# Reliance Agreement Guidance: Post-Approval Submissions when Penn is the Central IRB / Single IRB / IRB of Record

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This document is designed to provide guidance on the requirements and submission processes for Amendments, Continuing Review, Reportable Events, and Study Closure. It is expected that this document will be most helpful to research team members at Penn and at external sites that are relying on the Penn IRB as the single IRB (or IRB of Record) for their participation in a multi-site trial. 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. Submission Basics

The University of Pennsylvania IRB requires that all Continuing Review, Modification, Exception, Deviation, Closure, and Reportable Event submissions be created in the Penn HS-ERA electronic submission system. Only individuals with a Pennkey are able to access this system. Therefore, each study will need to identify a member of the study team that can serve as a Point of Contact to the other relying sites. This Point of Contact will compile information from the local sites and then create the submissions to the Penn IRB in the HS-ERA system. Study teams that rely on the Penn IRB should be provided with the Penn IRB guidance regarding reliance agreements. It is encouraged that relying study teams reference the Penn IRB website for information about reporting requirements throughout the study and to communicate regularly with the Penn point of contact.

If there are any questions during the submission process, relying site personnel can contact the study team's designated Point of Contact or Penn IRB staff. Information on the most appropriate Penn IRB staff to contact can be found on the How to Submit: Reliance Agreement Page of the Penn IRB website.

## 2. Reportable Events

A Reportable Event is an incident that has the potential to be classified by the IRB as an unanticipated problem posing risks to participants or others. In general, an incident is considered to be a Reportable Event when it is both (1) unexpected in terms of nature, severity, or frequency, and (2) related to participation in the research.

The Penn IRB requires investigators to submit reportable events for review within 10 working days of discovery. There is one exception to this requirement. If the reportable event involves a subject death that is unexpected and related to research participation, investigators are required to submit a report to the IRB within 3 days. If you do not have enough information to submit a complete Reportable Event submission within this timeframe, you must still submit a partial Reportable Event submission. Included in the partial submission should be an indication that a follow up report will be provided once additional information has been obtained.

For complete information about determining what events require reporting and when to report them, please review the How to Submit: Reportable Event Page of the IRB website. These same criteria apply for all sites relying on the Penn IRB.

The research team at the Relying Site where the event occurred should download and complete the Reportable Event form. Once completed, this form should be sent to the designated Point of Contact for submission to the Penn IRB through the HS-ERA submission system.

Please note that for timeliness of reporting considerations, the Penn IRB will not consider the report to be received until it has been submitted through the HS-ERA submission system. If you have any questions about the reporting requirements, please feel free to contact Penn IRB staff.

Occasionally, the Penn IRB will reach out to the local site IRB during the review of 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.

Per the terms of the reliance agreement, the Penn IRB will notify the local site IRB if it is found that the event qualifies as an unanticipated problem involving risks to subjects or others. If this determination requires 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 reportable events.

## 3. Protocol Wide Amendments

All amendments/modifications to currently approved research must be approved by the IRB prior to implementation, *except* when necessary to eliminate apparent immediate hazards to the human subjects.

When a modification to the protocol or other study documents is being applied to all study sites, the Penn research team will draft and submit the modification to the Penn IRB through the HS-ERA submission system. It is expected that

the research team Point of Contact will reach out to relying investigators and research teams to get their input on changes to the site consent forms and any other local considerations.

While uncommon, it is possible that a relying site may choose to implement a protocol amendment in a manner that differs from Penn or the other relying sites. If there are site specific changes to a protocol-wide amendment, the IRB should be informed of these changes. These alterations should be documented by revising that sites Participating Site Application Supplemental form. A tracked and clean version of that form can be included in the modification submission.

Once the research team Point of Contact has received feedback from the relying sites, the Point of Contact should create the modification submission in HS-ERA. The complete submission package should include:

- The completed Modification Application Form (this form is available on the forms page of the IRB website)
- A summary of changes document that outlines the requested changes and their rationale
- Tracked and clean version of all amended documents
- Any new documentation that is being submitted to the IRB for review
- Revised consent forms for each relying site
- If applicable, revised Participating Site Application Supplemental Forms

## 4. Site Specific Amendments

All amendments/modifications to currently approved research must be approved by the IRB prior to implementation, *except* when necessary to eliminate apparent immediate hazards to the human subjects.

Changes to site specific documents, such as contact information on the consent form or the addition of site-specific recruitment materials, must be submitted to the Penn IRB through the HS-ERA submission system. It is expected that the relying site investigator and research team will complete the modification application form, revise the necessary study documents and forward those documents to the designed Point of Contact who will create and submit the HS-ERA Modification application.

If the site-specific modification updates the information previously provided in the Participating Site Application Supplemental form, it is expected that a tracked and clean version of the supplemental form will be included in the modification.

Once the relying site team has compiled all the necessary documents, they should be sent to the research team Point of Contact. The Point of Contact should create the modification submission in HS-ERA. The complete submission package should include:

- The completed Modification Application Form (this form is available on the forms page of the IRB website)
- A summary of changes document that outlines the requested changes and their rationale
- Tracked and clean version of all amended documents
- Any new documentation that is being submitted to the IRB for review
- If applicable, revised consent forms for the relying site (tracked and clean)
- If applicable, revised Participating Site Application Supplemental Forms (tracked)

## 5. Deviations

A deviation is an unintentional action or process that departs from the IRB approved study protocol that is identified retrospectively (after the event occurred). All study teams should record, assess and develop corrective actions for all deviations that occur during the conduct of the research study. Deviations should be assessed in the context of the protocol and the Penn IRB reporting criteria to determine whether expedited IRB reporting is required.

Deviations can be categorized as major or minor. This categorization will affect IRB the reporting criteria:
Major deviations require separate expedited reporting to the IRB within 10 business days of their discovery.

A major deviation is a deviation from the IRB approved protocol, human research regulations, or human research university policies that adversely affects:

- the rights and welfare of participants, including actual or potential substantive harm, OR
- the scientific integrity of the study

These deviations require expedited reporting because they require an assessment of noncompliance by the IRB.

For additional information on what is considered a deviation, please view the Penn IRB SOPs or the How to Submit – Deviations page of the IRB website.

On the Forms page of the IRB website, there is a deviation report form. If any Deviation meets the expedited reporting criteria noted above, the team at the site where the deviation occurred should download and complete this form. Once completed, this form should be sent to the designated Point of Contact for submission to the Penn IRB through the HS-ERA submission system.

Please note that for timeliness of reporting considerations, the Penn IRB will not consider the report to be received until it has been submitted through the HS-ERA submission system. If you have any questions about the reporting requirements, please feel free to contact Penn IRB staff.

Occasionally, the Penn IRB will reach out to the local site IRB during the review of deviations. 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.

Per the terms of the reliance agreement, the Penn IRB will notify the local site IRB if it is found that the deviation qualifies as serious and/or continuing non-compliance. If this determination requires 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.

At the time of continuing review, each site is required to provide information about site deviations with their Relying Site Supplemental Form. Requirements for submitting deviations at Continuing Review are based on the monitoring plan designated by the protocol. The Penn site Point of Contact should review the protocol and provide clear instructions to

the relying sites about appropriately recording and reporting deviations at the time of continuing review. Please see section 7 below for complete information regarding requirements for deviation reporting at continuing review.

## 6. Exceptions

An exception request is a **prospective, one-time, intentional action** or process that departs from the IRB approved study protocol.

**Prospective**- This means that the study team plans to perform study activity outside of the parameters and procedures set forth in the IRB-approved protocol. If an exception is submitted to the IRB for approval after it has already taken place, it is then considered a deviation regardless of whether sponsor or other monitoring approvals were obtained in advance.

**Intentional**- An exception request will not be approved if it was unintentional. For example, if a subject is enrolled and later it is discovered that they met an exclusion criterion but will be allowed to continue on the study- this should be submitted as a deviation NOT an exception as this was not planned prospectively and was unintentional. Retrospectively submitting a deviation as an exception request will not be approved.

**One-time** request intended for a single occurrence- Each time an exception is to be implemented separate IRB approval must be obtained. If the same exception request is submitted multiple times for the same study, the IRB may suggest or require a change to the protocol to eliminate the need for repeat or common exceptions.

For additional information on what is considered an exception, please view the Penn IRB SOPs or the How to Submit – Exception page of the IRB website.

On the Forms page of the IRB website, there is an exception request form. The research team at the relying site where the exception will occur should download and complete this form.

If the exception does not need to be approved within 48 hours, then the completed exception request form should be sent to the designated Point of Contact for submission to the Penn IRB through the HS-ERA submission system.

If the exception request requires IRB review and approval within 48 hours, the relying site research team can email the request to the Penn IRB directly. The request should be sent to IRB Director, Associate Director, and Assistant Director. Contact information is available on the IRB website. It is also recommended that the research team designated Point of Contact also be copied on the email in order to ensure that appropriate documentation is completed after IRB review has occurred.

## 7. Continuing Review

Continuing Review is a process by which the IRB re-evaluates whether a protocol is being conducted in compliance with the criteria for approval that are applied during initial review. When continuing approval is required, review must occur at least annually (364 days from approval). The expiration date for a research study is noted in the original approval letter, subsequent renewal or modification letters and will be provided on stamped informed consent forms (if applicable).

If the study lapses in approval at any time, no research related activities may occur at any sites, unless the PI contacts the Penn IRB in advance, and it is determined that continuation during expiration is appropriate for subject safety. If any activity has occurred during the lapse in approval, those activities should be documented in the appropriate section of the continuing review form.

It is expected that the research team Point of Contact will reach out to relying investigators and research teams prior to the expiration date and ask them to complete the Continuing Review Relying Site Supplement form. This form is designed to obtain information from relying sites that is needed to compile a study wide progress report. The relying site investigators and teams should be prepared to give the Point of Contact information on the following:

- Information about enrollment, including a description of enrollment status, whether the study is open to enrollment, the number and status of enrolled subjects at the site, and information related to any subject withdrawals
- Information about study progress including a narrative summary of the study activities that occurred during the approval year, including notable comment on enrollment progress, subject experiences, any delays in study activities, and expected activities for the coming year
- Information about financial conflicts of interest for research staff.
- Information about Adverse Events (For research that is Greater Than Minimal Risk only). At the time of continuing review, the Penn IRB does not require summaries of adverse events that did not require expedited IRB reporting. Each relying site is required to assess each adverse event in real time in context of the protocol and the Penn IRB reporting requirements. At the time of continuing review each site will be asked to confirm whether the Penn IRB adverse event reporting criteria is being applied. The point of contact will prepare a summary within the progress report of any events that required expedited reporting according to the form instructions.
- Information about Deviations (For research that is Greater Than Minimal Risk only). As previously noted, all study teams should record, assess and develop corrective actions for all deviations that occur during the conduct of the research study. The Penn IRB requires different levels of reporting of deviations at continuing review depending on the protocol specified site monitoring plan for quality control and identifying deviations. The point of contact should be familiar with the protocol specified monitoring plan and communicate regularly with each site according to the Multi Site Management plan to ensure each site is recording deviations appropriately / consistently and is prepared to submit this information at the time of continuing review.

    A. If the protocol indicates that an external, sponsor designated, monitoring entity will conduct monitoring for quality control at all sites by reviewing study documents then the continuing review submission should only include a summary of any deviations that met the criteria for expedited reporting (if any).This summary would not require additional information from relying sites at the time of renewal. This summary would appear in the progress report and no additional deviation-related documents would be expected with the submission.

    B. If the protocol indicates that each site investigator and their team must internally monitor their site for quality control and identification of deviations, then the continuing review submission must provide the Penn IRB with detailed information about ALL deviations recorded at each site (regardless of whether they met the expedited reporting criteria). The IRB is willing to accept site deviation information in a variety of formats as long as the required information is present.

        - Narrative summary of deviations for each site described within the relying site supplemental CR form
        - Logs of deviations for each site submitted individually as a supplemental document
        - One compiled master log of all site deviations developed by the lead site

- Please note that required information for reporting deviations includes:
  - when each deviation occurred,
  - a description of each deviation,
  - the PI assessment of the effects of the deviations on subject's safety, rights, welfare and the integrity of the study data,
  - corrective actions put in place in response to each deviation or to prevent recurrence
- In addition to the site-specific deviation accounts, the progress report prepared by the point of contact must include an overall assessment of the total deviations to provide broader comment as instructed in the Single IRB CR Application form.

The research team Point of Contact will distribute the Continuing Review Relying Site Supplement. Once the research team Point of Contact has received the completed forms, the Point of Contact will complete the Continuing Review Application – Single IRB Version Form and provide an overall progress report that discusses activities across all sites. Those reports will be combined, and the Point of Contact will create and submit the Continuing Review application in HS-ERA.

## 8. Study Closure

A formal closure request should be submitted once study activity has been completed at a relying site. The IRB will approve a closure request if all subjects have completed study related visits and procedures, no further contact with subjects is needed for reasons related to the research and there is no further access to identifiable subject data for research purposes. In addition, if the study is industry sponsored, the close out visit should occur before submitting a closure request to the Penn IRB.

On the Forms page of the IRB website, there is a study closure form. The research team at the relying site requesting closure should download and complete this form. Once completed, this form should be sent to the designated Point of Contact for submission to the Penn IRB through the HS-ERA submission system.