TITLE: External Institutional Review Boards & Reliance Agreements for Multi-Site Research		POLICY/PROCEDURE NUMBER: IRB 10	
AUTHOR:	Jana L. Lacera, RN, MSA, CDM	APPLICABLE TO:	CHS CIRB
SUPERSEDES:	Facilitated Review IRB 4.1 Institutional Authorization Agreement (IAA): Collaborations with Non-Local institutions and Investigators IRB 10	ISSUED BY:	CHS CIRB
DATE ORIGINATED:	6/8/2007	DATE EFFECTIVE:	7/2021
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X	CFNI Munster, Indiana	X	Community Hospital Munster, Indiana	X	St. Catherine Hospital East Chicago, Indiana	X	St. Mary Medical Center Hobart, Indiana

POLICY STATEMENT/PURPOSE:

The Office of Human Research Protections (OHRP) and the Federal Food and Drug Authority (FDA) permit the option of an IRB relying upon another IRB for research oversight. When relying on another IRB or when serving as the Reviewing IRB for an outside organization, a formal relationship must be established between the CHS CIRB and the outside organization through a Reliance Agreement or an IRB Authorization Agreement (IAA).

Following careful consideration, the CHS CIRB will not assume the role of a Reviewing IRB since it does not have the considerable resources or the infrastructure necessary to support the responsibilities of a Reviewing IRB.

A fully executed Reliance Agreement must be in place and the Reviewing IRB must approve Community Healthcare System's (CHS) involvement in the research prior to engaging in the human subject research. Research and/or clinical investigation involving human subjects cannot begin until the CH investigator receives a letter from the CHS CIRB acknowledging that there is a signed Reliance Agreement.

Reliance Agreement or Institutional Authorization Agreement (IAA): A formal, written document indicating a collaborative arrangement between institutions that allows one or more institutions to cede human subjects research oversight to another IRB. A Reliance Agreement describes the responsibilities of the Relying IRB, institution and researcher as well as the responsibilities of the Reviewing IRB and its institution. They also meet the requirements of the NIH Single IRB policy for multi-center studies. Reliance Agreements may be for a specific study, or for specific classes or categories of research.

The CHS CIRB office will evaluate all requests to cede to an External IRB to determine if a Reliance Agreement is appropriate. The CHS Institutional Official retains final authority to determine whether the CHS CIRB will enter into an agreement. The PI is encouraged to contact the CHS CIRB office if they are unsure if a Reliance Agreement is applicable.

The CHS CIRB may choose to review:

- The research in its entirety, or
- Only those components of the research in which CHS is engaged,

Each Reliance Agreement will be considered situation and context-dependent. Considerations of whether to enter into a Reliance Agreement may include:

- Minimization of duplicate effort;
- Engagement of the institutions;

- Lack of local expertise or involvement of certain types of research such as xenotransplantation, embryonic stem cell, phase I clinical trials;
- The location of the research interaction, intervention or subject recruitment;
- Whether there is a prime award for a contract, grant, or cooperative agreement,
- Whether there is a subcontract;
- Whether the External IRB has an equivalent human research protections program in place;
- Discussions between IRB administrators from each institution to assure an efficient communication process;
- Consultation with Institutional Officials.

DEFINITIONS:

Engaged in Research: An institution becomes "engaged" in human subjects' research when its employees or agents (all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility): [45 CFR §46.102(d),(f)]

1. intervene or interact with living individuals for research purposes;
2. obtain individually identifiable private information for research purposes,
3. obtain informed consent from human subjects; or
4. receive HHS funds even when all activities are carried out at another institution or by employees of another institution.

The Director of the IRB or designee will make the final determination regarding engagement in human subject's research.

The CHS CIRB does not enter into a Reliance Agreement unless the CHS components and/or its affiliates, as covered by its FWA, are engaged in the research.

Federalwide Assurance (FWA): A formal, written, binding attestation in which an institution assures the Department of Health and Human Services (HHS) that it will comply with applicable regulations governing research with human subjects at 45 CFR § 46.

External IRB: The reviewing IRB for a CHS or CHS affiliate site that is not the CHS CIRB, but rather another institutional IRB or a commercial IRB. A Reliance Agreement must be in place between the External IRB and the CHS CIRB to establish this relationship

Local Research Context: A Relying IRB is required to identify, interpret and communicate to the Reviewing IRB the requirements of any applicable state or local laws, regulations, institutional policies, standards, or other local factors, including local ancillary reviews and restrictions on use and disclosure of PHI. This includes federal laws and regulations other than human subjects protection regulations that are relevant to a research study for which review is being ceded under a Reliance Agreement.

Multisite Research: A multisite project is one that uses the same protocol to conduct non-exempt human subjects research at more than one site. All multisite research raises questions about whether sites are engaged in research and if so, how IRB oversight will be provided.

Relying IRB: A relying IRB is relying on or has ceded IRB review to another IRB (IRB of record or Reviewing IRB) to provide oversight for a specific study or set of studies.

Reviewing IRB (IRB of Record, single IRB, Central IRB): the IRB that accepts responsibility for IRB review of other sites that cede authority to it, taking the Relying sites' local context into consideration. In reviewing multisite research protocols, the Reviewing IRB may serve as a Privacy Board for use or disclosure of protected health information (PHI) for research purposes.

Single IRB Requirement in the Common Rule: Based on updates to the Common Rule, use of a Single IRB for oversight of non-exempt, federally-funded cooperative research projects located in the U.S. are required as of January 20, 2020. The list of funding agencies this rule is applicable to can be found at https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html

Single IRB (sIRB) policy for Multi-Site Research (NIH): NIH expects that all sites participating in multi-site studies, which involve non-exempt human subjects research funded by the NIH, will use a single IRB (sIRB) to conduct the ethical review required for the protection of human subjects. This policy applies to the domestic sites of NIH-funded multi-site studies where each site will conduct the same protocol involving non-exempt human subjects research.

SMART IRB: is not an actual IRB. It is an NIH-funded initiative that facilitates the federally mandated Single IRB requirement. It developed a Master IRB Reliance Agreement that encourages collaboration and consistency across IRBs, and offers flexible resources and tools in support of Single IRB review for IRBs and researchers.

External IRB Reliance Agreements (CHS CIRB Relying on an External IRB)

1. Master Agreements (Not Study Specific)

Master agreements allow signatory institutions to cede IRB review to another signatory institution. Signatory institutions are those that have signed onto the agreement. These agreements are not study-specific. Administrative review by the CHS CIRB is required to document the use of the agreement for each study. The CHS CIRB has entered into the following master agreements:

- SMART IRB
- National Cancer Institute (NCI) Adult and Pediatric Central IRBs for NCI research involving adult and child subjects
- Carle Cancer Center NCORP

2. Study-Specific Reliance Agreements (CHS CIRB Relying on an External IRB)

On a study-specific, case-by-case basis, the CHS CIRB may also chose to enter into a Reliance Agreement to rely on other commercial or institutional External IRBs. Investigators must indicate on the Facilitated Protocol Submission Form a request to enter into a Reliance Agreement.

Administrative review of the request should evaluate the following factors when considering a request to rely upon an External IRB:

1. The AAHRPP accreditation status of the proposed IRB;
2. The compliance history of the IRB (e.g., outcomes of prior audits or inspections, corrective actions);
3. Prior experience with the IRB;
4. The federal IRB registration and organizational FWA, as applicable;
5. The expertise and experience of the proposed IRB (e.g., with reviewing the type of research, research procedures, and subject population(s));
6. The research activities that will be conducted at or by CHS;
7. The risks and complexities of the proposed research;
8. The proposed reliance terms and procedures including the procedures for collaborative management of matters such as conflicts of interest, noncompliance, unanticipated problems and federal reports;
9. The plan for review and allowance of the incorporation of site-specific consent language; and
10. The plan for incorporation of other relevant local requirements or context information in the review process.

When reliance on a non-AAHRPP accredited IRB is proposed, the evaluation may also take into consideration one or more of the following based upon the risks of the research and the research activities that CHS will be involved in.

1. When the research is minimal risk (or the activities that CHS is involved with are minimal risk), a statement of assurance from the proposed IRB that its review will be consistent with applicable ethical and regulatory standards, and this will report any regulatory investigation, citation, or actions taken regarding the reviewing IRB, and , when applicable, the organization's FWA;

2. An attestation about, or summary of, any quality assessment of the reviewing IRB such as evaluation by an external consultant or internal evaluation of compliance using the FDA's self-evaluation checklist or AAHRPP's self-evaluation instrument;
3. The willingness of the External IRB to accommodate requests for relevant minutes and other records of the proposed study and/or to copy the CHS CIRB office on correspondence such as determination letters and notices of suspensions or terminations of IRB approval;
4. The willingness of the External IRB to accommodate a request for someone from the relying institution to serve as a consultant to the IRB or to observe the review of the proposed study; and/or
5. An assessment of the External IRB's policies and procedures.

PROCEDURE: Submission Process when the CHS CIRB will rely on an External IRB

Investigator Responsibilities

1. Prior to submission:
   - The Principal Investigator, the co-investigators and the clinical research staff must complete the CHS CIRB required CITI modules, Affirmation Statement and submit the required documents to their respective research department.
   - Complete the Budget Worksheet
   - Obtain approval from the appropriate research committee
   - Obtain Administrative Approval to conduct the research
2. The Principle Investigator/Clinical Coordinator prepares copies of the documentation to be submitted to the CHS CIRB. Documents to include:
   - Facilitated Protocol Submission Form; Review for Local Context
   - Most recent version of study protocol with appendices
   - Most recent External IRB initial or continuing review approval letter with the expiration date
   - One copy of the informed consent form(s) and HIPAA addendum (if applicable)
3. An investigator must submit a "Financial Interest Disclosure Addendum" if they have identified a financial conflict of interest for the study.
4. The investigators must present evidence of having obtained or are in the process of obtaining the necessary privileges to perform all of the procedures outlined in the study from the Credential's Committee.
5. **The Principal Investigator will continue to report to the CHS CIRB on the "External IRB Requests Modifications & Event Reporting" form over the course of the study:**
   - Key Personnel Changes
     - Addition of Key Personnel
     - Removal of Key Personnel
     - Change of Principal Investigator
   - Report of actions taken by a government oversight office submitted to either the External IRB or the Local Site
     - OHRP Determination Letter
     - FDA Warning Letter
     - FDA 483 Inspection Reports with Official action
     - FDA restrictions placed on the IRB or investigators
     - Compliance Actions taken under non-US authorities related to human research protections
   - Substantial changes to the study that may significantly affect the health and safety of the local research subjects
     - Study suspended
     - New risk information that would require re-consent of the subjects
     - Changes to research related injury language
     - Change to research related costs for the subject
   - Adverse Events
   - Protocol Deviations
   - Study closure with the External IRB
   - Principal Investigator Attestation

CHS CIRB Office Responsibilities

1. New protocols received by the department will be entered into the database and assigned a new protocol number.
2. All documentation received from the local PI will be retained in the CHS CIRB office,
3. An administrative review of the submission will be completed by the CHS CIRB office. Investigators will be contacted to provide clarification and/or additional documentation if necessary.
4. The submission will be forwarded to an independent reviewer who possesses the necessary expertise to competently assess the merit of the protocol within the local context. Additional reviewers may be assigned at the discretion of the CHS CIRB Chair. The reviewer(s) will complete their task within one (1) week and return the documents to the CHS CIRB office with their recommendation regarding the protocol.
   Options for recommendation:
   - Accepts the External IRB review of the protocol and approves the protocol for initiation within the local context. The External IRB then becomes the IRB of record. The CHS CIRB then becomes the Relying IRB. This information will be added to the agenda of the next convened meeting under "Facilitated Review" for the information of the CHS CIRB.
   - Does not accept the External IRB review of the protocol. The CHS CIRB office will request any further documentation if necessary. The entire protocol submission will then be placed on the agenda for Full Review.
5. The investigator will be notified in writing of the final determination of the CHS CIRB;
6. The CHS CIRB will only review the following items over the course of the study:
   - 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 IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections.
   - Substantial changes to the study that may significantly impact the health and safety of the local research subjects, i.e., study suspended, Adverse Events that are "definitely" or "probably" directly attributed to their participation in the study.
   - Any changes to the protocol or the consent that would require re-consent of the subject, i.e., new risk information that may affect their decision to continue participation.
   - Protocol deviations from the original design of the study.
   - Changes in study specific research personnel.
   - When the study is complete.
7. The CHS CIRB will request an Annual Status Update to maintain communication between the CHS CIRB and the Research Department.

CROSS REFERENCE(S):
Reliance Agreement (Form)
Institutional Review Board (IRB) Reliance Agreement (Form)
Reliance Agreement and Delineation of Responsibilities Addendum I
IRB 10.1: Individual Investigator Agreement
Individual Investigator Agreement Form

REFERENCE(S):
HHS: 45 CFR §46.103, §46.114
HHS: Extending an FWA to Cover Collaborating Investigators (January 31, 2005)
FDA: 21 CFR § 56.109, §56.114
FDA Information Sheets – Cooperative Research
FDA Information Sheets – Non-Local IRB Review
NIH: Policy on the Use of a Single Institutional Review Board for Multisite Research (January 25, 2018)

ACCEPTED BY:

Elizabeth Yee
Vice President, Clinical Ancillary Services

Andrej Zajac, M.D.
Chair, CHS CIRB

Jana L. Lacera, RN, MSA, CDM
Human Protections Administrator, CHS CIRB
Director, IRB/Bio-Ethics

DATE(S) REVISED: 6/2021

REVIEWED BY: CHS CIRB: 4/2020, 7/2021

Date	Initials
4/2020	JL
6/2021	JL