

Reliance Agreement Guidance: Penn is the Central IRB / Single IRB / IRB of Record FAQ

This document is designed to answer questions frequently asked by individuals who want to know more about Penn's policies and procedures related to Penn serving as the IRB of Record for external sites in multi-site trials. It is expected that this document will be most helpful to Investigators and research staff that will be submitting protocols to the Penn IRB. However, other research support staff and individuals affiliated with other IRBs may find the information in this guidance document to be helpful.

This document will not be helpful to individuals who are asking Penn to rely on another external IRB as the IRB of Record for their study.

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1. What is the Purpose of this Document?

It is now common practice for multi-site research studies to seek ethical review and approval of the proposed research by a single IRB. As part of this practice, one IRB is designated as the IRB of Record and the IRBs at other sites agree to rely on that single IRB's review. The University of Pennsylvania is willing to serve as the single IRB of Record for multi-site trials. This document seeks to answer commonly asked questions related to:

- 1) The circumstances when Penn will serve as the IRB of Record
- 2) The process for executing a reliance agreement between the Penn IRB and an External IRB
- 3) The study team's role in the process of executing reliance agreements
- 4) The process for review of modifications, continuing reviews, and reportable events.

This document does not discuss Penn relying on external IRBs.

2. What is a Reliance Agreement?

A Reliance Agreement (or an IRB Authorization Agreement) is a written agreement between an Institution conducting human subjects research and another Institution or Organization that is operating an IRB. The written agreement outlines the relationship between the two entities and how the Institution conducting the research is willing to rely on the other Institution's IRB for ethical review of the research. The agreement also includes a commitment that the IRB will adhere to the requirements of the Institution's Federalwide Assurance (FWA). These agreements can be executed for an individual study or they can cover multiple studies. A copy of the agreement must be kept on file at both institutions and be made available upon request to OHRP or any U.S. Federal department or agency conducting or supporting the research covered by the agreement.

The Penn IRB has also signed onto the SMART IRB Master Reliance agreement. This agreement has been signed by over 400 institutions. The Penn IRB is willing to serve as the IRB of Record IRB according to the terms set in the SMART IRB agreement. Additional information on this agreement and what documentation is necessary can be found in the Reliance Agreement Guidance: SMART IRB Agreement FAQ document.

If you are executing a Reliance Agreement with an IRB that has not signed either a Master agreement with Penn or the SMART IRB agreement, the reliance agreement will be executed via a standalone IRB Authorization Agreement. The University of Pennsylvania has a template IRB Authorization Agreement that can be downloaded from the forms page of the IRB website. The Penn IRB is also willing to execute agreements using a template provided by an external Institution or Organization.

3. Who at the Penn IRB should I talk to about reliance agreements?

There are multiple people at the Penn IRB who can assist you with questions about reliance agreements. As this list is subject to change, you should refer to the How to Submit: Reliance Agreement page of the IRB website for contact information for the members of the Penn Reliance Agreement team.

Please be aware that the reliance agreement process can be quite different than the traditional IRB review and approval process. Parties involved may include the Penn IRB, the External IRB, the research team at Penn, the research team at the external site, the study sponsor, a CRO, and other additional points of contact. Occasionally, individuals submitting reliance agreements will end up receiving conflicting information from these sources. Please do not hesitate to contact the Penn IRB with any questions about the process. We have experience working with a variety of IRBs and are happy to help you get your questions answered and make the process as smooth as possible.

4. What does it mean when Penn serves as the single IRB?

When Penn serves as the single IRB, it means that the Penn IRB, as the IRB of record, conducts the ethical review to establish that the protocol meets the DHHS and/or FDA regulatory criteria for IRB approval (risks to subjects are minimized, there is a favorable risk to benefit ratio, informed consent will be appropriately sought, etc.). This review applies to all sites that agree to rely on the Penn IRB through an IRB authorization agreement. The Penn IRB will also be responsible for the ongoing ethical review of the study and this includes continuing review, review of modifications, and review of reportable events. These reviews will occur at convened IRB meetings or through the expedited review process as appropriate per the Federal Regulations governing human subjects research and the Penn IRB's Standard Operating Procedures.

When other sites rely on Penn as the single IRB, the other sites maintain their responsibility to ensure that it adheres to the Institutional policies and practices established by their Research Protections Programs. This review may be performed administratively by the other sites' IRBs.

5. What are the study team responsibilities when Penn serves as the single IRB?

If Penn is serving as the single IRB of Record, then the Penn study site will have additional responsibilities beyond their role as an enrolling site and/or a Data Coordinating Center. This is because all submissions for IRB review must be submitted through the HS-ERA platform. In order to access HS-ERA, the submitter must have an active Pennkey. Therefore, the Penn study team will need to identify someone who can perform the following tasks:

- Submission of the protocol for initial IRB review
- Submission of protocol modifications to add study sites that agree to rely on the Penn IRB
- Submission of protocol-wide modifications that impact all study sites
- Submission of site-specific modifications for sites that are relying on the Penn IRB
- Submission of protocol-wide continuing review applications that include information on the progress reported by all sites relying on the Penn IRB
- Submission of deviations, exceptions, and reportable events from any site that relies on the Penn IRB.

These activities require a significant amount of coordination between the submitter and the study teams at each site. The IRB recommends that you identify a study team member who will serve as the point of contact and be responsible for these coordinating activities. Depending on the number of sites and the complexity of your study, these coordinating activities could require the commitment of significant resources.

If someone external to Penn will be responsible for coordinating documents from the study sites and submitting to the Penn IRB, a member of the Penn study team will need to acquire a Pennkey for that individual and provide HS-ERA training.

6. Are all the study sites required to rely on a single IRB for a multi-site study?

If you are seeking federal funding from the NIH for your protocol, you are required to implement a single IRB structure for multi-site studies. The NIH has implemented a new policy that took effect on January 28, 2018. This policy mandates the use of single IRB Record for new proposals for multi-site studies.

More information on the NIH Single IRB policy can be found here:
<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html>

This policy only applies to grant proposals submitted after the January 28, 2018 effective date. Studies that are not funded by the NIH or were funded prior to the deadline are not currently required to implement a single IRB structure.

In addition, the Federal Policy for the Protection of Human Subjects (also known as the Common Rule) has been revised and will generally require Single IRB review for multisite studies. The effective date for this policy is January 20, 2020.

7. Are there resources available to help me with these tasks?

The Department of Medicine Clinical Trials Unit (DOM CTU) is able to provide support for a wide spectrum of clinical trials. This support includes assistance with coordinating activities related to Penn serving as a Single IRB for multi-site trials. Services are provided on a fee-for-service basis or % effort. For additional information, please visit this website: <https://www.med.upenn.edu/scrcm/department-of-medicine-clinical-trials-unit.html> or contact Amanda Baer at 215-349-5023 or baer2@mail.med.upenn.edu.

Independent IRBs such as the Western IRB and the Quorum IRB do offer regulatory support for trials that utilize their IRBs as the Single IRB of Record. For more information on these services, you should review the independent IRBs' websites. If you would prefer to utilize an external, independent IRB as the Single IRB for your multi-site protocol, please contact Penn IRB staff to discuss this option. The Penn IRB is willing to consider these agreements on a case by case bases.

8. When is the Penn IRB willing to serve as the single IRB?

The Penn IRB is willing to serve as the IRB of Record under the following scenarios:

- The Children's Hospital of Philadelphia IRB is willing to rely on the Penn IRB through a Penn/CHOP Agreement
- The study is a federally funded multi-site clinical trial and Penn is serving as the lead site or has been selected as the IRB of Record as part of the NIH proposal review and approval process
- An Investigator Initiated multi-site trial where the Penn Investigator is the lead PI
- If the Penn research team is conducting a multi-site study where external sites are not enrolling subjects but are engaged in other research related activities.

Whenever you have questions about whether or not Penn is willing to serve as the IRB of Record, please contact the Penn IRB to discuss the scenario before submitting your protocol in HS-ERA. Please contact any of the individuals identified as reliance agreement points of contact on the IRB website.

9. What questions should I consider during the protocol planning stages?

Because there are additional study team responsibilities when Penn serves as the IRB of Record, there are some questions you will want to consider early on in the protocol planning stages. This information may be helpful when drafting grant applications or negotiating budgets for industry sponsored studies.

- How many sites are expected to participate in the study?
- How many sites will be willing to rely on the Penn IRB?
- If applying for a grant, do you need letters of support from the other site IRBs indicating that they will rely on the Penn IRB?
- Who will be responsible for collecting documents from other sites and compiling IRB submissions?
- Who will be responsible for disseminating IRB approval letters and responding to questions or concerns raised by the IRB?
- For industry sponsored studies, do you plan to bill sponsors for your study team coordinating activities?
- For industry sponsored studies, the IRB charges additional fees when it serves as the single IRB. Are these fees accounted for in the clinical trial agreement?
- For federally funded studies, the IRB charges fees when it serves as the single IRB that can be billed as direct costs. Are these fees accounted for in the budget?
- How often to you expect to create protocol wide amendments that will require review and approval?
- How often to you expect to create site specific amendments that will require review and approval?

The number of sites and the complexity of the trial will determine how much effort is involved in coordinating single IRB review. Large multi-site studies are expected to require significant time and coordination. If you have any questions about what's necessary when Penn serves as the single IRB, please email the IRB reliance agreement team.

10. How do I get a letter of support from the IRB for my grant application?

If you are submitting a grant proposal for a multi-site study, you may want to include a letter from the Penn IRB indicating our willingness to serve as the Single IRB of Record. If this is the case, please contact Patrick Stanko request this letter of support. A template letter can be provided upon request.

11. Is the initial IRB review different when Penn serves as the single IRB of Record?

There are no substantial changes to the Penn IRB's initial review process when Penn serves as the Single IRB or IRB of Record. The application will still be screened by IRB staff before it is scheduled for review. The protocol may undergo either convened or expedited review. During that review, the IRB will determine if the protocol can be approved or if minor or substantial revisions are required before approval can be granted.

The only change is that, in addition to determining whether the criteria for IRB approval have been met, the IRB will also consider whether it is willing to serve as the single IRB.

12. What additional information do I need to include in my initial IRB application?

The IRB HSERA application Centers Page asks you to indicate if you are asking for Penn to serve as the IRB of Record for other external study sites. You should answer “Yes” to that question and include the following pieces of information in your application:

1. The approximate number of study sites
2. How you plan to complete the following activities:
 - a. Ensure all Relying Site Study Teams have the most current version of the protocol, consent, documents, and other supporting materials.
 - b. Ensure that all Relying site Study Teams use the same version of the protocol, including a description of the procedures that must be followed in order to amend the protocol.
 - c. Communicate with, collect information from, and disseminate information to other sites regarding:
 - i. Local Consent requirements
 - ii. Study updates (e.g., recruitment holds for interim analyses, closure to enrollment) or other changes to the study
 - iii. Continuing Reviews
 - iv. Local changes of protocol (e.g., personnel updates, COI updates)
 - v. Reportable events
 - vi. Study closure
 - vii. The plan for collection and management of data from all sites
 - d. Submit documents from Relying site Study Teams to the Penn IRB for review.

Please note that you are not required to identify sites by name at the time of initial application. This will be required after initial IRB approval has been granted and you are requesting that a site be approved by the Penn IRB under a reliance agreement.

This plan can be revised as needed as sites are identified and the team develops its internal processes and procedures. The IRB evaluates your response to ensure that a plan is in place and that the IRB has sufficient expertise and experience to serve as the single IRB of record for your multi-site trial.

13. What is the SMART IRB? How do I use the SMART IRB?

The SMART IRB agreement is a master IRB authorization agreement that has been signed by over 400 institutions. It sets terms and conditions upon which any of the participating institutions can rely on each other’s IRBs.

This agreement was created to facilitate reliance agreements by avoiding circumstances where IRBs needed to review and negotiate the terms of every reliance agreement for every protocol.

The Penn IRB has signed onto the SMART IRB and is willing to execute reliance agreements according to its terms. If you will be using the SMART IRB Master agreement for your study, you will not have to use a separate protocol specific IRB authorization agreement.

If you are using the SMART IRB, you need to determine how you will want IRBs to document the use of the SMART IRB. There are multiple ways that this can occur:

- You can use the SMART IRB Exchange or SMART IRB Online Reliance System
- You can request that relying IRBs draft acknowledgment letters where they indicate that they are relying on Penn per the SMART agreement

Additional information on the SMART IRB agreement can be found in the Reliance Agreement Guidance: SMART IRB Agreement FAQ document.

14. What information do I share with other sites after IRB review has taken place?

After you have received Penn IRB approval, you should inform the other study sites that the IRB approved protocol and consent form are now available and that study sites can inquire about whether their local IRBs are willing to rely on the Penn IRB as the IRB of Record.

You should inform the site that they will need to work with you and their local IRB to complete the following:

- A fully executed IRB Authorization Agreement (if applicable)
- A site specific consent form
- A completed Central IRB Review: Participating Site Addition Form. This form can be downloaded from the Forms page of the IRB website. This form should be completed after the relying site team has obtained a Local Context Review from their local IRB.

You will want to give the study team an editable version of the IRB approved consent form. It is recommended that you convert the approved consent form into a template document with placeholders for site specific information. Instructions on how to revise a Penn IRB approved consent into a template consent are available on the IRB website.

It is recommended that you also provide the sites with additional guidance materials related to the Penn IRB SOPs and their responsibilities when relying on the Penn IRB as the IRB of Record. Draft materials have been developed by the Penn IRB and are available on the IRB website.

15. How does a relying site obtain a Local Context Review?

After you have received initial Penn IRB approval and sent documents to the study teams at your potential relying sites, those study teams must obtain a local context review. This is when the relying site's human research protections program reviews the study documents to make sure they adhere to the relying sites institutional policies and procedures for human subjects research.

Each relying site's human research protections program will conduct its local context review differently. The relying site research team should contact their IRB or other applicable research oversight office to find out exactly how local context review should be completed.

The following tasks are expected to occur as part of the local context review:

- The relying sites' IRB will review and sign the IRB Authorization Agreement (if applicable)
- The relying site's IRB (or other designated oversight office) will verify that the study team has completed its institutional human subjects research training requirements
- The relying site's IRB (or other designated oversight office) will determine if there are any additional requirements that the study team must adhere to in order to comply with local institutional policies and best practices
- Any applicable Ancillary Review Committees (Radiation Safety, Pharmacy, Institutional Biosafety, etc.) will review the study.
- The study team will revise the Penn IRB approved consent form by inserting site specific language that is required per institutional policy. If necessary, the revised consent may be reviewed by the relying site's IRB and other applicable Ancillary Review Committees
- If members of the study team have potential financial conflicts of interest, they will be reviewed according to the institutions conflict of interest policies.

If the local context review process requires any site specific changes to the protocol procedures or the consent form, those changes should be documented in the Central IRB Review: Participating Site Addition Form. The Penn IRB will review and approve those changes when it approves the addition of the study site.

The IRB Authorization Agreement negotiation process is different for every site. It is recommended that the negotiation be completed before you submit a modification asking the Penn IRB to approve the additional study site. Therefore, the Penn IRB recommends that you begin this negotiation process as soon as possible and you may choose to begin that process while initial IRB review and approval is ongoing. The Penn IRB is willing to help navigate this process by talking to relying site research teams and relying site IRBs as necessary. If you have any questions about this process, please contact the Penn IRB.

16. How do I get Penn IRB approval for a new relying study site?

Study sites can be submitted to the Penn IRB for approval via the Modification submission in HS-ERA. Once initial IRB approval has been granted, the Penn site point of contact should ask each relying site to provide them with the following:

- The IRB authorization agreement (**if necessary)
- A copy of the site-specific consent form: Include both a clean version for stamping and a version with all changes to the template tracked/highlighted
- A completed Study Site Addition form. This form can be downloaded from the Forms page of the IRB website.

**Regarding the IRB authorization agreement, this document may not be necessary if the Penn IRB and the relying site have already executed a master agreement. If both sites agree to use the SMART IRB agreement, you should have some documentation supporting this decision. This typically is an email from either the SMART IRB online reliance systems or a letter from the Relying IRB indicating their agreement to abide by the terms of the SMART agreement. If you are using a protocol specific IRB authorization agreement, it is recommended you have the agreement signed by both IRBs before submitting a modification in HS-ERA. You can contact the Penn IRB staff via email for assistance in getting the agreement signed prior to formal submission.

Once you have received the documents from the study site, you should create and submit a modification in HS-ERA that includes these documents. The Penn IRB will then review the documents and evaluate any site-specific changes that were required as a result of the local site's local context review. If no significant changes are made, the submission will undergo expedited review.

Once the Penn IRB has approved the modification it will issue a letter indicating that the documents are approved and provide a stamped copy of the informed consent form. The expiration date on the consent form will align with the expiration date of the overall protocol.

Please do not include protocol wide amendment changes in a modification submission that includes the addition of a study site. You can include multiple study sites in one modification submission provided that all the documents are present for each additional study site.

17. What about Conflict of Interest Review?

The Penn Conflicts of Interest Standing Committee (CISC) is a part of Penn's Human Research Protections Program. It is not responsible for the review of potential conflicts identified by investigators and study team members at relying sites.

When you are adding a study site, you should indicate whether a member of the study team has a potential significant financial interest that was disclosed to the site's local Conflict of Interest Review Committee. If a conflict has been identified, you should not submit to the Penn IRB until the local site has reviewed the conflict and issued a management plan that has been agreed to by the member of the study team.

In your submission to the Penn IRB, you should include the results of the review and any applicable disclosures. The specific information that will need to be shared varies based on the reliance agreement that was executed. Typically, the Penn IRB will review the management plan and the informed consent form disclosure language when they approve the protocol.

It is strongly recommended that the relying site investigator make himself or herself aware of the review policies for reliance agreements before the agreement is submitted to Penn.

18. When can other study sites start enrolling subjects?

Having a fully executed reliance agreement and an additional site approval from the Penn IRB means that you have IRB approval to conduct the research at the external study site. However, you will still need to complete all the other applicable steps in the study start up process before you can enroll subjects on the study. These steps may include:

- Review by Local Ancillary Review Committees (Radiation, Biosafety, etc.)
- Execution of the clinical trial agreement or contract
- Completion of a billing analysis
- Completion of a site initiation visit

The local site should continue to follow its human research protections program's requirements to make sure all institutional steps are completed before the study begins enrollment.

19. Does the Penn IRB charge fees when it serves as the Central IRB?

The IRB may charge fees for serving as the single IRB of Record (sIRB) for federally funded, multi-site studies. These fees include an administrative fee for the approval of additional study sites and additional continuing review fees or modification fees for protocol wide changes.

The current IRB fee schedule for studies where the Penn IRB is serving as the single IRB (sIRB) is the following (Note: these fees are specific to federal funded studies only):

- Initial Review fee (fee per relying site) = \$1400
- Continuing Review fees (fee per relying site with study activity during the last approval period) = \$600
- Modification (fee per affected relying site) = \$300 per review (excluding: any administrative and/or minor revisions)

*Note: If a relying site is not affected by a modification submitted to the sIRB or if a site has minimal or no activity at the time of request for continuing approval, the fee will not be assessed for **that specific submission**.

The NIH policy states that the IRB of Record should bill for these additional administrative fees as direct costs. These fees should be included in grant proposals for federally funded, multi-site trials. If you have any questions about whether IRB review fees should be included in your proposal budget for multi-site research where you are asking the Penn IRB to serve as the single IRB of record (sIRB), please contact Patrick Stanko.

For Industry Sponsored Studies Only:

The fees described above are in addition to the Initial Review, Continuing Review and Modification Review fees described on the IRB Fees page of the IRB website: <https://irb.upenn.edu/mission-institutional-review-board-irb/irb-fees>

Reminder of the process: The HSERA application will include an internal financial contact and fund number. The information needed by the IRB to complete this process should be included in section regarding industry sponsored protocols. This information should be included at the initial submission, whether the contract is pending or not. The departments will bill the funding entity for this and other fees as part of the already existing billing process.

For contracts: IRB fees should be included in contract negotiations whether the study contract is finalized or not. It should appear as a line item in the budget of the formal contract as an upfront and non-refundable fee. ORS will help you with this if needed.

For more information or assistance, please contact Ed Fong at the IRB; edfong@upenn.edu or 215-573-0791.

20. How do I submit protocol wide and study specific modifications?

All modifications should be submitted via the HS-ERA electronic submission system. However, when you submit a modification you should note in the Modification Form whether these changes apply to all study sites or to a limited number of sites, which should be identified by name.

Additional instruction on the modification submission process can be found in the Reliance Agreement Guidance: Post-Approval Submissions document.

Please note that the Penn IRB is not required to review and approve every personnel change for every site. Personnel modifications should be reviewed and approved by the local site IRBs. Study personnel lists can be updated at the time of continuing review or other substantial modification.

21. What information about other study sites is required at the time of continuing review?

At the time of continuing review, the Penn IRB is required to evaluate the progress of both the Penn site and all the other sites that rely on the Penn IRB. This will include information about deviations, adverse events, and post-approval monitoring for all the relying sites. The study team is expected to compile one progress report that includes this additional information.

In order to compile the progress report, the study team's designated point of contact should download the Continuing Review Relying Site Supplement form from the forms page of the IRB website. The point of contact should forward this form to all relying site research teams (including the Penn research team). The relying site research teams (including the Penn research team) should complete the supplement and return the form to the designated point of contact.

After receiving all the relying site supplements, the Penn research team should use the information in those forms to complete the Continuing Review Application – Single IRB Version form. This form can be downloaded from the forms page of the IRB website.

Additional instruction on the continuing review submission process can be found in the Reliance Agreement Guidance: Post-Approval Submissions document.

22. How do I report deviations, exceptions and reportable events?

Deviations, exceptions, and reportable events that occur at Penn or at another relying sites should all be submitted to the Penn IRB according to Penn's reporting requirements. The Penn IRB will review these requests in its capacity as the single IRB of Record.

All site study teams should familiarize themselves with the Penn IRB's policies on reporting deviations, exceptions, and reportable events. These policies may differ from their local site reporting requirements.

Additional instruction on the deviation, exception, and reportable event submission process can be found in the Reliance Agreement Guidance: Post-Approval Submissions document.

23. What happens if the Penn IRB makes a serious and/or continuing noncompliance or unanticipated problem determinations?

Per the terms of the reliance agreement, the Penn IRB will notify the local site IRB of any determinations of serious and/or continuing noncompliance determinations and unanticipated problems involving risks to subjects or others. If these determinations require external reporting to the FDA or OHRP, the Penn IRB will work with the local site IRB to get their input before an external report is sent.

In certain circumstances, the Penn IRB may ask for the local site IRB's assistance in implementing the mandated corrective action plan.

As each event is unique, the Penn IRB will make every effort to respond to questions and assist both the local site IRB and the study team in resolving all identified issues. Please do not hesitate to contact the IRB Directors if you have questions about IRB review of deviations or unanticipated problems.

24. How do I submit Penn/CHOP cooperative review agreements when Penn will be the IRB of Record?

At this time, the process for reviewing Penn-CHOP cooperative review agreements is not changing. You should continue to include your Penn/CHOP determination form in your initial review request. Once this form has been signed by the Penn IRB, you should then submit to CHOP through the eIRB system.

25. I have other questions. Where do I go?

Please contact any member of the IRB Reliance Agreement Team (listed on the "How to Submit: Reliance Agreements" page of the IRB website) with any questions or issues you may have with the reliance agreement process.