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1. Purpose

This Standard Operating Procedure (SOP) is to document policies and procedures for Institutional Review Board (IRB) review of research conducted in more than one member of the Health Care Systems Research Network (HCSRN), formerly known as the HMO Research Network. The HCSRN member institutions are:

- Baylor Scott and White Health System
- Catholic Health Initiative
- Essentia Health
- Fallon Community Health Plan / Reliant Medical Group
- Geisinger Health System
- Group Health Cooperative
- Harvard Pilgrim Health Care
- HealthPartners
- Henry Ford Health System / Health Alliance Plan
- Kaiser Permanente Colorado
- Kaiser Permanente Georgia
- Kaiser Permanente Hawaii
- Kaiser Permanente Northern California
- Kaiser Permanente Northwest
- Kaiser Permanente Southern California
- Maccabi Healthcare Services
- Marshfield Clinic Health System /Security Health Plan
-
- Mid-Atlantic Permanente Medical Group
- Palo Alto Medical Foundation

The objectives of this SOP are to:

- 1.1 Reduce the burden on investigators from one HCSRN member who propose to conduct research in multiple HCSRN member institutions, and
- 1.2 Protect the authority of each HCSRN member IRB to choose to review and maintain oversight of research being conducted in its institution or to cede review authority to another HCSRN member IRB, consistent with federal regulation (DHHS 45 CFR 46), the HCSRN member's policies and procedures, and its Federal-wide Assurance (FWA).
- 1.3 For purposes of this SOP only, each Kaiser Permanente region that is a member of the HCSRN shall be considered a separate institution.

2. How the Multi-Site Process Works – In Brief

- 2.1 The Lead PI and collaborating (“Local”) PIs agree to use the process and check with relevant IRB contacts about any particular factors to address. The Lead PI prepares the IRB application used at his or her site. The application describes procedures at all involved sites. The Lead PI also prepares the HCSRN SOP cover sheet.
- 2.2 The Lead IRB receives the completed application from the Lead PI and reviews it. If the IRB approves the application and agrees to serve as IRB of record for the Ceding IRB(s), the Lead IRB prepares approval documentation accordingly and sends it to the Lead PI.
- 2.3 The Local IRB receives a copy of the completed application from the Local PI. The Local PI may need to submit additional site-specific materials. The Local IRB reviews the materials and, if it agrees to cede, prepares relevant documentation (typically including an IRB Authorization Agreement) and sends it to the Lead IRB.
- 2.4 The Lead IRB becomes the IRB of Record for the study and is responsible for continuing review as well as review of subsequent amendments and any adverse events and unanticipated problems.
- 2.5 The Ceding institution is responsible for review of local Significant Adverse Events and oversight of local conduct of the study; institutional procedures often mean this is coordinated through the Ceding IRB.

3. Scope

This SOP covers all multi-site data-only, epidemiologic, and health services research (for which participant informed consent and HIPAA authorization may or may not be required), performed in the Health Care Systems Research Network. This SOP **excludes** clinical trials.

A clinical trial is a prospective biomedical research study of human participants involving a licensed or investigational drug, device, or biologic that is designed to answer specific questions about biomedical or device interventions (e.g., treatments, devices, drugs, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or device interventions are safe and effective.

4. Definitions

The following definitions (indicated by ✓ in Appendix A, Definitions) and descriptions of responsibilities are essential to understanding this SOP.

- Ceding IRB
- Lead IRB
- Lead Principal Investigator (PI)
- Local Principal Investigator (PI)
- Reviewing IRB

Please see Appendix A for all pertinent definitions.

5. Responsibilities

5.1 Lead IRB

5.1.1. The **Lead IRB** is the designated IRB to which other HCSRN member IRBs may cede. The Lead IRB's responsibilities include:

- a. Communicating with the Lead PI;
- b. Accepting responsibility for review and oversight of the HCSRN multi-site study on behalf of any HCSRN IRB that has ceded review authority to the Lead IRB;
- c. As part of oversight responsibilities; making determinations regarding need for or waivers of authorization under the HIPAA Privacy Rule and
- d. Providing initial study approval documentation to ceding IRB(s).

5.2 Lead PI

5.2.1. The **Lead PI** is generally the PI who develops the protocol, or otherwise is designated as Lead PI for an HCSRN multi-site study. The Lead PI's responsibilities include:

- a. Overseeing the study being conducted in the HCSRN;
- b. Recruiting collaborating HCSRN PIs who will conduct the study;

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- c. Preparing the HCSRN multi-site Research Application Cover Sheet (Cover Sheet) and IRB application and coordinating their submission to the appropriate HCSRN IRBs;
- d. Communicating with the Lead IRB;
- e. Having the primary role in communicating with each Local PI, including forwarding all correspondence from the Lead IRB to each Local PI; and
- f. In conjunction with the Local PIs, communicating with reviewing IRBs to provide them study information.

5.3 Local PI

5.3.1. A **Local PI** is the HCSRN investigator for a site other than the lead site. Local PI responsibilities include:

- a. Working with the Lead PI to ensure that local procedures are described in sufficient detail in the IRB application – e.g., specific scientific review steps or research details such as personnel involved and their qualifications, dataset(s) being developed at the site, etc., to provide the Lead IRB with a full understanding of procedures and activities at the local site;
- b. Performing and/or supervising all research activities relating to the study conducted in his or her institution;
- c. Assuring that these activities are conducted in compliance with the IRB-approved protocol, institutional policies, federal and state regulations, and the FWA;
- d. Obtaining all institutional approvals including leadership, research review committee, and facility department approvals, etc., as required by the institution;
- e. Submitting the Cover Sheet, IRB application, and institution-specific materials to the institution's IRB and other institution-mandated committees;
- f. Communicating with his or her institution's IRB, as appropriate; and
- g. Communicating with the Lead PI, including forwarding any correspondence from his or her institution's IRB to the Lead PI.

5.4 Reviewing IRB

5.4.1. A **Reviewing IRB** is any HCSRN IRB, including the Lead IRB, which reviews the multi-site study (i.e., which has decided **not** to cede review authority to the Lead IRB), and, therefore, will concurrently review the study.

Responsibilities include:

- a. Reviewing, approving, and overseeing the study in accordance with applicable federal and state regulations, institutional policies, and its FWA;
- b. Communicating with the Local PI; and
- c. Obtaining information from the Local PI and the Lead PI, as appropriate.

5.5 Ceding IRB

5.5.1. A **Ceding IRB** is any HCSRN IRB that decides to cede review authority and oversight of the multi-site study to the Lead IRB. Responsibilities include:

- a. Reviewing the HCSRN multi-site research application and determining whether the IRB will retain or cede review authority; including assuring that local requirements have been met (e.g., human subjects training, conflict of interest disclosure) and specifying any conditions for ceding, such as insertion of site-specific consent language requirements;
- b. Communicating directly with the Lead IRB about the ceding decision, including initiation of the required IRB Authorization Agreement;
- c. Communicating with the Local PI, including the decision to cede;
- d. Communicating any local requirements for facilitated review to local PIs, including institution-specific information that should be detailed in the initial application, e.g. personnel involved and their qualifications, dataset(s) being developed at the site, etc., state regulations that make certain studies ineligible for ceding, and any post-approval documentation requirement (e.g., notification of study closure); and

- e. (Optional) If specified by Ceding Institution Procedures, reviewing Unanticipated Problems and protocol violations that occur at the ceding IRB's institution.

5.6 Ceding Institution

5.6.1. The **Ceding Institution** is where the Local PI is affiliated. Responsibilities include:

- a. Ensuring the safe and appropriate performance of the research at its institution. This includes, but is not limited to, administrative and business review, monitoring protocol compliance, managing any major unanticipated problems or protocol violations, managing any serious adverse events occurring at the institution, ensuring qualifications of research staff, their training and lack of conflicts of interest, and providing a mechanism by which complaints about the research can be made by local study participants or others;
- b. Maintaining mechanisms for conduct of any non-IRB activities, such as scientific review and HIPAA Privacy Rule responsibilities (e.g., data use agreements, business associate agreements, disclosure accounting. (Note that decisions related to a waiver of authorization are the authority of the Lead IRB unless otherwise agreed to.);
- c. Maintaining mechanisms for notifying the Privacy Office of any breaches and helping to meet institutional obligations under the HITECH (*Health Information Technology for Economic and Clinical Health*) Act, enacted as part of the American Recovery and Reinvestment Act of 2009, and the HIPAA Privacy and Security Rule;
- d. Maintaining an OHRP-approved Assurance for human subjects research; an OHRP IRB registration number; and compliance with state, local, or institutional requirements related to the protection of human subjects; and
- e. The management of Unanticipated Problems (UPs, e.g., confidentiality breaches) that occur at a ceding institution will be handled by that institution. The ceding institution will keep the Lead IRB fully informed of the actions it takes. Likewise, dealing with allegations of research misconduct at a ceding institution will be the responsibility of that institution, and the ceding institution will keep the Lead IRB fully informed. The Lead IRB will also inform the ceding

institution's IRB of any UPs at the ceding institution that come directly to its attention.

6. Policies

- 6.1 In every case, investigators are required to comply with their institution's policies, procedures, decisions, and conditions, as applicable to the study.
- 6.2 HCSRN PIs or representatives will not attempt to influence any HCSRN IRB about whether to cede review authority to another HCSRN IRB.
- 6.3 There will be a Lead PI for each proposed study.
- 6.4 A Local PI must be named for each HCSRN member institution participating in the study that is not the Lead institution.
- 6.5 The Lead and Local PIs should submit the HCSRN Multi-Site research application to all the participating HCSRN IRBs for review in close proximity to each other, with the Lead PI submitting first.¹
- 6.6 The Lead IRB is typically the IRB of the institution of the Lead PI. If the Lead PI is not affiliated with a particular institution (e.g., as in the case of some Kaiser Permanente investigators), the Lead IRB is typically the IRB of the institution contributing the greatest number of research records.
- 6.7 Each Local IRB must decide whether to cede authority to the Lead IRB for the study, for the research that is being conducted in its institution.
 - 6.7.1. Other institutional HIPAA Privacy Rule contract responsibilities (e.g., data use agreements, business associate agreements, disclosure accounting) remain the responsibility of each HCSRN member institution per its usual procedures.
 - 6.7.2. When a Local IRB cedes authority to the Lead IRB, it is assuring the Lead IRB that investigators and study staff meet the ceding institution's initial and on-going educational and training requirements as well as the institution's Conflict of Interest requirements.

¹ At institutions that employ electronic IRB submission systems, the PI should coordinate with the IRB Administrator what is required for the submission of an HCSRN study. If the Lead institution employs an electronic IRB submission system, it is likely that the Lead PI will have to supply a paper/PDF/soft copy to local investigators for submission to their respective IRBs.

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- 6.8 When more than one HCSRN IRB reviews multi-site research (i.e., one or more IRBs decide not to cede review to the Lead IRB), the IRBs are required to take reasonable steps necessary to minimize differences in decisions about, and requirements for, conducting the research, including documents associated with the research.
- 6.9 Each IRB must comply with applicable federal and state regulations, its institutional policies and FWA, and its own policies and procedures.
- 6.10 The Lead IRB may approve a multi-site study using an expedited review procedure, if the study meets federal regulatory criteria.
- 6.11 After ceding IRB review to another institution's IRB, the ceding institution remains responsible for ensuring compliance with the Lead IRB's determinations and with the terms of its own FWA.

7. Procedures

7.1 Designation of Lead IRB and Local PIs

- 7.1.1. The Lead PI will request that one HCSRN member institution's IRB (generally, his or her own) be designated as the Lead IRB.
 - a. The Lead PI will contact the Administrator or the Chair of the proposed Lead IRB to confirm this role.
 - b. If the proposed Lead IRB declines the role, the Lead PI may request that another HCSRN member IRB be the Lead IRB.
- 7.1.2. The Lead PI will appoint a collaborating individual from each HCSRN member institution that will be involved in the proposed research. This individual will function as the Local PI for that institution.
- 7.1.3. The Lead and Local PI's advance notice to their respective IRBs that an HCSRN Multi-site research application is forthcoming may minimize subsequent delays.

7.2 HCSRN Multi-Site Research Application

- 7.2.1. The Lead PI, in collaboration with all Local PIs, will complete an HCSRN Multi-Site Research Application Cover Sheet (Appendix B) and the Lead institution's IRB application form. The HCSRN multi-site research application consists of the Cover Sheet (Appendix B) plus the Lead IRB's application form, plus any institution-specific information requested by a Local IRB.
 - a. The Lead PI will indicate on the HCSRN Multi-Site Research Application Cover Sheet which institutions propose to participate in the research and the designation of the Lead IRB.
 - b. All HCSRN IRBs reviewing multi-site research will accept the Cover Sheet (Appendix B) and the Lead IRB's institutional application form.
 - c. The IRB application form should describe procedures at all relevant HCSRN sites in sufficient detail that the Lead IRB understands what procedures it is being asked to review, including compliance with state and local laws and any requested waivers of consent/authorization. The Local PI is advised to consult with the Local IRB about any specific requirements to incorporate at this point, including HIPAA authorizations, so as to limit the likelihood of being asked to supply additional information later.
- 7.2.2. The Lead IRB should be the first to receive the HCSRN multi-site research application, or roughly at the same time as the other HCSRN IRBs.
- 7.2.3. The Lead PI will send a copy of the HCSRN Multi-Site Research Application Cover Sheet and Lead IRB application to each Local PI for his or her review and approval.
- 7.2.4. Each Local PI will review and be named on the Lead IRB application, which indicates his or her support for the research, and willingness to serve as PI for the Local institution.
- 7.2.5. Each Local PI will obtain other institution-required approvals (e.g., research review committee) necessary to conduct the study at his or her institution.
- 7.2.6. The Local PI will submit a package to the local IRB which includes a) the Cover Sheet and signed HCSRN Lead IRB application and b) any additional materials required by the local IRB/institution. Such materials

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could include, for example, a listing of local personnel and their qualifications, conflict of interest statements, a description of the work to be undertaken at the site, the site's data dictionary, questionnaire, or other materials, and site specific consent form. The Local PI is also responsible for submitting these and other materials to other research review committees, as required.

- 7.2.7. When an HCSRN IRB cedes authority to the Lead IRB, the Lead IRB will also make necessary HIPAA authorization determinations² (i.e., approve authorization forms and waiver or alteration of authorization), unless specified by the ceding IRB.
- 7.2.8. If the Lead PI has already received approval of the study from the Lead IRB, a copy of that IRB's determination letter should be submitted with the multi-site research application to the IRB of each HCSRN member to which the application is being submitted.

7.3 Initial HCSRN Multi-Site IRB Review

- 7.3.1. Each institution's IRB will review the Cover Sheet and HCSRN Lead IRB application and determine whether to cede review authority to the Lead IRB or to review the research.
 - a. If review authority is ceded, the ceding IRB will document its decision as per its standard practice.
 - b. When IRBs cede review to the Lead IRB, Privacy Rule determinations are also ceded unless otherwise decided.
- 7.3.2. Each Local IRB will notify the Lead IRB and its PI in writing when it decides whether to cede review authority to the Lead IRB.

7.4 Concurrent Review by the Lead and Local IRBs

- 7.4.1. The Lead PI will submit continuing review reports, study modifications, and adverse events reports to the Lead IRB.
- 7.4.2. At institutions where the Local IRB **did not** cede to the Lead IRB, the Lead PI will assist each Local PI to submit the items to the IRB at his or her institution for review.

² Per 65 *Federal Register* 82692, December 28, 2000, a covered entity's responsibility is only to "obtain the documentation that one IRB or [P]rivacy [B]oard has approved the alteration or waiver of Authorization."

7.5 Reconciling Multiple IRBs' Different Decisions

- 7.5.1. When more than one IRB reviews the study and there are differences in the decisions made by the IRBs, the Chairs of the IRBs, or their designees, will attempt to resolve the differences in a reasonable timeframe.

7.6 Ceding Review Authority to the Lead IRB after Initial Review

- 7.6.1. After initial review, an IRB may still decide to cede review authority to the Lead IRB.
- a. The Local PI or Lead PI should contact the Lead IRB Administrator or Chair to confirm the Lead IRB's willingness to accept review authority.
 - b. The Local PI or Lead PI may make this request at the time of continuing review, or at other times, if the Local PI or Lead PI determines this is necessary.
- 7.6.2. If an IRB **does not** agree to cede after considering the request, the IRB will notify its PI of its decision.
- 7.6.3. If the Local IRB **does** agree to cede after considering the request, the IRB will notify its Local PI **and** the Lead IRB of its decision.
- a. The Local PI or IRB administrator will notify the Lead PI of the Local IRB's decision to cede.
 - b. The Lead PI will submit a protocol modification request to the Lead IRB specifying which HCSRN institution has ceded, including the name and contact information of the Local PI. The modification request should also include any new research activities that are specific to the Local PI.
 - c. If the Lead IRB approves the protocol modification including accepting review authority of the other IRB, the Lead IRB will communicate its decision to the Lead PI.
 - d. The Ceding and Lead IRB administrators will determine which records, if any, need to be transferred to the Lead IRB.

- e. The Lead IRB will provide notification to the IRB(s) that ceded review authority when the research is complete.

7.6.4. To add a new site to an existing protocol for research that has previously been reviewed and approved, the Lead PI will submit a modification to the Lead IRB and the Local PI will submit the Cover sheet and signed HCSRN Lead IRB application and related documents to his or her institution's IRB and other research review committees, as required.

7.7 Ongoing Review of Ceded Multi-site Research

7.7.1. The lead IRB is responsible for review of **all relevant information** at the lead and ceding institutions until the research ends. This includes amendments/modifications, continuing review, adverse events, etc. The Lead IRB will notify a ceding IRB of any amendments/modifications that would substantively change the nature of the research and potentially the decision to cede review to the Lead IRB. Substantive modifications include but are not limited to any changes to the protocol which increase the risk to participants or others, modifications for use and/or disclosure of new data, and adding new study sites or collaborating institutions where data will be shared. All submissions should be reviewed in accordance with the Lead IRB's SOPs.

7.8 Terminating Ceding Authority

7.8.1. If the Lead or Local IRB wishes to end the ceding agreement, the IRB administrators should coordinate to ensure a transition of oversight that protects human subjects: a) the Local IRB initiates steps for future oversight at the Local institution, and b) the Lead IRB file is updated to indicate the Lead IRB is no longer responsible for the ceding institution (this could include voiding of the IRB Authorization Agreement).

8. Document History

Version Number and Approval Date	Version & implementation instructions distributed on:	Implement by:
1 [Approved by the HCSRN Governing Board – June 12, 2008]	June 13, 2008	September 1, 2008
2 [Approved by the HCSRN Governing Board – August 19, 2010]	September 24, 2010	December 15, 2010
3 [Approved by the HCSRN Governing Board – July 21, 2011]	TBD	TBD

9. Document Approval

The designated HCSRN Member Institutional Official reviewed and approved this SOP. Approval signatures and dates are on file with the HCSRN Member Institution's IRB Administrator.

10. Appendices

Appendix A: Definitions

Appendix B: HCSRN Multi-site Research Application Cover Sheet

Appendix C: Process Flowchart

Appendix D: Frequently Asked Questions (and Answers)

DEFINITIONS

Alteration of Authorization: An IRB-approved modification of a procedure or form that enables research participants to authorize use or disclosure of their protected health information (PHI) for a particular study. Such alterations must be consistent with the HIPAA Privacy Rule and documented in the IRB records.

Authorization: A written agreement by an individual to permit use and/or disclosure of his or her PHI for a particular research project according to HIPAA Privacy Rule standards. This agreement is commonly incorporated as a separate section in the research consent form.

✓ **Ceding IRB:** The HCSRN IRB that transfers review authority to the Lead IRB.

Federal-wide Assurance (FWA): An agreement between a research institution and the Office for Human Research Protections (OHRP), stipulating terms by which the institution will protect the safety, welfare and rights of research participants in accordance with federal regulation (45 CFR 46).

Food and Drug Administration (FDA): The federal agency that regulates food, drugs and cosmetics, including the process by which investigational drugs, devices and biologics are evaluated and approved for marketing.

Health Care Systems Research Network (HCSRN): An organization of Health Care Systems research programs whose mission is to use their collective scientific capabilities to integrate research and practice for the improvement of health and health care among diverse populations.

Institution: For the purpose of this SOP, any member of the Health Care Systems Research Network, including each of the Kaiser Permanente members of the HCSRN individually. Responsible for handling local problems, conducting additional required reviews (e.g., scientific review) and executing any non-IRB study agreements, e.g., Data Use Agreements.

Institutional Review Board (IRB): A formal compliance committee comprised of scientific and non-scientific members with authority and responsibility to protect the safety, welfare and rights of research participants and to determine if proposed research can be conducted under its jurisdiction and under what conditions. IRBs are responsible for monitoring research until it is complete.



Standard Operating Procedure

Health Care Systems Research Network (HCSRN)

SOP HCSRN-001 Version 3

Approved: 7/21/2011

Implementation Date: [varies by institution]

Appendix A

IRB Review of Multi-Site Research

Investigational Device Exemption (IDE): A designation issued by the FDA, giving a device manufacturer or other sponsor the authority to conduct an evaluation of a "significant risk" investigational medical device.

Investigational New Drug (IND): A designation issued by the FDA, giving a "sponsor" the authority to evaluate an investigational drug by administering the investigational drug to human research participants according to FDA regulations.

✓**Lead IRB (sometimes called "IRB of record"):** The HCSRN IRB to which authority for review and oversight has been delegated by another HCSRN IRB. The IRB of record for the ceded sites.

✓**Lead Principal Investigator (PI):** The HCSRN representative who initiates or otherwise assumes HCSRN-wide leadership over the conduct of a study.

✓**Local Principal Investigator (PI):** The HCSRN representative responsible for the conduct of research in his or her institution.

Office for Human Research Protections (OHRP): A federal regulatory office within the Department of Health and Human Services responsible for compliance with 45 CFR 46. OHRP enters into Federal-wide Assurances with research institutions.

Privacy Rule: A comprehensive federal regulation regarding health information that implements the privacy requirements contained in HIPAA. The Privacy Rule establishes the conditions under which PHI may be used and/or disclosed by Covered Entities (CEs).

Protected Health Information (PHI): Identifiable health information, including any demographic or other descriptive data that could link the identity of an individual to his or her health information. It includes information maintained in paper medical records and in electronic databases or disease registries. It also includes identifiable information communicated verbally.

✓**Reviewing IRB:** HCSRN IRBs that include the Lead IRB and any other IRB participating in the research which decide not to cede review authority to the Lead IRB.

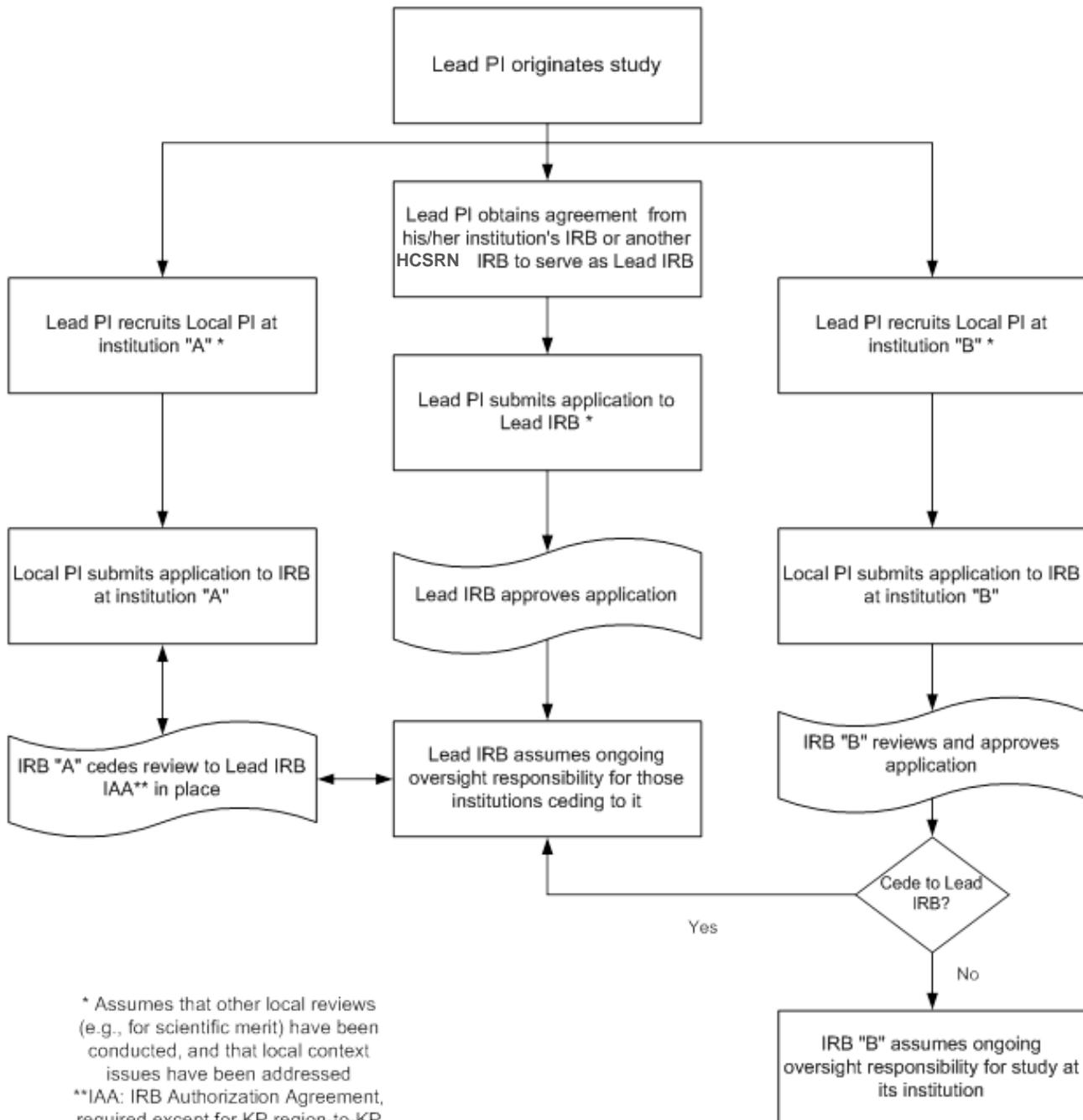
Waiver of Authorization: A waiver of the requirement for a written agreement by an individual, permitting the use and/or disclosure of PHI, as approved by the IRB.

COVER SHEET

Download a Word version of the Cover Sheet at: <http://www.hcsrn.org/en/Tools%20&%20Materials/IRB/>

 <p>health care systems research network</p>		Multi-Site Research Application Cover Sheet	
Complete/Formal Study Title (and sponsor protocol number, if applicable)			
Proposed Lead IRB (HCSRN Member)		Administrator Name	Phone
		Administrator Fax	Administrator E-mail
Information about the Lead Principal Investigator – Submission of this Cover Sheet by the Principal Investigator listed below (“Lead PI”) will verify that the Lead PI accepts responsibility for the information in the research application and agrees to be responsible for the conduct of the study throughout all participating HCSRN institutions in compliance with all applicable federal regulations.			
Lead PI Name	Address/Facility	Department	
Phone	Fax	E-mail	
Information about the Local Principal Investigator(s) and IRB Administrator(s) – Submission of this Cover Sheet by any Principal Investigator listed below (“Local PI”) will verify that the submitting Local PI accepts responsibility for the information in the research application as it pertains to the conduct of the study in his or her institution, and that the submitting Local PI agrees to conduct the study within his or her institution in compliance with all applicable federal regulations and institutional policies and procedures.			
Local PI Name	HCSRN Member Institution Name	Address	
Phone	Fax	E-mail	
Local IRB Administrator Name		Address	
Phone	Fax	E-mail	
Local PI Name	HCSRN Member Institution Name	Address	
Phone	Fax	E-mail	
Local IRB Administrator Name		Address	
Phone	Fax	E-mail	
Local PI Name	HCSRN Member Institution Name	Address	
Phone	Fax	E-mail	
Local IRB Administrator Name		Address	
Phone	Fax	E-mail	

PROCESS FLOWCHART



* Assumes that other local reviews (e.g., for scientific merit) have been conducted, and that local context issues have been addressed

**IAA: IRB Authorization Agreement, required except for KP region-to-KP region cedes

PLEASE SEE NEXT PAGE

IRB Review of Multi-Site Research

Lead IRB (*the IRB of record for the ceded sites*)

- Reviews the proposed research submitted by the Lead PI
- Accepts responsibility for study oversight from a ceding IRB

Ceding IRB

- Reviews proposed research submitted by the Local PI for its institution and cedes responsibility to the Lead IRB

Reviewing IRB

- Reviews proposed research submitted by the Local PI for its institution and oversees the study in its institution
- Communicates primarily with the Local PI, and communicates with Lead PI as required

Lead PI

- Originates the research protocol
- Oversees the study in its entirety in the HCSRN
- Prepares the HCSRN Multi-site Research Application Cover Sheet and the IRB application of the Lead IRB
- Recruits Local PIs
- Submits the proposed research to the Lead IRB
- Assists the Local PIs in preparing their research applications, as required
- Communicates with Reviewing IRBs as required

Local PI

- Submits the proposed research to the Local IRB
- Ensures that any institutional-specific application requirements are included in the multi-site research application
- Oversees the study at his or her institution and maintains ongoing communication with the Lead PI around project status and any problems



Standard Operating Procedure

Health Care Systems Research Network (HCSRN)
SOP HCSRN-001 Version 3
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Appendix D

IRB Review of Multi-Site Research

IRB APPROVAL OF HCSRN MULTI-SITE RESEARCH FREQUENTLY ASKED QUESTIONS (AND ANSWERS)

The goal of SOP HCSRN-001, IRB Review of Multi-Site Research, is to make human subjects review as efficient and timely as possible, while still recognizing the importance of each IRBs' responsibility for ensuring the safety, rights, and welfare of participants and subjects.

These FAQs, which accompany the SOP, are intended to assist both HCSRN investigators when they prepare and submit IRB applications for HCSRN multi-site research, and the staff of the various HCSRN IRBs when they review these submissions.

Investigators should note that, while it is strongly encouraged, IRBs are not required to cede review to the Lead IRB. Local IRBs may decide to retain review authority for their institution's portion of multi-site research.

Further questions that you might have should be addressed to your institution's IRB Director or Administrator. A roster of all HCSRN IRB Administrators can be found on the Health Care Systems Research Network website at:

<http://www.hcsrn.org/en/Tools%20&%20Materials/IRB/>

1. What is the correct order and timing for submitting my multi-site research study?

The goal of the multi-site process is to shorten the overall approval time required from multiple IRBs. In order to make this happen, the lead IRB should receive the study application before the local IRBs. This is to ensure that the lead IRB approves the study as written. If, by chance, the lead IRB were to change something in the submission and the same submission had already been submitted to the local IRBs, this could set up a back-and-forth that could result in unnecessary delays. In the lead IRB's approval notice to the lead PI, it would be advisable for that letter to note that it is willing to accept cedes from local IRBs.

Because another goal of the process is to get the local IRBs to cede to the lead IRB (note that this is a *goal*, it's not a *requirement* that IRBs have to follow), it's always good for the local IRBs to know that the lead IRB has approved the study and is willing to accept oversight before they initiate their review. It may be possible, with expedited reviews, to have a study approved less than a month after the lead IRB has approved it, depending on the schedules of the various IRBs involved.

IRB Review of Multi-Site Research

2. What are the correct lines of communication for an initial submission/review of a HCSRN multi-site research application?

The overall Principal Investigator (the lead PI) is responsible for submitting the entire application to the lead IRB. This can only be done after the lead PI has contacted local investigators to assure that any specific institutional requirements that the local IRBs have are included in the application. Each local investigator, of course, will communicate with his or her IRB Administrator to find out what the institution's IRB wants included.

3. Could excessive communication (requests for courtesy reviews) delay the review of my submission?

Yes, that's a possibility. Remember that the goal is to get the application through multiple IRBs as quickly as possible, and have the IRBs do their job of assuring the safety, rights, and welfare of participants and/or protection of study data. Any "extra steps" are likely to extend the process.

4. What are the correct lines of communication for doing a study modification?

It is the responsibility of the lead PI to collect all pertinent data from the local investigators **before** submitting a study modification to the lead IRB. Also, it is each local PI's responsibility to notify the lead PI of local proposed changes that warrant submission of an IRB modification. The lead IRB reviews the study modification on behalf of all the IRBs that have ceded to the lead IRB. Lead IRB decisions are communicated to the lead PI, who, in turn, communicates them to the local investigators.

If a local IRB has decided not to cede, that IRB would need to review the study modification as well. The study modification would be submitted to it by the lead PI in conjunction with the local investigator for that institution.

5. What are the correct lines of communication for doing a continuing review submission?

It is the responsibility of the lead PI to collect all pertinent data from the local investigators **before** submitting a continuing review. Continuing reviews are submitted by the lead PI to the lead IRB. The lead IRB reviews the continuing review on behalf of all the IRBs that have ceded to the lead IRB. Lead IRB decisions are communicated to the lead PI, who, in turn, communicates them to the local investigators. Local investigators should then submit updates to his or her respective IRB for documentation purposes.

If a local IRB has decided not to cede, that IRB would need to review the continuing review as well. The continuing review would be submitted to it by the lead PI in conjunction with the local investigator for that institution.

6. What are the correct lines of communication for reporting Unanticipated Problems (UP) involving risks to subjects or others where the UP is unanticipated, there is greater than minimal risk, and the UP is possible or definitely study-related?

Each institution should have a procedure in place for reporting Unanticipated Problems (UPs).

- When an UP occurs at the lead institution, it is the responsibility of the lead PI to submit the UP report to the lead IRB, as per lead IRB institutional procedures.
- When an UP occurs at an institution other than the lead institution, where the IRB has ceded to the lead IRB, it is the responsibility of the local investigator to submit the UP report to the lead PI, who, in turn, submits the report to the lead IRB, as per lead IRB institutional procedures.
- The local PI will typically have additional reporting requirements (e.g., Privacy Office or Compliance Office) and these bodies would handle any necessary investigation and corrective action in line with their usual procedures.
- When an UP occurs at an institution where the IRB has not ceded, it is the responsibility of the local investigator to submit the UP report to his or her institutional IRB, and to the lead PI, who, in turn, submits the report to the lead IRB, as UPs can affect the conduct of the study Network-wide.

7. What are the correct lines of communication for reporting protocol deviations and/or protocol violations?

Each institution should have a procedure in place for reporting both protocol deviations and/or protocol violations.

- When a protocol deviation or protocol violation occurs at the lead institution, it is the responsibility of the lead PI to submit the protocol deviation or protocol violation report to the lead IRB, as per lead IRB institutional procedures.
- When a protocol deviation or protocol violation occurs at an institution other than the lead institution, where the IRB has ceded to the lead IRB, it is the responsibility of the local investigator to submit the protocol deviation or protocol violation report to the lead PI, who, in turn, submits the report to the lead IRB, as per lead IRB institutional procedures.
- The local PI may have additional reporting requirements (e.g., Privacy Office or Compliance Office) and these bodies would handle any necessary investigation and corrective action in line with their usual procedures.
- When a protocol deviation or protocol violation occurs at an institution where the IRB has not ceded, it is the responsibility of the local investigator to submit the protocol deviation or protocol violation report to his or her institutional IRB, and to the lead PI, who, in turn, submits the report to the lead IRB.

IRB Review of Multi-Site Research

8. As a lead PI, do I need to call the IRB Administrator at each of the institutions we are wanting to have cede to the lead site?

No. The only Administrator you need to deal with at this point is the Administrator from your institution. Local investigators should communicate with their respective IRB Administrators to inform them that a multi-site study will be forthcoming.

After the lead IRB approves the study, it is the responsibility of the **IRB Administrator in the lead institution** to inform the lead PI of the lead IRB's determinations which may include; a) the lead IRB has approved a multi-site study, and b) the lead IRB is willing to accept a cede from the local IRBs.

If local investigators are waiting for lead IRB approval before submitting to their IRBs, the lead PI would then communicate this approval to the local investigators, who submit their applications to the local IRBs with the lead IRB's approval attached and a request to cede oversight to the lead IRB.

It is the responsibility of the **IRB Administrator in the local institution(s)** to inform the local investigator that his or her institution has ceded to the lead IRB, or has decided not to cede.

9. How long is it expected to take to get a multi-site research study reviewed?

Because it is anticipated that most multi-site studies can be reviewed by expedited review, it is possible, depending on individual IRB review schedules, to have a multi-site application reviewed in significantly less than two months from time of initial review by the lead IRB. However, if a local IRB decides that full-board review of a study proposal is necessary, this could stretch out the time.

10. What would be a 'significant' modification that would warrant submission to the lead and ceding IRBs?

Simply because a study is subject to the multi-site approval process does not alter the fact that a significant modification must be handled in the same way that it would if only one institution were involved.

- When the modification would affect the lead institution only, it is the responsibility of the lead PI to submit the modification request to the lead IRB, as per lead IRB institutional procedures.
- When the modification occurs in an institution other than the lead institution, where the IRB has ceded to the lead IRB, it is the responsibility of the local investigator to submit the modification request to the lead PI, who, in turn, submits the request to the lead IRB, as per lead IRB institutional procedures.
- For a modification that occurs in institutions covered by the Lead IRB, it is the responsibility of the lead PI to submit the modification request to the lead IRB, as per lead IRB institutional procedures. The lead IRB's determination will apply to the lead institutional and to all institutions that have ceded. In an institution that has not ceded, it is the responsibility of the PI in that institution to submit the modification request to the Reviewing IRB.

IRB Review of Multi-Site Research

- When the modification occurs in an institution where the IRB has not ceded, it is the responsibility of the local investigator to submit the modification request to his or her institutional IRB, **and** to the lead PI.

11. What if a modification involves changes in staffing (e.g., key personnel, research staff FTEs, etc.) or additional resources?

The procedures noted directly above in Question 10 still apply. It is the responsibility of the lead PI to assure that each of the ceding institutions can meet the additional staffing/resource requirements before submitting the modification. These communications between investigators are essential for conducting multi-site research.

Documentation that these communications have occurred and any issues have been resolved should be submitted to the lead IRB and will assist the lead IRB in making a more time-efficient review.

12. What if a modification involves a change in the data being used and disclosed?

When a local IRB cedes authority to the lead IRB, the lead IRB also makes necessary HIPAA Privacy Rule determinations (i.e., approval of authorization forms and waiver or alteration of authorization).

Other institutional Privacy Rule contract responsibilities (e.g., data use agreements, business associate agreements, disclosure accounting) are still the responsibility of each institution, as are other institution-specific agreements (e.g., Risk Assessment and Mitigation Process [RAMP] for Kaiser Permanente institutions). It is the responsibility of each local investigator to inform the relevant administrator at the Ceding Institution of any changes that need to be made to Data Use Agreements, Business Associate Agreements, etc. Lead PIs should request that local PIs notify their IRBs **and/or** the institutional function responsible for maintaining HIPAA-required agreements (e.g., DUAs, BAAs, etc.) when changes have occurred which may impact these documents.

13. What types of research are allowed to be submitted using the multi-site research review system?

With the release of Version 2 of this SOP, all multi-site research with the exception of clinical trials is covered by this process. When the process was first introduced, it covered low-risk, data-only studies (i.e., those not involving informed consent) only. With Version 2 of the SOP, the process has been expanded to include studies which required informed consent on the part of participants, but are not clinical trials.

Clinical trials are not included in the process. A *clinical trial* is a prospective biomedical research study of human participants involving a licensed or investigational drug, device, or biologic that is designed to answer specific questions about biomedical or device interventions (e.g., treatments, devices, drugs, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or device interventions are safe and effective.

IRB Review of Multi-Site Research

14. How is appropriate review of local context and local requirements assured?

The local IRB decides on a study-by-study basis whether to cede review. Before ceding, it determines that the lead IRB has reviewed necessary information. It may request that the Lead IRB review additional information (e.g., consent form edits reflecting local language). It could even do its own review before transferring ongoing oversight to the Lead IRB. Additionally, the ceding IRB/institution may develop procedures to stay informed of aspects of the study such as significant modifications and adverse events. It is the responsibility of the local IRB to ensure that applicable state and local laws are followed.

15. Will all of the Health Care Systems Research Network members accept the multi-site research application?

Yes. The multi-site process and application (i.e., cover sheet) has been agreed to by all HCSRN members and approved by the HCSRN Governing Board. A member institution may choose to not to cede to the Lead IRB, should it so desire.

16. Do I need to make any calls to the IRB Administrators in the institutions I'm planning to collaborate with?

No. If you're the lead PI, you need to be in contact with the IRB Administrator in your institution, as well as, of course, the local investigators in all the institutions participating in the proposed research. It is the local investigator's responsibility to communicate with his or her institutional IRB.

17. What differences are there between the lead site PI's responsibilities and the PI's from the local institutions?

The lead PI has a number of unique responsibilities. S/he is generally responsible for:

- Developing the protocol,
- Overseeing in its entirety the study being conducted in the HCSRN;
- Recruiting collaborating PIs in each institution (i.e., local PI) in which the study will be conducted;
- Preparing the Multi-site Research Application Cover Sheet (Cover Sheet) and IRB application and coordinating their submission to the appropriate HCSRN IRBs;
- Communicating with the Lead IRB;
- Having the primary role in communicating with each local PI, including forwarding all correspondence from the Lead IRB to each local PI; and
- In conjunction with the local PIs, communicating with local IRBs to provide study information to the Lead IRB.

IRB Review of Multi-Site Research

18. Do I need to have an engaged Principal Investigator in each participating institution?

Yes. Each multi-site study is required to have an investigator from each participating institution, who is responsible for the conduct of the study in that institution. Local investigators are responsible for:

- Performing and/or supervising all research activities relating to the study conducted in his or her institution;
- Assuring that these activities are conducted in compliance with federal regulations and institutional policies;
- Collaborating with the Lead PI to ensure that all institutional IRB requirements are met.
- Obtaining all institutional approvals including leadership, research review committee, and facility department, as may be required by the institution;
- Submitting the Cover Sheet, IRB application, and institution-specific materials to the institution's IRB and other institution-required committees;
- Communicating with his or her institution's IRB, as appropriate; and
- Communicating with the Lead PI, including forwarding any correspondence from the local IRB.

19. Will the lead IRB be checking the training and CVs for the investigators' and study staff from each participating institution?

No. Ensuring that training requirements are met and reviewing CVs is part of the initial approval process of any study.

Because a local IRB is responsible for determining whether it will cede to the lead IRB, the local IRB must review a complete application package for its institution before agreeing to cede. This would include CVs and training. In other words, the local IRB has assured itself that the qualifications of its investigators and staff are in order before agreeing to cede.

20. Will the lead IRB be checking for conflicts of interests (COI) for the investigators' and study staff from each participating HCSRN institution?

No. Ensuring that there are no conflicts of interest is part of the initial approval process of any study.

Because a local IRB is responsible for determining whether it will cede to the lead IRB, the local IRB must review a complete application package for its institution before agreeing to cede. This would include COI attestations from investigators and appropriate study staff. In other words, the local IRB has assured itself that there are no COIs for its investigators and staff and attestations are in order before agreeing to cede.

IRB Review of Multi-Site Research

21. If something goes wrong (e.g. breach of confidentiality, or an unanticipated problem) how does the event get communicated to all the correct individuals?

Each IRB should have a procedure in place for communicating unanticipated problems and compliance breaches to leadership and responsible parties at their institution.

When such an event occurs at an institution relying on an external IRB, the local investigator in the institution where the problem or breach occurred must immediately inform the lead PI, who must promptly inform the lead IRB (per lead IRB SOPs). The local investigator must also communicate the problem or breach directly to relevant bodies at the local institution, as specified by local P&Ps, for investigation and potential corrective action.

Although the lead IRB, when serving as IRB of record, is responsible for dealing with the breach in compliance with federal human subjects regulations,* the local institution is responsible for any HIPAA/HITECH requirements, local customer relations, etc.

If the breach involved more than one institution's data, the lead PI must immediately inform all other IRBs **and** local PIs (both ceding and non-ceding) and local investigators of the situation.

Reporting to regulators will follow local Institutional requirements, according to the institution's FWA.

22. What if the Lead IRB determines an adverse event is minor while a ceding IRB determines the same event is significant and requires corrective actions to be taken at the lead and ceding sites?

The ceding institution is still responsible for compliance at that institution. The ceding IRB in the institution where the event occurred is free to make a determination that an unanticipated problem needs to be reported to institutional leadership, and to regulator(s), if required.

It is **strongly urged** that the ceding and lead IRBs attempt to come to an agreement regarding the gravity of an unanticipated problem and subsequent course of action.

23. How are the research funding issues (direct and indirect cost assessment, budget negotiations, finance, contracts...) managed in the multi-site research application process?

Funding issues are distinct from IRB approval of multi-site research. All institutions must assure that funding is in place (or if anticipated, will be in place, according to established procedures) before research is allowed to progress.

*If the institution where the event occurred is a Kaiser Permanente region, and the lead institution is also a Kaiser Permanente region, it will be the lead IRB's responsibility to manage the event, in conjunction with the local IRB. If the event occurs in a non-Kaiser Permanente member of the HCSRN, then it is the responsibility of that institution to manage the event, and keep the lead IRB (regardless of where the lead IRB is located) fully informed of its efforts.

IRB Review of Multi-Site Research

24. How are the research operational issues (resource allocation, research staff assignment and supervision, data access, etc.) managed in the multi-site research application process?

The lead PI has overall responsibility for research operational issues, but the local investigators are responsible for performing and/or supervising all research activities relating to the study conducted in their institutions.

25. How is HIPAA (approval/waiver of authorization, agreement execution, training assessments, dataset validation, etc.) managed in the multi-site research application process?

It is the responsibility of the lead IRB to make necessary Privacy Rule determinations (i.e., approve authorization forms and waiver or alteration of authorization). Other HIPAA processes are the responsibility of institutional research administration.

26. Which institution (lead or ceding) is responsible for initiating and executing any Business Associate Agreements?

Any Privacy Rule contract responsibilities related to services required for the conduct of the research still the responsibility of each institutional PI.

27. Which institution (lead or ceding) is responsible for initiating and executing any Data Use Agreements?

Privacy Rule contract responsibilities (e.g., data use agreements, business associate agreements, disclosure accounting) are still the responsibility of each institution.

28. Can I start my multi-site research study once I have IRB approval from the lead site or do I have to wait until I have heard from each of the ceding sites?

The research can start in each of the institutions where it has been approved: in the lead institution and ceding institutions where the cede has been accepted by the lead IRB, and in non-ceding institutions where the non-ceding IRB has approved the research. It is entirely possible that some institutions may have approvals in place while others may not. Research may begin only in those institutions where IRB approvals are in place.

29. Can I start my multi-site research after I've received IRB approval from the lead and ceding sites or do I have to wait for the execution of all the HIPAA Agreements?

Again, if all IRB approvals and contractual and HIPAA agreements are in place in all institutions, research can begin in all institutions. It may not begin in those institutions where all required agreements are not in place.



Standard Operating Procedure

Health Care Systems Research Network (HCSRN)
SOP HCSRN-001 Version 3
Approved: 7/21/2011
Implementation Date: [varies by institution]
Appendix D

IRB Review of Multi-Site Research

30. As the lead PI, am I responsible for getting all the administrative approvals for the lead and all the ceding institutions?

As lead PI, you have overall responsibility for assuring that administrative approvals for the lead and all the ceding institutions are in place, but it is anticipated that you will work through the local investigators in each of the ceding institutions to accomplish this.

31. How do I handle adding a new local PI/site once a study already has IRB approval?

To add a new site to an existing protocol for research that has previously been reviewed and approved, the Lead PI would submit a modification to the Lead IRB and the Local PI will submit the cover sheet and signed HCSRN Lead IRB application and related documents to his or her institution's IRB and other research review committees, as required