

**IRB APPROVAL OF HMORN MULTI-SITE RESEARCH:
FREQUENTLY ASKED QUESTIONS (AND ANSWERS)**

The goal of SOP HMORN-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 HMORN investigators when they prepare and submit IRB applications for HMORN multi-site research, and the staff of the various HMORN 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 HMORN IRB Administrators can be found on the HMO Research Network website at:

http://www.hmoresearchnetwork.org/resources/resources_home.htm

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.

2. What are the correct lines of communication for an initial submission/review of a HMORN 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.

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.

- 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.

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 HMO 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 HMORN members and approved by the HMORN 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 HMORN;
- 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 HMORN 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.

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 HMORN 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.

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 HMORN, 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.

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. <Anything else specific we want to say about Privacy Board responsibilities?>

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.

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 HMORN Lead IRB application and related documents to his or her institution's IRB and other research review committees, as required