RR 404 ONGOING REVIEW

1. PURPOSE

This section elucidates the policy for the continuing review that occurs after approval and prior to review for renewal of IRB approval.

2. POLICY

IRB approval may be withdrawn at any time if warranted by the conduct of the research. The regulations authorize the IRB to establish procedures for the concurrent monitoring of research activities involving human participants. Periodic (continuing or ongoing) review of research activities is necessary to determine whether approval should be continued or withdrawn. All non-exempt research involving human participants must be reviewed (renewed) no less than once per year.

No research related activities, including new subject enrollment, may occur after the protocol expiration date unless the PI contacts the IRB and it is determined that it is in the best interest of participants to continue during the lapse in IRB approval.

IRB approval for the conduct of a study may be withdrawn at any time if the risks to the participants are determined to be unreasonably high; for example, more than an expected number of adverse events, unexpected serious adverse events; or evidence that the investigator is not conducting the investigation in compliance with IRB or University guidelines. Such findings may result in more frequent review of the study to determine if approval should be withdrawn or enrollment stopped until corrective measures can be taken or the study terminated. Continuing review includes, but may not be limited to the following activities:

- Site Visits and Third Party Verification (3.1)
- Review of Unanticipated Problems Posing Risks to Participants or Others or any Other Reportable Events (3.2)
- Modifications (3.3)
- Review of Significant New Findings (3.4)
- Review Of Oversight And Monitoring Reports/Findings (3.5)
- Reports from Employees, Staff and Faculty (3.6)
- Reports of Serious or Continuing Noncompliance (3.7)
- Suspension or Termination of IRB Approval (3.8)

3. SPECIFIC POLICIES

3.1 Site Visits/Audits and Third Party Verification

The IRB has the authority to observe, or have a third party observe, the consent process of research it has approved, and to verify that the study is being conducted as required by the IRB
and within the University Policies and Procedures and site-specific procedures as appropriate. Under the direction of the Director, IRB personnel or members may perform site visits or use another party either affiliated with the institution or not, to verify information in the study application, or in any interim, continuing review or renewal submissions.

The IRB will consider the following criteria to determine if a site visit or third party verification process is required:

- The research involves vulnerable populations or high risk procedures.
- The investigator has a history of serious or continuing non-compliance related to continuing review in the past three years.
- The IRB has reason to doubt the veracity of the information provided by the investigator.
- The information provided by the investigator is inconsistent with other information known to the IRB and the inconsistency cannot be resolved through communication with the investigator.
- Any other reason where the IRB believes verification should be required.

Other means of verification; sponsors may be asked to submit copies of monitoring reports. The IRB may conduct interviews with screened and/or enrolled participants as deemed necessary.

### 3.2 Reportable Events, including Potential Unanticipated Problems Increasing Risks to Participants or Others

Consistent with federal regulations, the University of Pennsylvania requires reporting to the IRB potential unanticipated problems posing risks to participants or others. Potential unanticipated problems are: (1) unforeseen; and (2) indicate that participants are at increased risk of harm.

The IRB requires researchers to submit reports of the following within 10 days of the time the event becomes known to the study team with one exception. The one exception for prompt reporting within 10 days applies to death of a research participant as noted below.

#### 3.2.1 Adverse Event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is both unexpected and related to research procedures.

An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts);

An event is “related to the research procedures” if the event is deemed probably or definitely related.

If the adverse event involved death as unforeseen and indicates participants or others are at increased risk of harm, report in three days.

#### 3.2.2 Unanticipated adverse device effect. Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect,
problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

3.2.3 Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:

- An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
- Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
- A paper is published from another study that shows that an arm of the research study is of no therapeutic value.

3.2.4 Any adverse event that represents a serious unexpected problem that is rare in absence of drug exposure (e.g. agranulocytosis, hepatic necrosis, or Stevens-Johnson syndrome).

3.2.5 Adverse event that would cause the sponsor to modify the investigator’s brochure, protocol, or informed consent to assure the protection of human participants.

3.2.6 Withdrawal from marketing for safety concerns of a drug, device, or biologic used in a research protocol.

3.2.7 Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.

Other Reportable events

3.2.8 Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.

3.2.9 Deviations, meaning an accidental or unintentional change to the IRB approved protocol) that placed one or more participants at increased risk, has the potential to occur again, or has the potential to qualify as serious or continuing noncompliance.

3.2.10 Breach of confidentiality

3.2.11 Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.

3.2.12 Premature completion of a study.

When ICH-GCP (E6) applies:

Problems researchers have to report to the IRB include:
• New information that might affect adversely the safety of the participants or the conduct of the clinical trial.
• Any changes significantly affecting the conduct of the clinical trial or increasing risks to participants.

The IRB will accept other reports when the investigator is unsure whether the event should be reported, and the IRB will review such reports to determine whether the event qualifies as a reportable event requiring further review and whether review by the convened board is necessary.

Principal investigators will submit a written report of the above events. Initial reports may be accepted by other means such as e-mail, or phone when necessary to ensure prompt reporting with a follow up written report.

For a reportable event requiring convened review to determine if the event is an unanticipated problem, the IRB Administrator selects the primary reviewer. When, possible the IRB member assigned to the initial primary review will review the event. Otherwise, reviewers will be selected based on their education, experience, and areas of expertise.

For reportable events deemed not to meet reporting criteria or to be no more than minimal risk, these should be summarized at the time of continuing review and IRB members/reviewers will review these events in aggregate and comment, if necessary.

Primary reviewers will have access to, as applicable, the sponsor protocol, investigator brochure, original IRB application form, consent document, event summary, and any other supplemental information required to complete the review.

All other IRB members will have access to the original application form; consent document, event summary, and any other supplemental information require completing the review.

The IRB may request a consultant opinion or engage the division or department chair to collect additional information on the event.

The IRB considers the following actions:

- Accept report or with no additional requirements
- Approve investigator’s proposed changes
- Administrative hold on the study pending IRB receipt of further information
- Modification of the protocol
- Modification of the information disclosed during the consent process
- Providing additional information to current participant the information may relate to the participant’s willingness to continue participation
- Making arrangements for clinical care outside the research or additional follow-up for participants
- Providing additional information to past participants
- Requiring current participants to re-consent to participation
- Observation of the research or the consent process
- Requiring additional training of the investigator
- Notification of investigators at other sites
- Obtaining additional information
- Termination or suspension of the research

When determining if the event qualifies as an unanticipated problem requiring external reporting, the following criteria are applied for DHHS regulated research:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

3.3 Modifications

Federal regulations require that all modifications in approved research, during the period for which approval has already been given, may not be initiated without prior IRB review and approval except where necessary to eliminate apparent immediate hazards to human participants. Sometimes modifications are noted or recognized after they occur. These changes will be reviewed by the IRB as events that may qualify as noncompliance and to determine whether the change was consistent with ensuring the participants’ continued welfare.

3.3.1 The IRB categorizes modifications into 3 types: Amendments, Deviations, and Exceptions that require reporting to the IRB.

Amendment

An amendment is a permanent, intentional action or process that revises/amends/modifies a previously approved research protocol. Information relating to protocol amendments will be provided to research participants when the information may relate to their willingness to continue to be a part of the research. Investigators or sponsors must submit requests for
changes to the IRB. Upon receipt of the protocol amendment, an IRB Administrator with the assistance of the Director, Associate Director, Assistant Director or Senior IRB Administrative staff determines the appropriate level of review.

Electronic protocols will have any revisions submitted via HS-ERA.

The IRB Modification Review Guidance provides direction that the IRB staff may utilize when preparing modifications for convened IRB review.

Minor modifications are defined as those that do not materially affect an assessment of the risks and benefits of the study and do not substantially change the specific aims/design of the study. Representative minor modifications include but are not limited to:

- The addition of research activities that would be considered exempt or expedited if considered independent from the main research protocol;
- A minor increase or decrease in the number of participants;
- Narrowing the inclusion criteria;
- Broadening the exclusion criteria;
- Changes to the dosage form (e.g. tablet to capsule or oral liquid) of an administered drug (when the dose and route of administration remain constant);
- Decreasing the number of biological sample collections, provided that such a change does not affect the collection of information related to safety evaluations;
- An increase in the number of study visits for the purpose of increased safety monitoring;
- A decrease in the number of study visits, provided the decrease does not affect the collection of information related to safety evaluations;
- Changes to improve the clarity of statements or to correct typographical errors, provided that such a change does not alter the content or intent of the statement;
- The addition or deletion of qualified investigators;
- The addition or deletion of study sites;
- Minor changes specifically requested by other University Committees with jurisdiction over research.

**Exception**

A prospective, one time, intentional action or process that departs from the IRB approved study protocol, intended for one occurrence.

Exception requests shall be submitted through HS-ERA for electronic protocols. Time sensitive exception requests requiring approval within 24 hours should be submitted via email and must include the IRB exception request form.
The IRB Exception Request Guidance provides direction for submitters when preparing exception requests for IRB review.

Upon receipt of an exception request, an IRB Administrator with the assistance of the Director, Associate Director, Assistant Director or Senior IRB Administrative staff determines the appropriate level of review. An IRB Chair will be consulted as needed.

The level of review required for exception requests (expedited or convened) is dependent upon the following factors:

- The time sensitivity of the request
- The level of risk involved in both the study itself and the planned alteration.
- Whether the exception request is thought to be in the best interest of the subject
- Whether the exception request holds out the prospect of direct benefit to the subject
- Whether the risk/benefit ratio specifically related to the exception request is favorable

The following exception requests are eligible for expedited review:

- Exception requests where the planned exception poses no more than minimal risk to the subject
- Exception requests where the planned exception may pose greater than minimal risk to the subject but the request is time sensitive and
  - The exception is in the best interest of the subject and/or the prospect of direct benefit exists
  - The risk/benefit ratio for the proposed exception request is favorable

The following exception requests will require convened IRB review:

- Exception requests where the planned exception may pose greater than minimal risk to the subject and any of the following apply:
  - It is unclear whether the exception is in the subject's best interest or whether there is the prospect of direct benefit to the subject
  - It is unclear whether the risk/benefit ratio is favorable
  - The request is not time sensitive and there is sufficient time to allow convened IRB review to occur

**Deviation**

An unintentional action or process that departs from IRB approval and is identified retrospectively. The deviation is reportable to the IRB within 10 days from the time the event becomes known to the study team only when: one or more participants were placed at increased risk of harm, or, the event has the potential to occur again, or the event has the potential to qualify as serious or continuing noncompliance.

When the IRB reviews the exceptions and deviations, a determination will be made as to whether information related to protocol changes should be provided to participants when such information might relate to their willingness to continue to take part in the research.
Supplemental materials, e.g. an addendum consent form, telephone script or participant letter may be required by the IRB.

### 3.4 Significant New Findings

During the course of a study, the IRB may review reports generated from the DSMB, adverse events, current literature, and other sources to ascertain the status of the study and assess whether or not the risk/benefit balance is still acceptable, whether or not new information needs to be conveyed to participants, or if a segment of the population may be bearing an undue burden of research risk or being denied access to promising therapy. Such significant new findings will be reviewed by the IRB chair, Director or other designated IRB members who shall decide whether such new information merits review by the IRB.

### 3.5 Review Of Oversight And Monitoring Reports/Findings

For studies that operate with a monitoring plan that includes oversight by a DSMB or equivalent (DMC, DRC, DSMC, etc...) the IRB requires copies of reports to be submitted at the time of original receipt from that entity. Submission of these reports may result in follow up correspondence or official submissions to ensure compliance with DSMB recommendations. Additionally, at the time of Continuing Review, the following processes are implemented:

For greater than minimal risk biomedical research currently enrolling subjects- Study teams are required to submit a monitoring summary with their continuing review which provides an assessment of the outcomes of the approved plan for monitoring/auditing which took place during the approval year.

### 3.6 Reports from Employees, Staff and Faculty

It is the responsibility of the investigative team, medical staff, nursing staff, or any other employee of this institution to promptly report to the IRB any findings, results, occurrence, or new information about a study being conducted at any facility under the jurisdiction of the IRB that could affect the rights and welfare of research participants. It is the responsibility of the IRB staff and members to act on any such information in order to protect research participants.

### 3.7 Reports of Serious or Continuing Noncompliance Federal Regulation; or the Requirements or Determinations of the IRB

Reports of serious or continuing noncompliance or the requirements or determinations of the IRB will be handled in accordance with SOPs 408 and 409.

### 3.8 Suspension or Termination of IRB Approval

A decision to suspend or terminate a protocol must include an explicit consideration for the rights and welfare of participants already enrolled in the study. If the suspension or termination is imposed on the investigator, an IRB Chair may be consulted about whether and how to continue the care of enrolled participants. The matter will be discussed at the next convened meeting of the IRB.

Any suspensions or terminations of approval shall include a statement of the reasons for the IRB’s action and shall be promptly reported by the IRB to the investigator, any appropriate
compliance offices, and Institutional Official. The timeframe for notification to the institutional official, sponsors, and regulatory agencies will depend on the urgency of the matter. Situations presenting immediate, unforeseen risk to participants will be reported immediately to the institutional official and sponsors. When the research is sponsored or supported by the Department of Health and Human Services, the Institutional Official, or authorized designee, will notify OHRP. For FDA regulated research, the Institutional Official, or designee, will notify FDA in writing after the IRB has made a final determination.

Enrolled participants will be notified if a protocol in which they are enrolled is suspended or terminated. The IRB will determine at a convened meeting how and when the notification will take place. The IRB will consider whether to notify former participants.

4. REFERENCES


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