Reliance Agreement Guidance:
Requesting External IRB Review FAQ

Institutional Review Board
3800 Spruce Street
First Floor Suite 151
Philadelphia, PA 19104-6006
Phone: 215-573-2540

This document is designed to answer questions frequently asked by individuals who want to know more about Penn's policies and procedures related to relying on external IRBs. It is expected that this document will be most helpful to research staff that will be submitting reliance agreement requests to the Penn IRB. However, Penn Investigators, 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 serve as the IRB of Record for other sites.

Table of Contents by Section:

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 engage in these reliance agreements with IRBs external to Penn. This document seeks to answer commonly asked questions related to:

1) The circumstances when Penn will rely on an external IRB
2) The process for executing a reliance agreement between the Penn IRB and an External IRB
3) Human Research Protection Program requirements for studies when Penn is not the IRB of Record
4) Penn's role in review of modifications, continuing reviews, and reportable events when a reliance agreement has been put in place.

This document does not discuss Penn serving as the IRB of Record for other sites.

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 FWA (Federalwide Assurance). 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 entered into IRB authorization agreements with external IRBs that cover multiple protocols. These agreements are called Master IRB Authorization Agreements. If you are relying on an external IRB that has executed a Master IRB Authorization Agreement with Penn, your application to the Penn IRB will not need a protocol specific IRB Authorization Agreement form to be signed by both Penn and the external IRB. As this list is subject to change, the Penn IRB website reliance agreement page has a list of external IRBs that are covered under master agreements. This list will be updated as necessary. If you have any questions about Master agreements or what documentation is necessary, please contact the IRB prior to submitting your HS-ERA application.

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 rely on another academic center's 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 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 with 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 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 lead 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 relies on an External IRB? What is the role of the External IRB?

Under normal circumstances, when a research study is submitted to the Penn IRB for review, two processes occur simultaneously:

1) there is a review to establish that the protocol meets the DHHS and/or FDA criteria for IRB approval; and
2) there is a review to ensure that the study adheres to the Institutional policies and practices established by the Penn Human Research Protections Program.

When Penn relies on an External IRB, it means that the External IRB, as the IRB of Record, performs the first review. The External IRB will be responsible for ensuring that the protocol meets the criteria for approval (risks to subjects are minimized, there is a favorable risk to benefit ratio, informed consent will be appropriately sought, etc.). The external IRB is also 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 External IRB's Standard Operating Procedures.

When Penn relies on an External IRB, the Penn IRB maintains its responsibility to ensure that it adheres to the Institutional policies and practices established by the Penn Human Research Protections Program. This review is performed administratively by the Penn IRB.

5. Is an application to the Penn IRB required if Penn will rely on an External IRB?

Yes. An HS-ERA application is required for the IRB to complete its administrative review of the study. This process will also result in the Penn IRB assigning the study a Penn IRB Protocol Number which is necessary to ensure that ancillary committee review and other business practices related to the conduct of the trial can be completed.

6. If I am relying on an External IRB, what does the Penn IRB look at after I complete the HS-ERA application?

The Penn IRB will review the application and uploaded documents to determine the following:

- If the members of the study team have appropriately met Penn human subjects research training requirements.

- If a financial conflict of interest has been reported, the Penn IRB will ensure that a management plan has been put in place before the study is considered open to enrollment at Penn.
- If the answers on the Bio page of the application have been completed correctly and appropriately triggered the required ancillary committee reviews.
- That the documents needed to execute the reliance agreement have been submitted and completed appropriately.
- That the informed consent form includes the necessary Penn required language.
- That any applicable additional state, local, or institutional policies or requirements will be followed.

Once the Penn IRB has determined that all the above requirements are met, they will sign the IRB Authorization Agreement (if necessary) and issue a letter acknowledging receipt of the protocol and the Penn IRB's willingness to rely on the External IRB. This letter will also include any additional instructions on next steps in the process.

7. Am I required to rely on an External IRB for a multi-site study?

Effective January 25, 2018, the NIH is mandating the use of a single IRB of 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

If your study is not subject to the NIH mandate, you are not currently required to rely on an External IRB for a multi-site study. In addition, the Penn IRB does not require that you use an External IRB for industry sponsored research however we recognize that most sponsors make this option available for multi-site studies.

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 multi-site studies. The effective date for this policy is January 20, 2020.

8. When is the Penn IRB willing to rely on an external IRB?

The Penn IRB is willing to rely on an external IRB under the following scenarios:

- The Children's Hospital of Philadelphia IRB is willing to serve as the IRB of Record through a Penn/CHOP Agreement
- All Phase III and IV protocols where the sponsor has identified a central IRB of Record.
- The Penn IRB is also willing to consider relying on an External IRB for some Phase I and II studies. These decisions are made on a case by case basis.
- The study is a federally funded multi-site clinical trial and the lead site is serving as the IRB of Record OR the central IRB of Record was selected as part of the NIH proposal review and approval process.
- If you are conducting a multi-site study that is not federally funded or industry sponsored, the Penn IRB will consider relying on an External IRB provided Penn is not the lead site. These decisions will also be made on a case by case basis.

In general, the Penn IRB is NOT willing to rely on an external IRB under the following scenarios:

- Investigator initiated studies where the Penn investigator designed the trial and is serving as the lead investigator.
- Studies where all subjects are enrolled at Penn and the majority of research procedures are performed at Penn.

Whenever you have questions about whether Penn is willing to rely on an external IRB as the IRB of Record, please contact the Penn IRB to discuss the scenario before submitting a reliance agreement request through HS-ERA. Please contact any of the individuals identified as reliance agreement points of contact on the IRB website.

9. What is the process for executing a reliance agreement when Penn is relying on External IRB?

Please refer to the separate guidance document titled, "Reliance Agreement Guidance: How to Apply for External IRB Review" This guidance is available on the IRB website and it provides step by step instructions on the submission process.

10. 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 need 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, please check with the IRB of Record to determine how they want to document the use of the SMART IRB. There are multiple ways that this can occur:

- Letter from Penn indicating that we agree to rely on the IRB of Record per the terms of the SMART IRB
- Separate acknowledgment document signed by the Penn IRB
- Completion of an agreement using the SMART IRB Exchange or SMART IRB Online Reliance System

If you have any questions about which method to use or what should be included in your reliance agreement application to the Penn IRB, it is recommended that you contact the Penn IRB for assistance. Additional information on the SMART IRB agreement can be found in the Reliance Agreement Guidance: SMART IRB Agreement FAQ document.

11. When can I start enrolling subjects?

Having a fully executed reliance agreement and an approval from the IRB of Record means that you have IRB approval to conduct the research at Penn. 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 Penn Ancillary Review Committees (RRSC, IBC, CAMRIS, etc.)
- Execution of the clinical trial agreement or contract
- Completion of a prospective reimbursement analysis and the assignment of a research billing number
- Completion of a site initiation visit

12. Does the Penn IRB charge a fee to execute a reliance agreement?

The University of Pennsylvania IRB charges a fee for executing a reliance agreement for industry sponsored studies to cover the costs associated with the IRB's related administrative responsibilities. This is a one-time administrative fee. There are no fees associated with continuing reviews or modifications when a central IRB is serving as the IRB of Record

The current IRB fee schedule for studies funded under a contract requesting that Penn rely on an external IRB is the following:

- Initial Review fee (administrative fee only) = $500

Reminder of the process: The HSERA application will include an internal financial contract 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 further information or assistance, please contact Ed Fong in the IRB, at edfong@upenn.edu or 215-573-0791.

13. An ancillary committee is requiring changes to the study documents. Should I submit these documents to the Penn IRB?

The Penn Ancillary Review Committees are part of the University's Human Research Protections Program. Their review and approval requirements do not change when Penn has agreed to rely on an external IRB.
If an Ancillary Committee requires a change to the consent form or other study documents, those revisions should be sent to the IRB of Record for review and approval. You do not need to submit the revised documents to the Penn IRB for review.

Please note that if the Ancillary Committee requires changes to the HS-ERA application or an entity is requiring that these changes be reviewed by the Penn IRB, you can submit the changes via an HS-ERA modification submission. The Penn IRB will review and acknowledge any revisions. However, this process will not replace the central IRB's review and approval of the revisions.

Please be aware that some external IRBs consider the ancillary committee review process to be a part of the local context review and would prefer that those reviews occur before you submit any documents to the external IRB for review. Please make sure you follow the external IRBs preferred submission process to avoid confusion and unnecessary delays.

14. What is the process if my study requires review by the Conflict of Interest Standing Committee (CISC)?

The Conflicts of Interest Standing Committee (CISC) is a part of Penn's Human Research Protections Program. Their review requirements do not change when Penn has agreed to rely on an external IRB.

If your initial application indicates that a member of your study team has a potential significant financial interest that was disclosed through FIDES, the Penn IRB will not sign an IRB authorization agreement until after the CISC review has occurred and a management plan has been agreed to.

The Penn IRB will review the management plan and advise the investigator on whether a disclosure should be added to the informed consent form. The Penn IRB will also review the disclosure language as part of its administrative review.

After the management plan has been agreed to and the Penn IRB has reviewed any applicable disclosures, the study team will need to submit information about the financial interest to the external IRB. The specific information that will need to be shared varies based on the reliance agreement that was executed and the external IRB's conflict of interest

review policies. Typically, the central IRB will review the management plan and the informed consent form disclosure language when they approve the protocol.

It is strongly recommended that the investigator make himself or herself aware of the review policies for reliance agreements and the external IRB conflicts of interest before the reliance agreement is submitted to Penn.

15. I received amended study documents that have been approved by the central IRB. Do I submit these documents to the Penn IRB?

Probably not. Most study wide administrative and substantial amendments will be reviewed only by the IRB of Record. For these amendments you are not required to submit the documents to the Penn IRB for acknowledgement or provide the Penn IRB with the central IRB approval letter. These documents should all be filed in your regulatory binder.

If the IRB of Record asks you to forward these documents to the Penn IRB for review and acknowledgment, you may submit them to the Penn IRB by creating a modification using the HS-ERA submission system.

Please note that some modifications do require review by the Penn IRB. These requirements are described in the PI assurance document.

Please note that if the ancillary committees that reviewed your study require notification of protocol amendments, you must still fulfil those requirements. If the committees prefer that you submit these modifications through the HS-ERA modification submission system, you may submit the amendments to the Penn IRB for acknowledgment.

16. What modifications must be submitted to the Penn IRB for review?

If you revise the online application or the study documents that are related to the Penn IRB's review responsibilities, you should submit those modifications to the Penn IRB for approval. These include:

- Addition or removal of study personnel
- Any revisions or updates related to conflict of interest review
- Any changes that may be impacted by state or local laws

You should create and submit these modifications through the HS-ERA system.

17. I've received a continuing review approval letter and stamped consent form from the IRB of Record. What do I do?

You should submit these documents to the Penn IRB for review and acknowledgement. The Penn IRB will acknowledge these letters and update its tracking system to reflect the new approval period. The documents should be submitted to the Penn IRB via an HS-ERA modification. You are not required to complete the Continuing Review Form.

Please note that if your study is a greater than minimal risk biomedical research project, you may still be required to complete a PICA for site monitoring and quality assurance. If any issues are identified during the monitoring, it should be reported to the central IRB according to their policies regarding reporting deviations and reportable events

18. Can my IRB approval expire at Penn?

Yes. The Penn IRB approval tracking system will be aligned with the approval period set in the central IRB's approval letters. However, if you do not submit continuing review approval letters to the Penn IRB, the tracking system will not be updated and your IRB approval at Penn will expire. No research activities should occur at Penn during a lapse in approval.

Reminder emails will be sent from the IRB to the Principal Investigator in the same manner that reminders are sent for expedited studies where Penn is the IRB of Record.

Please be aware that if your study expires multiple times, the Penn IRB may decide to terminate the reliance agreement and assume primary responsibility for ongoing oversight of the trial at Penn. This would require initial IRB review of the study by the Penn IRB and, likely a suspension of study enrollment at Penn. The Penn IRB would work with investigators to determine the most appropriate course of action for any active subjects.

19. Where do I submit deviations, exceptions, and reportable events?

Deviations, exceptions, and reportable events should all be submitted to the IRB of Record according to their reporting requirements. The Penn IRB will not review these requests when an external IRB is serving as the IRB of Record unless the external IRB has requested Penn's review.

Study teams should familiarize themselves with the external IRB's policies on reporting deviations, exceptions, and reportable events. These policies may differ from the Penn IRB reporting requirements.

Please note that occasionally, the IRB of Record will reach out to the Penn IRB during their review of deviations and reportable events. In addition, if the study team would like clarification or assistance from the Penn IRB during these reviews, you should contact a member of the Penn IRB Reliance Agreement team.

20. What happens if the IRB of Record makes a noncompliance or unanticipated problem determination?

Per the terms of the reliance agreement, the IRB of Record will notify the Penn 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 IRB of Record to ensure that reporting requirements are met. In addition, the Penn IRB may conduct its own review of the events that occurred and the corrective action plan. The Penn IRB reserves the right to send a supplemental report to the FDA or OHRP detailing the results of its additional review.

In certain circumstances, the Penn IRB may assist the IRB of Record in implementing the IRB of Record's mandated corrective action plan. As each event is unique, the Penn IRB will make every effort to respond to questions and assist both the IRB of Record and the study team in resolving all identified issues. Please do not hesitate to contact the Penn IRB Directors if you have questions about review of deviations or unanticipated problems.

21. How do I close the study?

You should first submit a closure request to the IRB of Record for review and approval according to their submission procedures. Once the central IRB has closed the study, you should submit a copy of the closure letter to the Penn IRB via an HS-ERA modification. The Penn IRB will then review the closure notification and issue its own protocol closure document.

22. If I am relying on CHOP through a Penn/CHOP determination form, do I still need to submit through HS-ERA?

No. At this time, the process for reviewing Penn-CHOP cooperative review agreements is not changing. These submissions will be processed without an HS-ERA submission. Please be aware that changes to this process are expected in the near future. The IRB will announce those changes prior to their implementation.

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

Before any documents are provided to the Penn IRB for an administrative review, the protocol should undergo initial review by the CHOP IRB. That review should include a completed Penn/CHOP determination form.

Once CHOP approves the study, they should provide you with a signed copy of the Penn/CHOP determination form. At that time, the CHOP IRB will send the Penn IRB a copy of the determination form, the consent form and the study protocol. Once the Penn IRB received those documents, we will begin our review of the reliance agreement request.

After we have reviewed the documents, we will email the Penn Investigator identified on the Penn/CHOP determination form and let them know if there are any questions about the protocol. That email will likely include the following requests:

1. A list of the study team members who are affiliated with Penn
2. Confirmation as to whether there are any potential financial interests that require a disclosure to CISC
3. Any other questions that may come up related to the conduct of the study at Penn.

Regarding the consent form, it is important to note the following:

- If Penn will be considered a separate clinical site, we may ask for a Penn site specific consent form. You may use the CHOP consent form as a template and include the Penn specific template language as described in the Reliance Agreement Guidance: Requirements for External Consent Templates available on the IRB Website.
- If Penn is not a separate clinical site and you will be enrolling subjects with the CHOP consent form, please make sure the consent form describes Penn's role in the project and identifies Penn as an entity that may receive PHI.

Once the Penn IRB's administrative review is complete, we will issue an acknowledgment letter and provide you with a signed copy of the Penn/CHOP determination form. You are required to submit the fully executed agreement to the CHOP IRB through their electronic submission system.

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

Please contact any member of the IRB Reliance Agreement Team with any questions or issues you may have about the reliance agreement process.