1 PURPOSE

1.1 This guidance establishes the process for Sharp HealthCare when collaborating with external Institutions to conduct a single research protocol or series of studies, and entering into reliance agreements with outside institutions.

1.2 The guidance begins when Sharp HealthCare is considering participation in research that requires Sharp HealthCare or a collaborating external Institution to serve as a central IRB (also referred to as IRB of Record).

1.2.1 A Sharp HealthCare affiliated principal investigator is planning or preparing to rely on an Institutional Review Board (IRB) of a non-Sharp HealthCare (external) institution for review of research or a clinical investigation activity that involves human subjects; or

1.2.2 A principal investigator is planning or preparing to rely on the oversight of the Sharp HealthCare IRB.

1.3 The guidance ends when the IRB of Record terminates the research or acknowledges the permanent closure of the research activity.

2 REVISIONS FROM PREVIOUS VERSION

2.1 If applicable, previous versions available in Human Research Protection Program (HRPP) Change Log.

3 DEFINITIONS

3.1 **Institutional Review Board (IRB) of Record (also known as Central IRB)**: The IRB of Record assumes IRB responsibilities for oversight of research conducted at another organization, per 45 CFR 46 and/or 21 CFR 56. When the research is conducted or supported by any Federal department or agency, the Relying Organizations designate the IRB of Record on its Federalwide Assurance (FWA) with the Federal Office of Human Research Protection (OHRP). See also Single IRB Process.

3.2 **Relying Organization**: The domestic entity in a single or multi-site study that will rely on the IRB of Record to carry out the site's initial and continuing IRB review of human subjects research for the single or multi-site study. A relying organization has entered into a Reliance Agreement with another organization's IRB.

3.3 **Reliance Agreement**: A formal, written agreement in which the reviewing IRB agrees to serve as the IRB of Record for a Relying Organization. The agreement documents the respective authorities, roles, responsibilities, and communication between an institution/organization providing the ethical review and a participating site relying on the IRB of Record. The agreement satisfies the specific responsibilities of the IRB of Record in satisfying the requirements of 45 CFR 46 and 21 CFR 50, 56. In NIH sponsored research, the coordinating center/awardee is responsible for ensuring Reliance Agreements are in place, and that documentation is maintained. See *HRP-574 - TEMPLATE AGREEMENT - IRB Authorization / Reliance Agreement*.

3.3.1 Commonly used Reliance Agreements for organizations include:

3.3.1.1 Memoranda of Understanding (MOU)

3.3.1.2 IRB Authorization Agreements (IRBAA)

3.3.1.3 Master Reliance Agreement (MRA)

3.3.1.4 Collaborative Review Agreement (CRA)

3.4 **Multi-Site Study (also known as Multi-Center Research):** A study that uses the same protocol to conduct non-exempt human subjects research at more than one site.

3.4.1 Protocols that address the same research questions, involve the same methodologies, and evaluate the same outcomes are considered to be the "same research protocol." Sites that are accruing research participants for studies that are identical except for variations due to local context consideration would be considered to be conducting the "same research protocol".

3.4.2 If a study is conducted or supported by any Federal department or agency and involves a separate site for study coordination or coordination of data and statistical

analyses and the site is conducting the same protocol as the other participating sites, then all sites would be expected to rely on the designated IRB of Record. The Relying Organizations designate the IRB of Record on its Federalwide Assurance (FWA) with the Federal Office of Human Research Protection (OHRP).

3.5 **Privacy Board:** A review body that may be established to act upon requests for a waiver or an alteration of the Authorization requirement under the Privacy Rule for uses and disclosures of protected health information (PHI) for a research study.

3.5.1 If a multi-site project also requires a privacy review under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), it may be appropriate for the IRB of Record to serve as the Privacy Board.

3.5.2 A Privacy Board may waive or alter all or part of the Authorization requirements for a specified research project or protocol. A covered entity may use and disclose PHI, without an Authorization, or with an altered Authorization, if it receives the proper documentation of approval of such alteration or waiver from a Privacy Board.

3.6 **Single IRB Process (sIRB)**: Institutions participating in federally funded cooperative research (involving more than one institution) must rely upon approval by a single IRB for the portion of research that is conducted in the U.S. (45 CFR 46.114). While participating institutions are expected to rely on the single IRB, they may conduct their own review in accordance with NIH policy on exceptions from single IRB review. See definition for “Institutional Review Board (IRB) of Record.”

4 POLICY STATEMENT

4.1 Sharp as the Relying Organization: To the extent permitted by law, Sharp HealthCare (SHC) may delegate tasks normally performed by Sharp’s IRB to the IRBs of other HRPP accredited organizations in cases where Sharp’s Institutional Official (or designee) believes doing so to be appropriate (including appropriately protective of subjects) and efficient.

4.1.1 Sharp will apply the following criteria in selecting an external IRB that qualifies to conduct the review of Sharp protocols:

4.1.1.1 The external IRB is currently registered with OHRP/FDA.

4.1.1.2 The external IRB is in good standing with OHRP/FDA (no recent warning letters, no open investigations).

4.1.1.3 For commercial IRBs: the commercial IRB is accredited by the Association for the Accreditation of Human Research Protections Programs (AAHRPP).

4.1.1.4 For non-commercial IRBs:

4.1.1.4.1 The IRB has an active FWA on file with the OHRP.

4.1.1.4.2 The Institution is AAHRPP-accredited or Sharp has determined the proposed IRB of Record meets Sharp standards per section 4.1.2.

4.1.1.4.3 The external IRB is located within the U.S.

4.1.1.4.4 The external IRB has processes in place to notify the Sharp IRB and researcher(s) of its approvals, determinations, reportable events (i.e., serious and/or continuing non-compliance, unanticipated problems), suspensions, and terminations.

4.1.1.5 The Sharp IRB determines that the external IRB can fulfill its responsibilities as outlined in the written reliance agreement.

4.1.2 Sharp will consider the qualifications of an external IRB that is not AAHRPP-accredited if such an arrangement is beneficial to Sharp, its investigators, and/or its research participants. The Principal Investigator or designee must request use of the non-accreddited IRB and the Director of Research may authorize reliance via *TEMPLATE LETTER: Authorization to Rely on Non-SHC IRB (HRP-573)* if the requested IRB meets the following criteria.

4.1.2.1 For minimal risk research, Sharp may:

4.1.2.1.1 Obtain an assurance from the non-accredited IRB that it will conduct its review consistent with the applicable ethical

standards and regulations, and that it will report any regulatory violations or investigations of the reviewing IRB by regulatory agencies, such as OHRP, the FDA, or regulatory agencies in other countries.

4.1.2.1.2 Request the reviewing IRB to attest that it has completed its own internal quality review process, such as use of AAHRPP's Evaluation Instrument for Accreditation to conduct a self-assessment or completion of the US FDA's self-evaluation checklist for IRBs (https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm512761.pdf), and/or the OHRP QA Self Assessment Tool (https://www.hhs.gov/ohrp/education-and-outreach/human-research-protection-program-fundamentals/ohrp-self-assessment-tool/index.html).

4.1.2.2 For greater than minimal research, Sharp may require additional oversight of an external IRB that is not AAHRPP-accredited, such as:

4.1.2.2.1 Reviewing relevant portions of the minutes of the external IRB meeting where the particular study is reviewed.

4.1.2.2.2 Reviewing external IRB records of the particular study being reviewed.

4.1.2.2.3 Evaluating relevant policies and procedures of the external IRB.

4.1.2.2.4 Confirming that external IRBs in countries outside the US have completed relevant certifications, when other credentialing is required by those countries.

4.1.2.2.5 Observing a portion of an external IRB meeting where the particular study is reviewed.

4.1.2.2.6 Including a Sharp IRB member or representative to serve as a consultant to the non-accredited IRB for review of a particular study.

4.1.2.2.7 Conducting not-for-cause monitoring of the external IRB.

4.1.2.3 In accordance with OHRP Guidance, when Sharp relies on the oversight of an external IRB of Record for review and approval of human research, there must be a formal written Reliance Agreement that clearly delineates the roles and responsibilities of each party.

4.2 Sharp IRB as the IRB of Record: The Sharp IRB may serve as the IRB of Record for an external institution, and will assume responsibility for review and approval of human research if such reliance benefits Sharp, its investigators, and/or its research participants.

4.2.1 Examples of when such reliance may be considered include research for which:

4.2.1.1 The Relying Organization has a conflicting interest.

4.2.1.2 Multi-site research in which the Sharp's and/or the Relying Organization's research team members are involved in minimal risk study activities only.

4.2.1.3 Phase II, III or IV multi-site, industry-initiated, industry-sponsored research.

4.2.1.4 Federally sponsored research for which a federally sponsored central IRB is duly constituted, or for federally sponsored research requiring the use of a central IRB.

4.2.1.5 Approval for Sharp IRB as the IRB of Record for an external Institution is already established.

4.2.2 In accordance with OHRP Guidance, when the Sharp IRB serves as the IRB of Record for review and approval of human research, there must be a formal written Reliance Agreement that clearly delineates the roles and responsibilities of each party.

4.2.3 Before choosing to act as an IRB of Record for external sites, the Sharp Director of Research, in conjunction with the IRB Chair, shall consider the following:

4.2.3.1 The number of external Relying Organization sites is reasonable in proportion to Sharp IRB resources to ensure appropriate oversight;

4.2.3.2 A Sharp investigator has a prominent role in the multi-site study;

4.2.3.3 Reliance on the Sharp IRB does not result in unreasonable liability to the Sharp IRB or the institution; and

4.2.3.4 The Relying Organization site(s) and investigators are in good standing with OHRP, FDA, and all applicable regulatory agencies.

4.3 There must be a working and communicative relationship between the IRB of Record and all Relying Organizations.

4.4 The Sharp Institutional Official (IO) or designee has the ultimate authority regarding whether or not to rely on an external IRB.

5 RESPONSIBILITIES

5.1 The **IRB of Record** is responsible for complying with all regulatory requirements as specified under the HHS regulations at 45 CFR Part 46 or the FDA regulations at 21 CFR 56, or to the extent specified in the reliance agreement.

5.1.1 For studies conducted or supported by any federal department or agency that has adopted the Federal Policy for the Protection of Human Subjects, known as the Common Rule, the IRB of Record will comply with the terms set forth in 45 CFR 46 (including Subparts A, B, C, and D), unless the research is otherwise exempt from these requirements, or the department or agency conducting or supporting the research has determined that the research shall be covered by a separate assurance.

5.1.2 For clinical investigations regulated by FDA under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act (21 U. S. 6. 355(i)), the IRB of Record will apply FDA human subjects regulations. These regulations include, but are not limited to, Protection of Human Subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), Investigational Drugs (21 CFR 312), Investigational Devices (21 CFR 812), and Application for FDA Approval to Market a New Drug (21 CFR 314).

5.1.3 For all other research involving human participants the IRB of Record will be guided by 45 CFR 46 when providing equivalent protections.

5.2 The roles and responsibilities of the relying organization and the IRB of Record will be outlined in HRP-409 – CHECKLIST – Reliance Roles and Responsibilities.

6 PROCEDURE

6.1 **Reliance Agreements:** Before any research activities may begin, a reliance agreement between the IRB of Record and the relying organization must be fully executed. The Sharp IRB Specialist works with the external IRB's Point of Contact to execute a Reliance Agreement.

6.1.1 This process begins when an SHC Principal Investigator or designee requests reliance on an external IRB (see 6.2) or when Sharp IRB is approached to act as the IRB of Record.

6.1.1.1 When Sharp IRB will serve as the IRB of Record for an external (non-Sharp) institution, the following must be submitted prior to execution of the reliance agreement:

6.1.1.1.1 Point of Contact for the Relying Organization; and

6.1.1.1.2 *FORM: Initial IRB Review Application (HRP-211_CIRB),* with all required supporting documents.

6.1.1.2 The Director of Research, in conjunction with the IRB Chair, will determine appropriateness of the reliance (see section 4: Policy Statement).

6.1.2 *TEMPLATE AGREEMENT – IRB Authorization / Reliance Agreement (HRP-574)* may be used.

6.1.3 *CHECKLIST –Reliance Roles and Responsbilities (HRP-409)* must be used to document the assigned roles and responsibilities of the relying organization and the IRB of Record.

6.1.4 The Reliance Agreement must be reviewed and signed by a Sharp IRB Co-chair. Authority to enter into (sign) a reliance agreement has been delegated to the IRB Co-chairs by the Institutional Official.

6.1.5 The Reliance Agreement must be kept on file at both Institutions (IRB of Record; Relying Organization) and provided to the Office for Human Research Protections (OHRP) upon request.

6.2 **Requesting Reliance with SHC IRB as the IRB of Record**

6.2.1 Lead Study Team at Sharp:

6.2.1.1 Coordinates communication between the Sharp IRB and the Relying Organization sites; and

6.2.1.2 Makes all submissions to the Sharp IRB on behalf of the Relying Organization sites.

6.2.2 Relying Organization sites that will be engaged in human subjects research:

6.2.2.1 Works in collaboration with the Sharp IRB and Lead Study Team to determine and complete HRP-409 – CHECKLIST – Reliance Roles and Responsibilities.

6.2.2.2 Provides all Relying Organization sites with details about the study, including the study-wide protocol and template consent document(s) so processes for local requirements can begin (coverage analysis, department approval, contract/budget, etc.) that will facilitate discussions with the Sharp IRB.

6.2.2.3 Collates information from Relying Organization site points of contact regarding potential local variations in study conduct, such as recruitment materials and process, consent process and language.

6.2.2.4 Follows all requirements of the Relying Organization with regard to ceded review, such as ensuring administrative requirements for documenting ceded review have been met before study activation occurs at a Relying Organization.

6.2.2.5 Provides the Relying Organization's Investigators with Sharp's IRB policies including, but not limited to, policies for reporting unanticipated problems, noncompliance, and subject complaints.

6.2.2.6 Provides a plan to coordinate the collection of reportable events from Relying Organizations.

6.2.2.7 Provides a plan for communicating with Relying Organizations across the lifetime of the study (i.e. regular conference calls, site initiation procedures and training materials).

6.2.3 Procedures during study implementation:

6.2.3.1.1 Notifies the Relying Organization's Investigators of all determinations by and communications from the Sharp IRB, including those for initial review, continuing review, amendment reviews, and reportable events.

6.2.3.1.2 Promptly reports to the Relying Organization's Investigators (or designees) any unanticipated problems involving risks to subjects or others, research-related subject injuries, or significant subject complaints from any participating sites that are related to or may affect subjects participating in the overall research.

6.2.3.1.3 In collaboration with the Sharp IRB, oversees the continuing review processes and requirements for the Relying Organization study teams, including lapse in approval for their site and any applicable corrective action plans.

6.2.3.1.4 Provides access, upon request, to study records for audit by the Sharp IRB and other regulatory or monitoring entities.

6.3 **Requesting Reliance on Non-Sharp IRB (Sharp as the Relying Organization)**

6.3.1 When the IRB of Record is not AAHRPP-accredited or its use is not mandated by the regulations (i.e. a single IRB) : A SHC Principal Investigator or designee requests the use of an external IRB of Record via email to research@sharp.com and provides applicable supporting documents and information.

6.3.2 The SHC IRB Specialist provides a study-specific *TEMPLATE: Authorization to Rely on Non-SHC IRB (HRP-573)* to Director of Research for signature after review of the protocol and informed consent document.

6.3.3 The SHC IRB Specialist issues the signed *TEMPLATE LETTER: Authorization to Rely on Non-SHC IRB (HRP-573)* to the Principal Investigator or designee.

6.3.4 When the IRB of Record is AAHRPP-accredited or the sIRB process is required by federal regulations, the Sharp Principal Investigator or designee may bypass 6.3.1 through 6.3.3.

6.3.5 The SHC Principal Investigator or designee must make a submission to IRBANA or research@sharp.com, including but not limited to:

6.3.5.1 *FORM: Initial Application for Reliance on Non-SHC IRB (HRP-211_CIRB)*

6.3.5.2 Current protocol

6.3.5.3 Draft Informed Consent Form, PHI Authorization, and CA Experimental Subjects Bill of Rights

6.3.5.4 External IRB Approval Letter for SHC Principal Investigator (when available)

6.3.5.5 *FORM: Principal Investigator's Attestation (HRP-219_CIRB)*

6.3.5.6 *FORM: Investigator Demographic Information (HRP-221)* for each research team member, unless already on file with the Sharp IRB Office

6.4 **Administrative Review of Study with Sharp as the Relying Organization**

6.4.1 When a study requesting use of an external IRB is submitted, the Sharp IRB Office will coordinate internal reviews by the following:

6.4.1.1 Contracts/Budget Specialist

6.4.1.2 Coverage Analyst

6.4.1.3 Administrative Review Committes (ARCs)

6.4.2 The Sharp IRB Specialists will revise the Informed Consent Form to include any local or institutional requirements, including but not limited to the following:

6.4.2.1 Verbiage consistent with the coverage analysis, contract, and/or budget

6.4.2.2 PHI authorization elements reqruied by HIPAA and California law

6.4.2.3 California Experimental Subject's Bill of Rights with signature line

6.4.3 The Sharp Principal Investigator or designee submits the final external IRB-approved Informed Consent Form to the Sharp IRB Office. The IRB Specialists confirm that all local and institutional requirements are met.

6.4.4 The IRB Office issues *TEMPLATE LETTER: Non-SHC IRB Reliance Permission to Proceed (HRP-558)* once all required materials have been received, and administrative reviews are complete.

6.5 **Reporting Requirements for Ongoing Research**

6.5.1 Relying Organizations report to the IRB of Record per the terms of:

6.5.1.1 The executed Reliance/Authorization Agreement; and

6.5.1.2 *CHECKLIST – Reliance Roles and Responsibilities (HRP-409) and;*

6.5.1.3 *TEMPLATE LETTER: Non-SHC IRB Reliance Permission to Proceed (HRP-558)* (when Sharp is the relying organization)

6.5.2 Sharp Principal Investigators relying on an external IRB are still required to report certain items to SHC IRB per the terms of 6.4.1.1 through 6.4.1.3. This includes but may not be limited to:

6.5.2.1 Any instance of possible non-compliance

6.5.2.2 Any unanticipated problems or unanticipated deaths

6.5.2.3 Any breach of confidentiality
6.5.2.4 Any addition or removal of local research team member(s)
6.5.2.5 Any addition or removal of Sharp-affiliated site(s)
6.5.2.6 Continuation approval letters from the IRB of Record
6.5.2.7 Enrollment numbers
6.5.2.8 Protocol status, including IRB of Record's acknowledgement of final closure reports

6.5.3 The Sharp IRB and the Sharp Center for Research reserve the right to revise the reporting requirements for ongoing research at anytime during the conduct of the research.

7 MATERIALS

7.1 POLICY: Human Research Protection Program (16500.99)
7.2 GUIDANCE: Definitions (HRP-001)
7.3 FORM: Initial IRB Review Application (HRP-211)
7.4 FORM: Initial Application for Reliance on Non-SHC IRB (HRP-211_CIRB)
7.5 FORM: Principal Investigator Attestation (HRP-219_CIRB)
7.6 CHECKLIST: Reliance Roles and Responsibilities (HRP-409)
7.7 TEMPLATE LETTER: Non-SHC IRB Reliance Permission to Proceed (HRP-558)
7.8 TEMPLATE LETTER: Authorization to Rely on Non-SHC IRB (HRP-573)
7.9 TEMPLATE AGREEMENT: IRB Authorization / Reliance Agreement (HRP-574)

8 REFERENCES

8.1 DHHS: 45 CFR 46.103(b)(2), 45 CFR 46.103(d), 45 CFR 46.109(d), 45 CFR 46.114
8.2 FDA: 21 CFR 56.109(e), 21 CFR 56.114, FDA Information Sheet: Non-Local IRB Review, and Information Sheet: Cooperative Research
8.3 ICH-GCP: 4.2.3
8.4 Experimental Subject's Bill of Rights (California Health & Safety Code 24172)
8.5 AAHRPP Tip Sheet 24: Single IRB Review
8.6 U.S. Department of Health and Human Services; Office for Human Research Protections: Institutional Review Board (IRB) Authorization Agreement
8.7 Final Common Rule (45 CFR 46.114(b)) [Effective date: 01/21/2019]
8.8 Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (81 FR 40325)
8.9 NIH Office of Science Policy_Implementation of the sIRB Policy https://osp.od.nih.gov/clinical-research/implementation-of-the-sirb-policy/ [Accessed 10/2/17]
8.10 Delegation of Institutional Official to IRB Chair Letter ["Dan Gross Delegation to IRB Chair for IRB Deferral 23Oct2013"]

This document is available via IRBANA, or by contacting research@sharp.com.