing IRB approval letter, the study will be suspended (expired) until the completed *FORM: Continuation Request or Final Closure Report (HRP-212)* and required supporting documentation has 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.

How is a Study Closed Out ?

When all activities associated with the conduct of the study - including data analyses - are complete, use *FORM: Continuation Request or Final Closure Report (HRP-212)* and submit 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 use *FORM: Status Change Report (HRP-215).* 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 a year or longer, re-opening the study using the status change form is not permitted – instead submit the request 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 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. In addition to completing *FORM: Alerts and Updates (HRP-226)*, if the research study is funded, follow the publication or dissemination requirements set forth by the sponsor.

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.

Medicare Coverage Analysis

A Medicare Coverage Analysis is required for all clinical trials in which any items or services may be billed to Medicare. 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 clinical trials. Routine costs 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). WORKSHEET: Medicare Coverage Analysis (HRP-349)* is to be completed and submitted to SHC Corporate Finance at clinicaltrials@sharp.com prior to enrolling any clinical trials participants.

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 858-499-4459 or research@sharp.com for assistance in negotiating the budget with the clinical trial sponsor.

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 858-499-4459 or research@sharp.com for assistance completing a service agreement.

Contracts/Clinical Trial Agreements

All research contracts between SHC and sponsor and/or research site are to be reviewed by the SCH 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 858-499-4459 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 Sharp HealthCare Corporate Finance at clinicaltrials@sharp.com

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).* Use *WORKSHEET: Subject Payments (HRP-316)* for information regarding prorating payments and subject withdrawal.

Investigational Drugs and Biologics

The SHC IRB is to issue approval of a clinical trial prior to the sponsor distribution and SHC 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 SHC IRB is to issue approval 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. In addition, see *WORKSHEET: IDE Clinical Study Information (HRP-309).*

The investigator or designee is to maintain accurate, complete, and current records relating to the investigators 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)* and *GUIDANCE: Investigational Devices (HRP-095)* for more information on the management of investigational devices.

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, sub-investigator, or study coordinator on Form FDA 1572 and/or *FORM: Initial IRB Review Application (HRP-211)* or *FORM: Modification Request (HRP-213)* 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) Protect the rights, safety, and welfare of subjects involved in the research.
2) Do not initiate human research activities until after receipt of the initial IRB approval letter.
3) Do not initiate human research activities until after the approval of entities, departments, or divisions whose resources will be used during the conduction of the research. See *GUIDANCE: Review of Scientific Merit, Organizational Feasibility, and Antibiotic Oversight (HRP-045)* for additional information. The SHC IRB typically does not issue approval until confirmation that these additional scientific and administrative approvals have been granted.
4) 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.
5) Ensure that research staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials and privileges (when relevant) 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.
6) 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 or permission 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.
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 C.

Pre-Screening and Screening

Pre-Screening

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 and 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 Devices (HRP-095)* for guidance on investigational devices.

Randomization/Entry Visit

After eligibility has been confirmed by the principal investigator, 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 Guidance

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 status.

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., pruritis), 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. The patient's primary caregiver 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 and SHC IRB within 2 working days if a death occurs, 5 working days for an emergency deviation, and 10 working days for other events. For deaths, 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 Exceptions

Protocol Deviation/Violation

If the reported deviation/violation involves an event that requires prompt reporting to the IRB or if it involves a failure to follow federal regulations, institutional policies governing human subject research, requirements or determinations of the IRB, then *GUIDANCE: Non-Compliance and Other Reportable Unanticipated Problems Involving Risks to Subjects or others (HRP-024)* is to be followed.

Protocol Exceptions

An exception to the currently approved protocol is a planned temporary variance that has received 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 13 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 SHC 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 SHC 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. See *GUIDANCE: Investigational Drugs and Biologics (HRP-096).*
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. Sharp 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: Definitions

For the most current Definitions listing, see *GUIDANCE: Definitions (HRP-001).*

1.1 Advance Directive: Documents written in advance of a serious illness in which a person states their choices for healthcare or names someone to make those choices. When a person is selected to make the medical decisions, the document is called a Durable Power of Attorney and the designated person is called an agent. The agent can serve as a legally authorized representative to provide surrogate consent. See *GUIDANCE: Legally Authorized Representatives (Surrogate Consent) (HRP-013)*.

1.2 Adverse Event (AE): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can arise from any use of the drug (e.g., off-label use, in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

1.3 Agent: A Sharp HealthCare (SHC) employee in the course of their on-duty time or a non-SHC person who is engaged by SHC for the purposes of review of human research. Legal counsel has the ultimate authority to determine whether someone is acting as an agent of SHC. See *POLICY: Human Research Protection Program (16500.99)* for more information.

1.4 Allegation of Non-Compliance: An unproved assertion of Non-Compliance. See *GUIDANCE: Non-Compliance and other Reportable Unanticipated Problems Involving Risks to Subjects or Others (HRP-024)*.

1.5 Amendments: Changes to an IRB approved research protocol that are to be submitted and approved by the IRB before implementation (e.g. revised consent document, changed in personnel, additional risks). Amendments involving more than minor changes or changes that pose more than minimal risk will be reviewed by the full committee.

1.6 Assent: A child's affirmative agreement to participate in research. Mere failure to object is not the same as assent.

1.7 Biologic: Any therapeutic serum, toxin, anti-toxin, or analogous microbial drug applicable to the prevention, treatment or cure of disease or injuring. See *POLICY: Investigational Drugs (43019.01)* and *GUIDANCE: Investigational Drugs and Biologics (HRP-096)*.

1.8 California Experimental Subject's Bill of Rights (CA BOR): A list of rights of a subject in a medical experiment as set forth under Health & Safety Code § 24172. It is the policy of Sharp HealthCare that all research subjects or their representatives sign and date this document in addition to providing their signature on the informed consent.

1.9 Capacity to Consent (to research): The ability of the individual to understand the choices presented, to appreciate the implications of choosing one alternative or another, and to make and communicate a decision (e.g., whether or not to participate in a study). See *GUIDANCE: Legally Authorized Representatives (Surrogate Consent) (HRP-013)*.

1.10 Case Report (also called Limited Case Series): A description of the clinical characteristics or treatment(s) provided to a single patient or a small group of patients that share a common condition, which did not involve activities defined as research. See *GUIDANCE: Case Reporting Using Existing Data (HRP-094)*.

1.11 Case Report Form (CRF): A printed, optical or electronic document designed to record all of the protocol-required information to be reported to the clinical trials sponsor or entered into the research database for each clinical trial participant.

1.12 Central Tendency: The single most representative value or typical value of a set of data and it is computed using a variety of measures that are each calculated differently.

1.13 Children: Children means under the following:

1.13.1 DHHS and FDA: Persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

1.13.2 California Law: The legal age for consent is generally 18, but there are important exceptions (see Minors who may consent as Adults).

1.14 Clinical Research Coordinator (CRC): The CRC works under the supervision of the Principal Investigator (PI) and can serve as a designee across the continuum of the study.

1.15 Clinical Trial: A biomedical or behavioral research study of human subjects designed to answer specific questions about diagnostic procedures or therapeutic interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new diagnostic procedures or therapeutic interventions are safe, efficacious and effective.

1.16 Code of Federal Regulations (CFR): The United States code which codifies the general and permanent rules and regulations published by the executive departments and agencies of the federal government of the U.S.

1.17 Coded Data: Replacing identifiable data/private information (e.g. name or social security number) with a 'code' (e.g. letters, symbols or numbers) with the goal of protecting the subject.

1.18 Coded Samples: Biological samples that are identified by a code or link to the subjects' identities rather than by a direct identifier such as a name or medical record number. These samples may also be called "linked." See *GUIDANCE: IRB Review of Research using Human Biological Materials (HRP-087)*.

1.19 Common Rule: the federal rules and regulations that IRBs must adhere to. There were codified in 1991 in the Department of Health and Human Services (DHHS) Policy for the Protection of Human Subjects (45 CFR 46). This policy is frequently called the "The Common Rule" because it has been adopted by all federal agencies and departments conducting or supporting human subjects' research.

1.20 Community: Individuals with a common issue or problem, individuals with a common interest, or individuals in a geographical area.

1.21 Community Based Participatory Research (CBPR): 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.

1.22 Community Based Research (CBR): Research that is conducted in partnership with researchers and members of the community.

1.23 Compliance: Adherence to protocol specifications, good clinical practice (GCP) and regulatory requirements. See *GUIDANCE: Non-Compliance and Other Reportable Unanticipated Problems Involving Risks to Subjects or Others (HRP-024).*

1.24 Concomitant Medications: Any prescribed or over-the-counter medications, folk and herbal treatments, vitamin supplements, and drugs or agents used on the street to alter body or mind function.

1.25 Confidentiality: Describes the protections taken to safeguard data/information obtained from subject.

1.26 Conflicting Interest: An individual involved in research review is automatically considered to have a conflicting interest when the individual or the individual's immediate family have any of the following:

1.26.1 Involvement in the design, conduct, or reporting of the research.

1.26.2 Ownership interest, stock options, or other ownership interest related to the research of any value exclusive of interests in publicly-traded, diversified mutual funds.

1.26.3 Compensation related to the research of any amount in the past year or of any amount expected in the next year, including compensation for costs directly related to conducting research.

1.26.4 Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright or licensing agreement.

1.26.5 Any other reason for which the individual believes that he or she cannot be independent.

1.26.6 See *GUIDANCE: Financial Conflicts of Interests (HRP-055).*

1.27 Continuing Non-Compliance: A pattern of non-compliance that suggests the likelihood that, without intervention, instances of non-compliance will recur, a repeated unwillingness to comply, or a persistent lack of knowledge of how to comply. See *GUIDANCE: Non-Compliance and Other Reportable Unanticipated Problems Involving Risks to Subjects or Others (HRP-024)*.

1.28 Continuing Review – Periodic re-review of a research study by the IRB to evaluate if risks to participants remain reasonable in relation to potential benefits, and to evaluate if the study continues to meet regulatory and institutional requirements. Continuing review shall be conducted at intervals appropriate to the degree of risk but not less than once per year. (45 CFR 46.109€; 21 CFR 56.109(f).

1.29 Controlled Substances Act (CSA): The CSA is the federal United States drug policy under which the manufacture, importation, possession, use and distribution of certain substances is regulated. See *POLICY: Investigational Drugs (43019.01)* and *GUIDANCE: Investigational Drugs and Biologics (HRP-096)*.

1.30 Corrective Action: An action usually required of the Principal Investigator, which is necessary to reduce the risk to the subjects and/or prevent a recurrence of the reported protocol deviation/violation. Examples of corrective actions include revision of the protocol and/or consent form, re-consent of subjects, further training of study staff, or formal notification to the appropriate government oversight agencies. See *GUIDANCE: Non-Compliance and Other Reportable Unanticipated Problems Involving Risks to Subjects or Others (HRP-024)*.

1.31 Covered Entity: An organization that has to comply with HIPAA. A Covered Entity is one of the following *(See 45 CFR 160.103 for further information)*:

1.31.1 A Health Care Provider that includes doctors, clinics, psychologists, dentists, chiropractors, nursing homes, pharmacies; but only if they transmit any information in an electronic form in connection with a transaction for which HHS has adopted a standard.

1.31.2 A Health Plan that includes Health Insurance Companies, HMOs, Company Health Plans, Government programs that pay for health care, such as Medicare, Medicaid, and the Military and Veterans healthcare programs.

1.31.3 A Health Care Clearinghouse that includes entities that process non-standard health information they receive from another entity into a standard (i.e., standard electronic format or data content), or vice-versa.

1.32 Data Manager: An individual who handles the data gathered during a study. Responsibilities may also involve managing data entry, database generation and/or maintenance. Compliance with regulations and protection and integrity of private information and study data.

1.33 Deception – Deception is the intentional misleading of subjects or intentional withholding of information about the nature of a study. Deception limits the ability of subjects to provide truly 'informed consent' however, it is sometimes necessary for certain types of behavioral research. Deception is often justified because humans act differently depending on circumstances, and full disclosure of study information may bias the results.

1.34 De-identified data: Data is considered de-identified when unique identifiable information (e.g., name, address, social security number, telephone number, etc.) is removed from the data so that the subjects/source cannot be identified.

1.35 Data and Safety Monitoring Board (DSMB) or Committee: A committee of scientists, physicians, statisticians and others that collect and analyze data during the course of a clinical trial. The DSMB monitors adverse events and data to identify trends (such as an indication that one treatment is significantly better than another) that warrant study modification, termination, or notification to the subjects when information is obtained that might affect their willingness to continue. The National Institute of Health (NIH) requires that DSMBs oversee all Phase III clinical trials. The SHC IRB may require DSMB monitoring when the degree of risk is significant.

1.36 Descriptive Statistics: Ways of summarizing and describing sets of data by using tables, graphs, measures of central tendency and measures of variability.

1.37 Designated Reviewer: The Institutional Review Board (IRB) chair or an experienced IRB member designated by the IRB chair to conduct expedited reviews. See *GUIDANCE: Expedited Review Preparation (HRP-031)* and *GUIDANCE:* Expedited *Review Conduct (HRP-032)*.

1.38 Deviation: The term "protocol deviation" is not defined by either the HHS (45 CFR 46) or the FDA (21 CFR 50) human subjects regulations. For SHC IRB purposes, a protocol deviation is a minor or administrative departure from the SHC IRB approved protocol made by the PI or site personnel without prior IRB approval that does not affect the study plan or the rights, safety or welfare of human subjects. See *FORM: Deviation Summary Sheet (HRP-225)*.

1.39 Dispense: To prepare, label and provide drugs or biologics (including investigational drugs and biologics) to those who are to use them. See *POLICY: Investigational Drugs (43019.01)* and *GUIDANCE: Investigational Drugs and Biologics (HRP-096).*

1.40 Distribution: The receipt, storage and dispensing of drugs (including investigational drugs or biologics). See *POLICY: Investigational Drugs (43019.01*) and *GUIDANCE: Investigational Drugs and Biologics (HRP-096)*.

1.41 Distribution in statistics: A set of numbers and their frequency of occurrence collected from measurements of a population/data. A distribution is a summary of the data by the number of observations in each category, value or interval.

1.42 Documentation: All records, in any form (including but not limited to written, electronic, magnetic and optical records; and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct and/or results of a clinical trial, and the factors affecting a clinical trial and the actions taken.

1.43 Drug: Any chemical compound that may be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation or prevention of disease or other abnormal condition. See *POLICY: Investigational Drugs (43019.01)* and *GUIDANCE: Investigational Drugs and Biologics (HRP-096).*

1.44 Drug Administration: The direct application of a drug to the body of a patient or research subject by injection, inhalation, ingestion or other means. See *POLICY: Investigational Drugs (43019.01)* and *GUIDANCE: Investigational Drugs and Biologics (HRP-096)*.

1.45 Drug Enforcement Agency (DEA): The United States Drug Enforcement Agency, a federal law enforcement agency charged with the responsibility of combating drug abuse and enforcing laws and regulations for drugs or medical devices. See *POLICY: Investigational Drugs (43019.01)* and *GUIDANCE: Investigational Drugs and Biologics (HRP-096)*.

1.46 Elective: HRPP content that is for informational purposes and the document does not need to be completed or retained.

1.47 Emergency Deviation: A deviation from the SHC IRB approved protocol that occurred in an emergency situation, such as when a departure from the protocol is required to protect the life or physical well-being of a participant. The sponsor and SHC IRB are to be notified as soon as possible, but not later than five days after the emergency situation occurred. See *FORM: Unanticipated Problem or Event Report (HRP-214)*.

1.48 Emergency Use: The use of an investigational drug or device on a human subject in accordance with a treatment/procedure in a life threatening situation in which no comparable or standard acceptable treatment is available. See *GUIDANCE: Emergency Use Review (HRP-023)*.

1.49 Estimated Number of Subjects: The number of subjects the investigator wishes to enroll in a particular study. This number can change, depending on the stage and goal of the study. For example, a pilot study may have 5 subjects and a Phase III clinical trial may have 500 subjects.

1.50 Exempt Research: Certain kinds of research involving minimal or less than minimal risk may be "exempt" from IRB oversight when the activities fall into one or more of the exempt categories at 45 CFR 46.101. Investigators are not permitted to determine if their research is exempt. Investigators must submit proposed exempt research to the IRB for review and exempt determination.

1.51 Expedited Review: Federal regulations allow for an expedited review (one reviewer only) for certain kinds of research involving no more than minimal risk. IRB Chairs and specialists are designated to conduct expedited reviews at SHC. See *GUIDANCE: Expedited Review Conduct (HRP-032)*.

1.52 Experienced IRB Member: An IRB member is considered experienced if the IRB chair considers the IRB member to have sufficient experience in and knowledge of conducting IRB reviews.

1.53 Experimental Subject's Bill of Rights: The California Research Subjects Bill of Rights should be present at the onset of the consenting process before every California subject participating in the research signs the informed consent form. It is the policy of Sharp HealthCare that all research subjects or their representatives sign and date this document in addition to providing their signature on the informed consent.

1.54 Expiration Date: The first date that the protocol is no longer IRB approved. The date after the end date of the approval period.

1.55 Finding of Non-Compliance: Non-compliance in fact. See *GUIDANCE: Non-Compliance and Other Reportable Unanticipated Problems Involving Risks to Subjects or Others (HRP-024)*.

1.56 Food and Drug Administration (FDA): The United States Food and Drug Administration, a federal agency responsible for monitoring trading and safety standards in the food and drug industries.

1.57 Full Board Review: Research involving greater than minimal risk must be reviewed at a fully convened meeting, where a majority of the committee members are present.

1.58 Guardian: An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

1.58.1 In California, a guardian may be either parent, if both parents have legal custody, the parent or person having legal custody, a court appointed guardian, or others as consistent with an order of a court having jurisdiction over the minor.

1.58.2 A guardian has the authority to consent on behalf of a child to general medical care. This authority, however, is subject to restrictions.

1.59 Good Clinical Practice (GCP): An international quality standard that is provided by the International Conference on Harmonisation (ICH), an international body that defines standards, which governments can transpose into regulations for clinical trials involving human subjects. These include the protection of human rights as a subject in a clinical trial. They also provide assurance of the safety and efficacy of newly developed investigational drugs and include standards for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials or studies.

1.60 Health Insurance Portability and Accountability Act (HIPAA): This act went into effect April 14, 2003. The law generally prohibits health care providers such as health care practitioners, hospitals, nursing facilities and clinics from using or disclosing protected health information without written authorization from the individual (HIPAA Authorization). It is often call the "Privacy Rule."

1.61 Human Research: Any activity that either:

1.61.1 Is research as defined by Department of Health and Human Services (DHHS) and involves human subjects as defined by DHHS; "a systematic investigation, including research

development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

1.61.1.1 A systematic investigation is an activity that involves a prospective plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a question.

1.61.1.2 Investigations designed to contribute to generalizable knowledge are those designed to draw general conclusions, inform policy, or generalize findings beyond a single individual or an internal program (e.g., publications or policy).

1.61.2 Is research as defined by the U.S. Food and Drug Administration (FDA) and involves human subjects as defined by the FDA, "any experiment that involves a test article or one or more human subjects, and that meets any one of the following:

1.61.2.1 Must meet the requirements for prior submission to the FDA under section 505(i) of the Federal Food, Drug and Cosmetic Act meaning any use of a drug other than the use of an approved drug in the course of medical practice;

1.61.2.2 Must meet the requirements for prior submission to the FDA under section 520(g) of the Federal Food, Drug and Cosmetic Act meaning any activity that evaluates the safety or effectiveness of a device; OR

1.61.2.3 Any activity, the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. "

1.62 Human Subject as Defined by DHHS: A living individual about whom an investigator (whether professional or student) conducting research obtains

1.62.1 Data through intervention or interaction with the individual, or

1.62.2 Information that is both Private Information and Identifiable Information.

For the purpose of this definition:

1.62.2.1 Intervention: Physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

1.62.2.2 Interaction: Communication or interpersonal contact between investigator and subject.

1.62.2.3 Private Information: Information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

1.62.2.4 Identifiable Information: Information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

1.63 Human Subject as Defined by FDA: An individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. A human subject includes an individual on whose specimen a medical device is used.

1.64 Human Subject Training: Human subjects training is required for research approval at many institutions, including SHC. A frequently used program is one offered by the National Institutes of Health (NIH) at http://phrp.nihtraining.com/users/login.php. Many funding agencies require key research personnel to complete educational modules relevant to their research as a condition of funding.

1.65 Identifiable Information: Information that is individually identifiable (i.e., the identity of the research participant is or may readily be ascertained by the investigator or associated with the information).

1.66 Identified Biological Samples: Specimens with a personal identifier (such as a name or medical record number) that allows researchers to link the biological information derived from the research directly to the individual from whom the material was obtained. See *GUIDANCE: IRB Review of Research using Human Biological Materials (HRP-087)*.

1.67 Immediate Family: Spouse, domestic partner; and dependent children.

1.68 Inferential Statistics: Statistical methods that are used to generalize from a sample of data to make inferences about a larger population.

1.69 Informed Consent: A person's voluntary agreement to participate in research, once they've understood the possible risks and benefits of participation. Consent may be written or oral in defined circumstances.

1.70 Informed Consent Form (ICF): A document delineating the purpose of the research with a description of the experimental procedures involved and the foreseeable risks and benefits to the subject. See *TEMPLATE: Informed Consent Document with California Bill of Rights (HRP-502), TEMPLATE: Consent – Emergency Use (HRP-506), TEMPLATE: Consent – Short Form (HRP- 507)* and *TEMPLATE: Consent Form for Case Report (HRP-508)*.

1.71 Institutional Official (also known as Organization Official): At SHC, the Institutional Official is the Executive Vice President.

1.72 Institutional Review Board (IRB): The SHC IRB is an independent committee comprised of at least five members from disciplines relevant to the research being reviewed. At least one member must be unaffiliated with SHC. The membership should consist of both men and women. Members may include staff, nurses, physicians, pharmacists from SHC and persons from the local San Diego community.

1.73 Interaction: Communication or interpersonal contact between an investigator, designee and research participant.

1.74 Intervention: Physical procedures by which data are gathered (for example venipuncture) and manipulations of the participant or the participant's environment that are performed for research purposes.

1.75 International Conference on Harmonisation (ICH): The complete name of ICH is the "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use". The objective of ICH is to increase international harmonisation of technical requirements to ensure that safe, effective, and high quality medicines are developed and registered in the most efficient and cost-effective manner.

1.76 Investigational Device: A new, non-FDA approved medical device or procedure which is regulated as part of a research or clinical trials protocol, or an FDA-approved medical device which is being used for a new purpose. See *POLICY: Investigational Devices (16509)* and *GUIDANCE: Investigational Devices (HRP-095)*.

1.77 Investigational Device Exemption (IDE): An exemption issued by the FDA to allow the use of investigational devices in human subjects. The IDE permits use of the device in a clinical investigation to evaluate the safety and/or efficacy of the investigational device. See *POLICY: Investigational Devices (16509)* and *GUIDANCE: Investigational Devices (HRP-095)*.

1.78 Investigational Drug: A pharmaceutical form of an active ingredient being tested or used as a reference in a clinical trial. This includes drugs with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or drugs used to gain further information about an approved use. See *POLICY: Investigational Drugs (43019.01)* and *GUIDANCE: Investigational Drugs and Biologics (HRP-096)*.

1.79 Investigational New Drug (IND) Application: Means by which permission may be obtained to 1) ship an investigational drug, biologic or agent across state lines and 2) use in humans prior to an FDA review of clinical data has determined a new drug, agent, or biologic is safe and effective for a specific use. Testing of an investigational drug may proceed once a valid IND is in effect or an IND exemption

has been granted by the FDA. See *POLICY: Investigational Drugs (43019.01) and GUIDANCE: Investigational Drugs and Biologics (HRP-096)*.

1.80 Investigational Product (IP) (also known as Test Article): Any drug, biological product or medical device for human use in a clinical trial. See *POLICY: Investigational Drugs (43019.01)*; *GUIDANCE: Investigational Drugs and Biologics (HRP-096); POLICY: Investigational Devices (16509);* and *GUIDANCE: Investigational Devices (HRP-095)*.

1.81 Investigator (also known as researcher): The investigator is the person responsible for the conduct of the research. If the research is conducted by a team of individuals, the principal investigator (PI) is the responsible leader of the team.

1.82 Investigator-Initiated (also known as sponsor-investigator): An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.

1.83 Key Personnel: These are individuals in a research project who include but are not limited to: Principal Investigators (PIs), Sub-Investigators, study coordinators, regulatory specialists, recruiters, and anyone else performing study procedures and interventions.

1.84 Legally Authorized Representative (LAR): An individual or judicial, or other body authorized under applicable law to grant permission on behalf of a prospective subject for their participation in research activities. See *GUIDANCE: Legally Authorized Representatives (Surrogate Consent) (HRP-013)*.

1.85 Limited Case Series (also called Case Report): A description of the clinical characteristics or treatment(s) provided to a single patient or a small group of patients that share a common condition, which did not involve activities defined as research. See *GUIDANCE: Case Reporting Using Existing Data (HRP-094)*.

1.86 Mean: The mean is defined by adding up all the values for a given variable and then dividing the sum by the number of values included. The mean is one type of measure of central tendency.

1.87 Median: The median literally is the value in the middle of a set of values. The median is defined by lining up the values, from largest to smallest. The one in the dead-center is the median. The median is one type of measure of central tendency.

1.88 Medical Experiment (per California Health and Safety Code 24178):

- 1.88.1 The severance or penetration or damaging of tissues of a human subject or the use of a drug or device, electromagnetic radiation, heat or cold, or a biological substance or organism, in or upon a human subject in the practice or research of medicine in a manner not reasonably related to maintaining or improving the health of the subject or otherwise directly benefiting the subject; or
- 1.88.2 The investigational use of a drug or device; or
- 1.88.3 Withholding medical treatment from a human subject for any purpose other than maintenance or improvement of the health of the subject; and
- 1.88.4 The medical experiments relate to the cognitive impairment, lack of capacity or serious or life threatening diseases and conditions of research participants.

1.89 Minimal Risk: A risk is minimal when the probability of magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in the participant's daily life or during the performance of routine physical or psychological examinations or tests.

1.90 Minor: A person less than 18 years of age, whether or not they meet the federal definition for a "child." In California, certain people under 18 years of age are legally able to consent for treatments or procedures involved in research, such as "Emancipated", "Self-Sufficient," and certain "Un-emancipated" Minors.

1.91 Minor Modification: Does not materially affect an assessment of the risks and benefits of the study and does not substantially change the specific aims/design of the study.

1.92 Mode: This statistic tells the value that appears the most often for a given variable. It is possible to have more than one mode, and it is possible to have no mode. The mode is one type of measure of central tendency.

1.93 Monitor: A monitor is a type of research auditor, usually employed by the drug/device sponsor, who ensures that research protocols are being followed and documented appropriately. Monitors visit research sites regularly to inspect study documents and medical records and to validate research data.

1.94 Multi-Center Research: A research study conducted at more than one institution (nationally and/or internationally) using the same protocol, each with its own Principal Investigator. Many clinical trials involving drugs/biologics/devices are conducted at more than one site.

1.95 Non-compliance: Any action or activity associated with the conduct or oversight of research involving human participants that fails to comply with either the research plan as approved by the SHC IRB, or federal regulations or SHC institutional policies governing human subjects' research.

1.96 Non-Significant Risk (NSR) Device: An investigational device that does not meet the definition of a significant risk device. See *POLICY: Investigational Devices (16509)* and *GUIDANCE: Investigational Devices (HRP-095).*

1.97 Normalizing/Standardizing/Transforming Data: Accurate interpretation of many statistical tests is difficult if a dataset fails to satisfy important assumptions about the data. Adjustment for such violations may be achieved by normalizing/standardizing/transforming a dataset by mathematical means.

1.98 Normative/Normed Data: Data points of a second data set are placed relative to the original data obtained from a large sample for the purpose of comparison. The originally collected sample is typically referred to as the norm group because it is the group upon which the new group's data is compared.

1.99 Not Human Subjects Research (NHSR): A study which uses specimens/data from non-research repositories or databases (the specimens/data have no links to identifiable private data). See *GUIDANCE: Repositories - Banking of Specimens and Data (HRP-086)*.

1.100 Original Medical Record/Source Documents: Original documents, data and records, including; hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or questionnaires, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, laboratories and at medico-technical departments involved in conducting the clinical trial.

1.101 Outcomes Research: Studies that aim to identify and evaluate effective care processes that improve the quality of patients' lives. See *GUIDANCE: Conducting Outcomes Research at Sharp HealthCare's Outcomes Research Institute (HRP-097)*.

1.102 Participant (also known as subject): See Human Subject as identified by DHHS and Human Subject as identified by FDA in definitions above.

1.103 Planned Emergency Research: Research involving human subjects who are in need of emergency medical intervention (e.g., comparison of methods for providing cardiopulmonary resuscitation), but who cannot give informed consent because of their life-threatening medical conditions and who do not have an available legally authorized representative.

1.104 Principal Investigator: The 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.

1.105 Privacy: Privacy refers to the subject and his/her control over the extent, timing and circumstances of sharing oneself (physically, emotionally, behaviorally, or intellectually) with others.

1.106 Private Information: Information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been

provided for the specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., medical records).

1.107 Protected Health Information (PHI)/HIPAA Authorization: (PHI) is any information about health status, provision of health care, or payment for health care that can be linked to a specific individual. The HIPAA Privacy Rule permits the use and disclosure of PHI if certain standards are met and the individual signs a PHI Authorization Form.

1.108 Protocol: The formal design of an experiment or research activity. The protocol includes a description of the research methodology, the eligibility requirements for prospective subjects and controls, the treatment regime(s), and the proposed methods of analysis that will be performed on the collected data.

1.109 Protocol Deviation: A minor or administrative departure from the SHC IRB approved protocol that was made by the PI or site personnel without prior IRB approval and does not affect the study plan or the rights, safety or welfare of human subjects. Examples of minor or administrative deviations include; 1) follow-up visits that occurred outside the protocol required time frame because of the participant's schedule or 2) blood samples obtained at times close to but not precisely at the time points specified in the protocol. See *FORM: Deviation Summary Sheet (HRP-225)* for reporting requirements.

1.110 Protocol Violation: A failure to comply with the study protocol as approved by the SHC IRB. A violation is a serious non-compliance with the protocol that can result in the exclusion of a subject or their results in the study and in some cases a charge of research misconduct. See *GUIDANCE: Non-Compliance and Other Reportable Unanticipated Problems Involving Risks to Subjects or Others (HRP-024)*, *GUIDANCE: Research Misconduct (HRP-003)* and *FORM: Unanticipated Problem or Event Report (HRP-214)* for reporting requirements.

1.111 Range: The range is the mathematical difference between the highest and lowest values for a given variable. It is the simplest measure of variability to calculate but it depends only on the extreme values in the data set and does not use all of the data. The range is one type of measure of variability.

1.112 Regulatory Specialist: The individual responsible for completing the IRB and sponsor regulatory paperwork.

1.113 Reportable Event: A protocol deviation or violation that is likely to adversely affect the rights and welfare of the research subjects, the safety of the research subjects, or the integrity of the research data. See *GUIDANCE: Non-Compliance and Other Reportable Unanticipated Problems Involving Risks to Subjects or Others (HRP-024)*, *GUIDANCE: Research Misconduct (HRP-003)* and *FORM: Unanticipated Problem or Event Report (HRP-214)* for reporting requirements.

1.114 Required: HRPP content is requisite information and the document must be completed and filed appropriately.

1.115 Research: See Human Research

1.116 Research Misconduct: Fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. Research Misconduct does not include honest error or difference in opinion. See *GUIDANCE: Research Misconduct (HRP-003)*.

1.116.1 "Fabrication" is making up data or results and recording or reporting them.

1.116.2 "Falsification" is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.

1.116.3 "Plagiarism" is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

1.117 Research/Subject Advocate: Individuals who work with research subjects and promote subject rights. Their range of activities can vary. Some advocates may help subjects make an informed decision about research participation by explaining possible risks and benefits.

1.118 Restricted: Investigators who have continuing non-compliance and serious non-compliance concerns or complaints brought against them by the IRB or others may be restricted. See *GUIDANCE: Non-Compliance and Other Reportable Unanticipated Problems Involving Risks to Subjects or Others (HRP-024)* for a list of possible restrictions.

1.119 Sample Size: The number of subjects participating in the research, typically denoted *N* or *n* in research literature. Generally, different sample sizes lead to different accuracies of measurement.

1.120 Serious Adverse Event (SAE): An undesirable experience associated with the use of a medical product in a patient. The event is serious and should be reported to the FDA and the SHC IRB when the patient outcome is; death, life-threatening, requires initial or prolonged hospitalization, disability or permanent damage, congenital anomaly/birth defect, required intervention to prevent permanent impairment or damage (devices) or other serious medical events (e.g. drug dependence). See *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)* for reporting requirements.

1.121 Serious Non-Compliance: Non-compliance that adversely affects the rights or welfare of subjects. See *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)* for reporting requirements.

1.121.1 For Department of Defense (DoD) research Serious non-compliance includes failure of a person, group, or institution to act in accordance with DoD Instruction 3216.02 and its references such that the failure could adversely affect the rights, safety or welfare of a human subject; place a human subject at increased risk of harm; cause harm to a human subject; place a human subject at increased risk of harm; cause harm to a human subject; affect a human subject's willingness to participate in research; or damage or compromise the scientific integrity of the research data.

1.122 Significant-Risk (SR) Device: An investigational device that:

1.122.1 Is intended as an implant and presents a potential for serious risk to the health, safety or welfare of a subject;

1.122.2 Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety or welfare of a subject;

1.122.3 Is for a use of substantial importance in diagnosing, curing, mitigating or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety or welfare of a subject; or

1.122.4 Otherwise presents a potential for serious risk to the health, safety or welfare of a subject. See *POLICY: Investigational Devices (16509)* and *GUIDANCE: Investigational Devices (HRP-095)*.

1.123 Source Data: All information in original records or certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source document (original records or certified copies), and serve to verify the research record.

1.124 Source Documents (also known as Original Medical Records or Research Records): Original documents, data and records, including; hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or questionnaires, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, laboratories and at medico-technical departments involved in conducting the clinical trial.

1.125 Sponsor: The entity (e.g., pharmaceutical manufacturer) or individual who initiates the clinical trial and is responsible for registering the clinical investigation and submitting clinical trial information to the Clinical Trial Registry Data Bank (www.clinicaltrials.gov). *See GUIDANCE: Clinicaltrials.gov Registration for SHC-Initiated Clinical Trials (HRP-048)*.

1.126 Sponsored/Funded Research: Sponsored or funded research is research that is financially supported by an outside entity. The funding may come from a pharmaceutical company, a foundation, a donor or the government.

1.127 Sponsor-Investigator (same as investigator-initiated)**:** An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.

1.128 Standard Deviation: Indicates how tightly all the various data points are clustered around the mean in a set of data. When the data points are tightly bunched together around the mean, the standard deviation is typically small. When the data points are spread apart around the mean, this tells you that you have a relatively large standard deviation. The standard deviation is defined as the square root of the variance. Standard deviation is one type of measure of variability.

1.129 Statistical Significance: Used to assess the probability or error in a study's findings. Tests of statistical significance allow researchers to determine the probability of the results occurring by chance alone. Typically, as the probability level decreases, confidence increases that the results are not due to chance but due to the intervention.

1.130 Subject (also known as participant): See Human Subject as identified by DHHS (3.32) and Human Subject as identified by FDA (3.33) in definitions above.

1.131 Subject Identification Code: A unique identifier code that is assigned by the sponsor, investigator or designee to each research subject (participant) to protect the subject's identity and confidentiality in the research file. The Subject Identification Code is used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data, and on all research documents that go to the sponsor, or outside of SHC.

1.132 Surrogate Consent: The use of a legally authorized representative with reasonable knowledge of the research subject, who shall include any of the persons and/or in descending order of priority, described under California law (Health and Safety Code 24178). See *GUIDANCE: Legally Authorized Representatives (Surrogate Consent) (HRP-013)*.

1.133 Suspension of IRB Approval: An action of the IRB, IRB designee, Institutional Official or designee of the Institutional Official to temporarily or permanently withdraw IRB approval of some or all research procedures short of a termination of IRB approval. Suspended studies remain open and are subject to continuing review. See *GUIDANCE: Suspension or Termination of IRB Approval by Other than the Convened IRB (HRP-026)*.

1.134 Termination of IRB Approval: An action of the IRB, IRB designees, Institutional Official or Institutional Official designee to permanently withdraw IRB approval of all research procedures. Terminated studies are permanently closed and no longer need continuing review. See *GUIDANCE: Suspension or Termination of IRB Approval by Other than the Convened IRB (HRP-026).*

1.135 Test Article (also known as Investigational Product (IP): Any drug, biological product or medical device for human use. See *POLICY: Investigational Drugs (43019.01), GUIDANCE: Investigational Drugs and Biologics (HRP-096), POLICY: Investigational Devices (16509),* and *GUIDANCE: Investigational Devices (HRP-095)*.

1.136 Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. See *FORM: Unanticipated Problem or Event Report (HRP-214)*.

1.137 Unanticipated Problem: Events that are; unanticipated; and related or possibly related to the research; and suggest that the research places the subject or others at increased risk for harm (physical, psychological, criminal or civil liability, damaging to the subjects financial standing, employability, or reputation). *See FORM: Unanticipated Problem or Event Report (HRP-214)*.
For VA research, unanticipated problems that may substantively compromise the effectiveness of the facility's human research protection or oversight programs may also constitute Unanticipated Problems. See *CHECKLIST: Additional Veterans Administrator (VA) Criteria (HRP-432)*.

1.138 Unexpected Adverse Drug Experience (also known as Unanticipated Adverse Drug Event): Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan. Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed, (e.g., included in the investigator brochure), rather than from the perspective of such experience not anticipated from the pharmacological properties of the pharmaceutical product. See *FORM: Unanticipated Problem or Event Report (HRP-214)*.

1.139 Unidentified Biological Samples: Biological samples where identifiable personal information is not collected and cannot be retrieved by the investigator. These samples may also be called "anonymous." See *GUIDANCE: IRB Review of Research using Human Biological Materials (HRP-087)*.

1.140 Unlinked Biological Samples: Biological samples from which the identifiers are removed and no code or link to the subjects' identities exists. These samples may also be called "anonymized." See *GUIDANCE: IRB Review of Research using Human Biological Materials (HRP-087)*.

1.141 Variability: This term refers to how spread out the values in a distribution are and it is computed using a variety of measures that are each calculated differently. The greater the spread a dataset displays, the greater variability that dataset shows.

1.142 Variance: A statistic used to define how close values in a distribution are to the middle of the distribution. The mean, median or mode of a distribution may be used as an indication of the middle of the distribution. The variance is defined as the average squared difference of the scores from the measure of central tendency. The variance is one type of measure of variability.

1.143 Ward: As defined by FDA, a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.

Appendix B: Prisoners

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

1. Sentenced under a criminal, civil, or military statute;
2. 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
3. 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 C: Additional Research Requirements for Federal Agencies

Appendix C-1: Department of Defense (DoD) Research Requirements

1. When applicable, research protocols must be reviewed and approved by the IRB prior to the Department of Defense (DoD) approval. Consult with the DoD funding component to see whether this is a requirement.
2. For non-exempt research, the SHC IRB must consider the scientific merit of the research.
    a. The SHC IRB may rely on outside experts to provide an evaluation of the scientific merit.
3. DoD employees (including temporary, part-time, and intermittent appointments) may not be able to legally accept payments to participate in research and should check with their supervisor before accepting such payments. DoD employees cannot be paid for conducting research while on active duty.
4. DoD military personnel must follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty or off-duty.
5. Components of the DoD might have stricter requirements for research-related injury than the DHHS regulations.
6. There may be specific educational requirements or certification required.
    a. Initial and continuing research ethics education is required for all personnel who conduct, review, approve, oversee, support, or manage human participants' research.
    b. The DoD may evaluate the education policies to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.
    c. The SHC IRB specialists, chairs, members, researchers and research staff are to be aware of any specific educational requirements contained in DoD regulations and will become educated about these requirements as appropriate to the research.
7. Though the DoD has adopted the HHS Subpart B regulation, it replaces the phrase "biomedical knowledge" with "generalizable knowledge" throughout Subpart B of 45 CFR 46[3].

    The applicability of Subpart B is limited to research involving pregnant women as participants in research that is more than minimal risk and included interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as participants.
8. Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g[4].
9. The DoD prohibits research involving any person captured, detained, held, or otherwise under the control of DoD personnel (military and civilian, or contractor employee). Such persons include: enemy prisoners of war, civilian internees, retained persons, lawful and unlawful enemy combatants. Such persons do not include DoD personnel being held for law enforcement purposes[5]. A prisoner of war under the DoD is a

[3] http://www.dtic.mil/whs/directives/corres/pdf/321602p.pdf
[4] http://www.gpo.gov/fdsys/pkg/USCODE-2010-title42/pdf/USCODE-2010-title42-chap6A-subchapIII-partH-sec289g.pdf
[5] http://www.med.navy.mil/sites/nmrc/documents/secnavinst_3900_39d.pdf

detained person as defined in Articles 4 and 5 of the Geneva Convention Relative to the Treatment of Prisoners of War of August 12, 1949. In particular, one who, while engaged in combat under orders of his government, is captured by the armed forces of the enemy.

10. In evaluating risk, the DoD's phrase "ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests" in the definition of minimal risk (section 219.102[i] of Reference [c]) shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).
11. Non-exempt classified research must be conducted following the requirements of Instruction 3216.02 13.
12. For questions specific to a particular protocol, consult with the appropriate DoD funding component.
13. Any determinations of serious or continuing non- compliance of DoD supported research must be promptly (no longer than within 30 days) reported to the DoD human research protection officer.

Other specific requirements of the DoD research can be found in the Additional Requirements for Department of Defense Research section in the SHC IRB's *WORKSHEET: Additional Federal Criteria (HRP-318)*.

Appendix C-2: Environmental Protection Agency (EPA) Research Requirements[6] [7]

1. Researchers who participate in any project that collects data from or about humans are responsible for communicating with their EPA Human Subjects Research (HSR) officer to ensure that all EPA requirements are met prior to starting an IRB approved study. All HSR conducted or supported by EPA must be approved by the EPA HSR Review Official as compliant with EPA Regulation 40 CFR 26 (Protection of Human Subjects) or be determined to meet regulatory criteria for exemption before research can begin.
2. In addition to the researchers being responsible for ensuring compliance with EPA HSR requirements, the IRB is also responsible for ensuring that EPA requirements are met prior to approving EPA-supported HSR.
3. The EPA does not allow research that intentionally exposes pregnant woman (and therefore her fetus), nursing woman or a child to any substance regulated by the EPA.
4. Research involving intentional exposure of non-pregnant or non-nursing adults must comply with the provisions of 40 CFR 26.
5. **Observational Research:**
    a. The SHC IRB will apply 40 CFR 26 and 45 CFR 46 Subpart B when reviewing observational research involving pregnant women and fetuses.
    b. The SHC IRB will approve observational research involving children that does not involve greater than minimal risk only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 40 CFR 26.406.
    c. The SHC IRB will approve observational research if it finds that an intervention or procedure presents more than minimal risk to children. EPA will not conduct or fund observational research that includes such an intervention or procedure unless the IRB finds and documents that:

[6] http://www.gpo.gov/fdsys/pkg/CFR-2010-title40-vol1/xml/CFR-2010-title40-vol1-part26.xml#seqnum26.203
[7] http://www.epa.gov/osa/phre/hsr.htm

i. The intervention or procedure holds out the prospect of direct benefit to the individual subject or is likely to contribute to the subject's well-being;
ii. The risk is justified by the anticipated benefit to the subjects;
iii. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
iv. Adequate provisions are made for soliciting the assent of the children and permission of the parents or guardians, as set forth in 40 CFR 26.117.

Appendix C-3: Department of Energy (DOE)Research Requirements [8] [9] [10] [11]

When following DOE requirements:

- Research involving human participants also includes studies of the intentional modification of the human environment.
- Generalizable includes the study of tracer chemical, particles or other materials to characterize airflow.
- Generalizable also includes studies in occupied homes or offices that:
    - Manipulate the environment to achieve research aims.
    - Test new materials.
    - Involve collecting information on occupants' views of appliances, materials, or devices installed in their homes or their energy-saving behaviors through surveys and focus groups.
- Generalizable should be viewed in terms of the contribution to knowledge within the specific field.
- The SHC IRB is responsible for ensuring that DoE requirements are met prior to approving DoE-supported human subjects research.
- Researchers are responsible for communicating with their Department of Energy (DoE) Program Officer to ensure that all DoE requirements are met prior to starting an IRB approved study.
- Researchers are required to complete and comply with the requirements outlined in the CHECKLIST: Department of Energy *Research Requirements (HRP-423)* for use by researchers conducting human subjects research that uses Personal Identifiable Information (PII). Any compromise of PII must be reported immediately to the DOE as specified in the DOE checklist.

[8] http://humansubjects.energy.gov/research/policy.htm
[9] http://humansubjects.energy.gov/worker-studies/files/cfrtext.pdf
[10] http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
[11] https://www.directives.doe.gov/directives-documents/0443.1-BOrder-b/@@download/file

Appendix C-4: Department of Justice (DOJ) National Institute of Justice (NIJ) Research Requirements [12] [13]

The SHC IRB does not review research involving prisoners. For other types of research within the Department of Justice (DOJ) National Institute of Justice (NIJ), researchers are responsible for communicating with the program officer to ensure that all NIJ requirements below are met prior to starting an IRB approved study:

1. **Privacy Certificate**[14]: All projects are required to have a privacy certificate approved by the NIJ human subjects protection officer.
2. **Employee Confidentiality Statements**[15]: All researchers and research staff are required to sign employee confidentiality statements, which are maintained by the responsible researcher.
3. **Child Abuse Reporting**: Under a privacy certificate, researchers and research staff do not have to report child abuse unless the subject signs another consent document to allow child abuse reporting.
4. **Confidentiality Statement in Consent Form**: The confidentiality statement on the consent document must state that confidentiality can only be broken if the subject reports immediate harm to subject or others.
5. **De-identified Data Sent to Archive**: A copy of all data must be de-identified and sent to the National Archive of Criminal Justice Data, including copies of the informed consent documents, data collection instruments, surveys, or other relevant research materials.

Research conducted within the Bureau of Prisons implementation of bureau programmatic or operational initiatives made through pilot projects is not considered to be research.

The SHC IRB is responsible for ensuring that DoJ-NIJ requirements are met prior to approving DOJ-NIJ funded human subjects research.

[12] http://www.gpo.gov/fdsys/pkg/CFR-2003-title28-vol2/pdf/CFR-2003-title28-vol2-part46.pdf
[13] http://www.nij.gov/funding/humansubjects/Pages/human-subjects.aspx
[14] www.nij.gov/funding/.../Pages/privacy-certificate-guidance.aspx
[15] http://www.nij.gov/funding/humansubjects/Pages/employee-confidentiality.aspx

Appendix C-5: Department of Veterans Affairs (VA) Research Requirements[16]

Medical Director Responsibilities

The medical center director:

- Is responsible for the facility's research program, and is assisted by the Research and Development Committee.
- Is responsible for ensuring there are adequate resources to support the operations of the HRPP so that those operations are in compliance with all VA and other federal requirements that govern human participants research protection.
- Oversees all VA Researchers and Research Staff.
- Ensures that IRB members, Researchers and Research Staff are appropriately knowledgeable to conduct research in accordance with ethical standards and all applicable regulations.
- Develops and implements an educational plan for IRB members, staff, Researchers, and Research Staff including initial and continuing education.
- Fulfills all educational requirements mandated by the VA Office of Research and Development (ORD) and OHRP.
- Is responsible for ensuring a local research participant outreach program is implemented that includes a reliable mechanism for research participants to communicate with researchers & with an informed VA representative who is independent of research study in question (e.g., providing contact information in the consent document).
- Ensures the IRB functions independently.
- The chair, or co-chairs, and members have direct access to the medical center director for appeal if they experience undue influence or if they have concerns about the IRB.
- Appoints one or more research compliance officers to conduct annual research consent document audits and triennial regulatory audits, and to assist in the VA facility's assessments of regulatory compliance with all applicable local, VA and other federal requirements, but not limited to, Office of Research Oversight requirements.
    - Unless a waiver for a part-time research compliance officer is approved by the under secretary for health, each VA facility conducting research must designate at least one full-time research compliance officer.
- Report any appointment, resignation, or change in status of the research compliance officer to Office of Research Oversight VHA Central Office, with a copy to the relevant ORO research officer, within 10 business days after the appointment, resignation, or change takes effect.
- Report to ORO in writing within five business days after being notified of a research problem or event (including serious and continuing non-compliance, unanticipated problems involving risks to participants or others, and suspensions and terminations) for which such reporting is required.

[16] http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=2531

  - The medical center director's written report is required regardless of whether disposition of the event has been resolved at the time of the report.
  - Follow-up reports detailing any additional findings and appropriate remedial actions must be provided to the relevant ORO office at intervals and in a manner specified by that office.
  - Provides a copy of any ORO compliance reports regarding the research program to the associate chief of staff for research, Research and Development Committee, any relevant research review committee(s), and the research compliance officer in a timely fashion.
- Reports the following research events to ORO Central Office, with a simultaneous copy to the appropriate ORO research officer, as indicated in the following:
  - IRB changes in number of IRBs and changes in membership rosters.
- Ensures the provision of services by the IRB is established through a memorandum of understanding or other written agreement that outlined the responsibilities of the VA facility and the academic affiliate
  - Substantive Memorandum of Understanding (MOU) changes must be reported to ORO Central Office within five business days.
- Accreditation problems must be reported to ORO Central Office within five working days.

VA Directives

Researchers conducting research at a Department of Veterans Affairs (VA) facility or research involving veterans must comply with the Common Rule, Subparts B, C, and D and the following VA-specific directives:

- 38 CFR 16, VA Protection of Human Subjects.
- Veterans Health Administration (VHA) Handbook 1058.01, Requirements for Reporting Research Events to Facility Oversight Committees and the Office of Research Oversight.
- VHA Handbook 1200.05, Requirements for the Protection of Human Subjects in Research which specifies:
  - **Classified Research.** Classified research involving human subjects cannot be approved by a VA IRB or R&D Committee or performed at a VA facility, including space leased to, and used by VA.
  - **Planned Emergency Research.** Planned emergency research must not be granted approval by a VA IRB or R&D Committee and cannot be conducted by VA.
- Office of Research Oversight (ORO) Publications – For OHO directives and handouts related to compliance and monitoring for VA research programs are available online at: http://www.va.gov/ORO/oropubs.asp.
- Local VA Standard Operating Procedures

Applicable VA Policy Sections

The following VA policy sections address protections in addition to DHHS and FDA requirements, other agency regulations, and state laws.

For additional VA requirements, see *CHECKLIST: Additional Department of Veterans Affairs (VA) Research Criteria (HRP-432)*.

VA Requirements for IRB Composition and VA Representation

The SHC IRB complies with the following additional requirements when reviewing VA research:

- The SHC IRB to have at least two VA representatives who are at least 5/8th VA-compensated appointments and are neither WOCs (individuals not receiving compensation) nor those with Interagency Personnel Agreement (IPA) appointments.
- At least one of the two VA representatives are to have scientific expertise (per VA Handbook 1200.05, physicians, nurses, pharmacists, social workers, statisticians and clinical allied health professionals are considered scientists).
- At least one of the two VA IRB members must be present during the review of VA research.
- VA representatives serve as full-voting members for the IRB.
- VA IRB members may review non-VA research matters coming before the IRB.
- VA IRB members must comply with VA requirements for training for disclosing and updating potential financial and non-financial conflicts of interest.
- Under certain circumstances, a waiver for VA representation on the IRB may be obtained from the VA Chief Research and Development Officer CRADO.

VA Research Compliance Officer and the IRB

The SHC IRB recognizes the following possible roles for the VA Research Compliance Officer (RCO):

- The RCO may not serve as a voting or non-voting member of the IRB
- The RCO may serve as a non-voting consultant, upon request by the IRB.
- The RCO may attend meetings of the IRB when requested by the IRB.

Requirements for VA Multi-Site Research

Before initiating VA research at multiple sites, the researcher must provide the SHC IRB with the following, as relevant to the research:

- Contact information for and documentation of approval from the collaborating VA facilities' IRBs of record;
- Documentation of approval from collaborating VA committees and subcommittees as required by participating VA sites, the federal VA, and other federal agencies; and
- Written notification from the VA ACOS/R (Associate Chief of Staff/Research) that the research may be initiated.

VA Research Approval

In addition to IRB approval, VA research is subject to approval from the following:

- Research and Development Committee (RDC): The SHC IRB may serve as a subcommittee of the RDC
- VA Protocol Review Subcommittee (PRS): The PRS reviews VA research to confirm researcher qualifications to conduct the research, assess for conflicts of interest, and verify the research is scientifically sound and complies with VA requirements.
- Subcommittee on Research Safety
- Privacy Officer
- Information Security Officer
- Biosafety Committee
- Other VA committees as relevant to the research.

Researchers are advised to contact the VA Research Office (www.research.va.gov) for details about the VA committee review process.

The VA Research Office documents VA committee decisions as follows:

- An ACOS/R letter confirms approval by the RDC) and all other appropriate VA committees and informs the researcher the research may be initiated.
- The PRS Committee review form documents the PRS Committee review.

Appendix D: 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 http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf.

Appendix E: Other Resources

- International Conference on Harmonization – Good Clinical Practice (ICH-GCP) Requirements
- 45 CFR 46 - Human Subjects
- Declaration of Helsinki
- 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
- National Bioethics Advisory Commission (NBAC)
- Office of Research Integrity (ORI)
- Public Responsibility in Medicine and Research (PRIM&R)