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 or 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, in which Sharp HealthCare is engaged; or

1.2.2 A principal investigator from an external institution 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, External IRB, or Single 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 (sIRB).

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, 21 CFR 50, and/or 21 CFR 56. In NIH sponsored research, the coordinating center/awardee is responsible for ensuring Reliance Agreements are in place, and that documentation is maintained. See *TEMPLATE AGREEMENT: IRB Authorization / Reliance Agreement (HRP-574).* Commonly used Reliance Agreements for organizations include:

3.3.1 Memoranda of Understanding (MOU)

3.3.2 IRB Authorization Agreements (IRBAA)

3.3.3 Master Reliance Agreement (MRA)

3.3.4 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)**: Effective January 20, 2020, 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 organizations in cases where Sharp's Institutional Official (or designee) believes doing so to be appropriate and efficient and/or if the use of a external IRB is required per 45 CFR 46.114.

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:

- The IRB has an active FWA on file with the OHRP.
- The Institution is AAHRPP-accredited or Sharp has determined the proposed IRB of Record meets Sharp standards per section 4.1.2.
- The external IRB is located within the U.S.
- 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.
- 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, and/or if the use of a central IRB is required per 45 CFR 46.114. *TEMPLATE LETTER: Authorization to Rely on Non-SHC IRB (HRP-573)* is not required when the use of a central IRB is required per 45 CFR 46.114. The Principal Investigator or designee must contact the Sharp IRB Office via research@sharp.com to request use of the non-accredited IRB. The Sharp Director of Research may authorize reliance via *TEMPLATE LETTER: Authorization to Rely on Non-SHC IRB (HRP-573)* if the proposed IRB of Record meets the following criteria.

4.1.2.1 For minimal risk research, Sharp may:

- 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.

- Request the proposed IRB of Record attests that it has completed its own internal quality review or self-assessment process, via completion of one or more of the following:
  - AAHRPP's Evaluation Instrument for Accreditation; and/or
  - U.S. FDA's Written Procedures Checklist; and/or
  - OHRP's QA Self Assessment Tool.

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

- Reviewing relevant portions of the minutes of the external IRB meeting where the particular study is reviewed.
- Reviewing external IRB records of the particular study being reviewed.
- Evaluating relevant policies and procedures of the external IRB.
- Confirming that external IRBs in countries outside the US have completed relevant certifications, when other credentialing is required by those countries.
- Observing a portion of an external IRB meeting where the particular study is reviewed.
- Including a Sharp IRB member or representative to serve as a consultant to the non-accredited IRB for review of a particular study.
- Conducting not-for-cause monitoring of the external IRB.

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 Before choosing to act as an IRB of Record for external institutions, the Sharp Director of Research, in conjunction with the IRB Chair (when appropriate), shall consider the following:

4.2.2.1 The number of external Relying Organizations is reasonable in proportion to Sharp IRB resources to ensure appropriate oversight;

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

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

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

4.3 The Sharp Institutional Official (IO) or designee has the ultimate authority regarding whether or not to rely on an external IRB or to serve as the IRB of Record for external institutions.

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 Relying Organization is responsible for complying with the requirements of the IRB of Record, any applicable institutional requirements, and any applicable regulations, including but not limited to 45 CFR 46, 21 CFR 50, 21 CFR 56, 21 CFR 312, 21 CFR 812, and/or 21 CFR 814.

5.3 In accordance with OHRP guidance, the roles and responsibilities of the relying organization and the IRB of Record must be clearly delineated in a formal written Reliance Agreement, or via *CHECKLIST: Task Responsibilities – IRB of Record and Relying Sites (HRP-409)*.

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

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 institution's Point of Contact to execute a Reliance Agreement.

6.1.1 *TEMPLATE AGREEMENT: IRB Authorization / Reliance Agreement (HRP-574),* or a reliance agreement template provided by the external institution may be used.

6.1.2 *CHECKLIST: Task Responsibilities – IRB of Record and Relying Sites (HRP-409)* may be used to document the assigned roles and responsibilities of the relying organization and the IRB of Record, when such roles and responsibilities are not outlined in the Reliance Agreement.

6.1.3 The Reliance Agreement must be reviewed and signed by a Sharp IRB Co-chair. Legal counsel should review the Reliance Agreement, when appropriate. Authority to enter into (sign) a reliance agreement has been delegated to the IRB Co-chairs by the Institutional Official.

6.1.4 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 When Sharp IRB will serve as the IRB of Record for an external institution, the following must be submitted to IRBANA/CREDIT or research@sharp.com prior to execution of the Reliance Agreement:

6.2.1.1 Point of Contact for the Relying Organization; and

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

6.2.2 Lead Study Team at Sharp:

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

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

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

6.2.3.1 Works in collaboration with the Sharp IRB and Lead Study Team to determine roles and responsibilities of the IRB of Record and the Relying Organization.

6.2.3.2 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.

6.2.3.3 Collates information from Relying Organization's point(s) of contact regarding potential local variations in study conduct, such as recruitment materials and process, consent process and language.

6.2.3.4 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.

6.2.3.5 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.

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

6.2.3.7 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).

6.2.4 Procedures during study implementation:

6.2.4.1 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.

6.2.4.2 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.

6.2.4.3 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.

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

6.3 Requesting Reliance on External IRB (Sharp as the Relying Organization)

6.3.1 The SHC Principal Investigator or designee must make a submission to IRBANA/CREDIT or research@sharp.com, including but not limited to the following items:

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

6.3.1.2 Current protocol

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

6.3.1.4 External IRB Approval Letter for SHC Principal Investigator and external IRB approved consent documents (when available)

6.3.1.5 Any HIPAA waivers granted by the external IRB or requests for HIPAA waivers from the Sharp IRB, if applicable

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

6.3.1.7 *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 confirm internal reviews by the following:
- 6.4.1.1 Contracts/Budget Specialist
- 6.4.1.2 Coverage Analyst
- 6.4.1.3 Administrative Review Committees (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 required by HIPAA and California law
- 6.4.2.3 California Experimental Subject's Bill of Rights with signature line
- 6.4.2.4 If study requires testing for certain diseases and conditions (e.g., Hepatitis, HIV), statement that California law requires health care providers and other specified persons to report to a designated agency (i.e., local and/or state health department).
- 6.4.2.5 The protections provided by Genetic Information Nondiscrimination Act (GINA) for research involving genetic testing or the collection of genetic information, as required by California law.

6.4.3 The Sharp IRB Specialists will notify the Principal Investigator or designee when submission to the external IRB may proceed.

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

6.4.5 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: Task Responsibilities – IRB of Record and Relying Sites (HRP-409)* (if applicable) and;
- 6.5.1.3 *TEMPLATE LETTER: Non-SHC IRB Reliance Permission to Proceed (HRP-558)* (when Sharp is the relying organization)
- 6.5.1.4 Applicable guidances and/or SOPs

6.5.2 Sharp Principal Investigators relying on an external IRB are required to report certain items to the Sharp IRB in addition to the reporting requirements of the IRB of Record. This includes but may not be limited to:
- 6.5.2.1 Financial conflict of interest management plans
- 6.5.2.2 Determinations of serious and/or continuing non-compliance by the IRB of Record
- 6.5.2.3 Determinations of unanticipated problems involving risks to subjects or others
- 6.5.2.4 Any breach of confidentiality
- 6.5.2.5 Any addition or removal of local research team member(s)
- 6.5.2.6 Any addition or removal of Sharp-affiliated site(s)
- 6.5.2.7 New consent forms and/or revisions to the Sharp IRB inserted language in previously approved consent forms (e.g. revisions to language referenced in 6.4.2)
- 6.5.2.8 Continuation approval letters from the IRB of Record, or, if continuing review is not required, confirmation of administrative oversight from the IRB of Record (if applicable)
- 6.5.2.9 *FORM: Administrative Status Update (HRP-216)* at the time that 6.5.2.8 is submitted with signed *FORM: Principal Investigator's Attestation (HRP-219_CIRB)* (if applicable)

6.5.2.10 Protocol status changes, including IRB of Record's acknowledgement of final closure reports

6.5.2.11 Within 5 business days, report with a completed *FORM: Promptly Reportable Information (HRP-214):*

- Audit, inspection, or inquiry by a federal agency (e.g., FDA Form 483)
- Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA Restrictions placed on Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections.
- Any litigation, arbitration, or settlements initiated related to human research protections.
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding the SHC HRPP.

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.

6.5.4 The Sharp Principal Investigator or designee is responsible for ensuring that any protocol amendments affecting internal review documents (see 6.4.1.1 – 6.4.1.3) are sent for review by the appropriate Sharp Center for Research staff member(s) per *FORM: Initial Application for Reliance on Non-SHC IRB (HRP-211_CIRB)*.

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: Promptly Reportable Information (HRP-214)
7.6 FORM: Principal Investigator Attestation (HRP-219)
7.7 FORM: Principal Investigator Attestation (HRP-219_CIRB)
7.8 FORM: Investigator Demographic Information (HRP-221)
7.9 CHECKLIST: Task Responsibilities – IRB of Record and Relying Sites (HRP-409)
7.10 TEMPLATE LETTER: Non-SHC IRB Reliance Permission to Proceed (HRP-558)
7.11 TEMPLATE LETTER: Authorization to Rely on Non-SHC IRB (HRP-573)
7.12 TEMPLATE AGREEMENT: IRB Authorization / Reliance Agreement (HRP-574)

8 REFERENCES

8.1 DHHS: 45 CFR 46
8.2 Application for FDA Approval to Market a New Drug (21 CFR 314).
8.3 FDA: 21 CFR 50, 21 CFR 56, 21 CFR 312, 21 CFR 812, 21 CFR 814
8.4 FDA: Information Sheet - Non-Local IRB Review
8.5 Experimental Subject's Bill of Rights (California Health & Safety Code 24172)
8.6 AAHRPP Tip Sheet 24: Single IRB or EC Review
8.7 U.S. Department of Health and Human Services Office for Human Research Protections: Institutional Review Board (IRB) Authorization Agreement
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
8.10 Delegation of Institutional Official to IRB Chair Letter ["Amy Adome Delegation to IRB Chair for IRB Deferral 25Jun2021"]

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