RR 404 CONTINUING 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

No investigator has a right to conduct research within this institution. Rather, it is a privilege granted by society as a whole and the Trustees of the University of Pennsylvania in particular.

IRB approval may be withdrawn at any time if warranted by the conduct of the research.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 subjects. 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(continuing or ongoing) review of research activities is necessary to determine whether approval should be continued or withdrawn.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 subjects must be reviewed (renewed) no less than once per year.

**No research related activities may occur after the protocol expiration date unless the PI contacts the Office of Regulatory Affairs, IRB and the Executive Chair (or authorized designee) determines that it is in the best interest of subjects 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IRB approval for the conduct of a study may be withdrawn at any time if the risks to the subjects are determined to be unreasonably high.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 Such findings may result in more frequent review of the study to determine if approval should be withdrawn or enrollment stopped until corrective measures can be taken or the study terminated.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
- Review of Serious and Unexpected Adverse Events and Unanticipated Problems Posing Risks to Subjects or Others
- Review of Significant New Findings
- Modifications

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 IRB Associate 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 subjects as deemed necessary.

3.2 Unanticipated Problems Involving Risks to Subjects or Others and Other Reportable Events

Consistent with federal regulations, the University of Pennsylvania requires reporting to the IRB of unanticipated problems posing risks to subjects or others. 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 problems within 10 working days 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 an unexpected death; and other participants or others may be at increased risk of harm, the investigator is required to report the death to the IRB within 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 subjects.

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 (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 subjects.

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 Violation, meaning an accidental or unintentional change to the IRB approved protocol) that placed one or more participants at increased risk, or has the potential to occur again.

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.
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 meets the threshold for an unanticipated event presenting risk to the participant.

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 with a follow up written report.

The IRB staff, when necessary in conjunction with the IRB chair, review reports and decide whether the event meets the definition of an unanticipated problem increasing risks to subjects or others.

Events that meet these criteria will be considered unanticipated problems involving risks to participants or others, will be reviewed by the convened IRB, and will be reported according to CO 602.

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.

Primary reviewers will receive the sponsor protocol, investigator brochure, original IRB application form, consent document, copy of the report form, any supplemental information.

All other IRB members will receive the original application form, consent document, copy of the report form, any supplemental information.

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 from the PI in a time period not to exceed 90 days.
- 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.
- Alteration of the frequency of continuing review.
- 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. If this action is taken, the IRB Executive Director will notify the Institutional Official to initiate any reporting actions. If the IRB does not consider the event to represent an unanticipated problem involving risks to participants or others, no further action needs to be taken.

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 subjects. Sometimes modifications are noted or recognized after they occur. These changes will be reviewed by the IRB as events that may represent unanticipated problems involving risks to participants or others 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 subjects 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 in writing. Upon receipt of the protocol amendment, an IRB Administrator with the assistance of the IRB Executive Chair, or Senior IRB Administrative staff determine the appropriate level of 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 in remuneration;

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

If the action disrupts the study progress, such that the study design and results would be compromised, and the action compromises the safety and welfare of study subjects, prior documented IRB approval is required.

**Deviation**

A one time, unintentional action or process that departs from the IRB approved study protocol, involving one incident and identified retrospectively, after the event occurred. If the impact on the protocol disrupts the study design or compromises the safety and welfare of the subjects, the deviation must be reported to the IRB within 10 business days.

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. The investigator will be advised if subjects need to be informed.

**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 subjects, 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 Executive Chairperson, chairperson or their designee who shall decide whether such new information merits review by the IRB.

3.5 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 subjects. It is the responsibility of the IRB staff and members to act on any such information in order to protect research subjects.

3.6 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.

3.7 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 subjects already enrolled in the study. If the suspension or termination is imposed on the investigator, the IRB Executive Chair may be consulted about whether and how to continue the care of enrolled subjects. 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, IRB Executive Chair 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 subjects 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 will notify OHRP. For FDA regulated research, the Institutional Official will notify FDA in writing after the IRB has considered the matter at the next convened meeting.

Enrolled subjects 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 subjects if the reason for termination or suspension was associated with risks not disclosed in the consent process.

4. REFERENCES

45 CFR 46.103; 21 CFR 56.108; 45 CFR 46.109; 21 CFR 56.109; 45 CFR 45.115;
21 CFR 56.115; OHRP Guidance on Continuing Review, January 15, 2007; FDA Information Sheets, Continuing Review after Study Approval; OHRP Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others, January 15, 2007; FDA Final Guidance on Adverse Event Reporting to IRBs, January 2009

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