IRB Policy and Procedure Number:  
Version Number:  
Effective Date:  
Title: Continuing Review Policy and Procedures  

Purpose  
To provide a policy and procedure for the research community and the Princeton University Institutional Review Board (IRB) for continuing review and approval of previously approved research. This policy also addresses the procedures which the IRB will follow for determining which projects require review more often than annually. Continuing review is a monitoring tool to ensure that ongoing safeguards are in place to protect the rights and welfare of human subjects enrolled in research studies.  

Regulatory Background  
The Department of Health and Human Services (DHHS) regulations (45 CFR 46.109(e)) require continuing review of ongoing research at intervals that are appropriate to the level of risk for each non-exempt research, but not less than once per year (45 CFR 46.103(b)(4)(ii). During continuing review, the IRB will consider any new information, re-assess the informed consent process and any newly submitted changes to the research to assure that, among other things, risks to subjects are being minimized and are still reasonable in relation to anticipated benefits, if any, to the subjects and the knowledge that is expected to result.  

Investigators may not continue any research activity beyond the expiration date without IRB approval. The IRB must review and approve all human subject research studies that are not exempt at intervals appropriate to the degree of risk, at least once per year, as required by 45 CFR 46.  

Continuing review of research must occur as long as the research remains active for long-term follow up of participants, even when the research is permanently closed to the enrollment of new subjects and subjects have completed all research-related interventions. Continuing review of research must occur even when the only remaining research activities are analysis of individually identifiable private information.  

Scope  
This policy and procedure applies to all Investigators, including students, conducting human research under the jurisdiction of the Princeton IRB.  

Responsibilities  
Principal Investigator: Investigators are responsible for submitting continuing review requests at least 30 days prior to the expiration date, to ensure the IRB has sufficient time to review the continuation request. Investigators are responsible for providing all continuing review materials as well as a separate Modification Request Form for any proposed changes.  

IRB Administrator(s): Staff will make a preliminary determination about whether a continuing review request should undergo expedited or full Committee review. IRB staff will perform preliminary
reviews of continuing review documents to ensure completeness of the submission and request additional information as appropriate. Staff will also aid the IRB Committee in identifying important issues and concerns that should be considered during review.

IRB Member(s): IRB members are responsible for assessing the continuing review and related information to ensure that the research continues to meet the criteria for approval, that new information or study materials, if any, do not change the risk/benefit ratio and that the informed consent process continues to be adequate. The IRB member(s) make the final risk assessment and determine whether the continuing review should be reviewed through expedited or full Committee review procedures.

Definitions

Minimal Risk: Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Unanticipated problems involving risk to participants or others: Unanticipated problems involving risks to participants or others refer to any incident, experience, outcome, or new information that:
1. Is unexpected
2. Is related or possibly related to participation in the research, and
3. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Policy

Determining the Frequency of Continuing Review
The Princeton IRB will determine the frequency of continuing review for each research project to ensure continued protection of human subjects in research. The IRB will consider the following factors when deciding on an appropriate interval for continuing review:

- The nature of any risks posed by the research project;
- The degree of uncertainty regarding the risks involved;
- The vulnerability of the subject population;
- The experience of the Investigators in conducting research;
- The IRB’s previous experience with the Investigators (e.g., compliance history, previous problems with the Investigator obtaining informed consent, or prior complaints from subjects about the Investigator);
- The projected rate of enrollment; and
- Whether the research project involve novel interventions.

At the time of initial review of a research project, the IRB will determine and specify the duration of the approval period along with the interval by which continuing review must occur (e.g., 4 months, 6 months, or 1 year) in order for the research to continue. During the time of continuing review, the IRB will consider whether the current frequency of review for the research study is adequate or should be adjusted. This will be documented in a notice of approval and correspondence to the
Investigator(s) (45 CFR 46.103(b)(4) and 46.109(d)).

For example, if the Princeton IRB initially approved a research study for a period of a year and at the first annual continuing review determined that the risks posed to the subjects have increased significantly, the IRB will re-approve the project after determining that the criteria for approval under 45 CFR 46.111 remain satisfied, but require that the next continuing review occur in 6 months.

Procedure

It is the Investigator’s responsibility to ensure that continuing review requests are submitted for review in advance of the expiration date. As a courtesy, the IRB Office will send out reminder notices to Investigators at least 6 weeks before the expiration date.

Investigators must submit the following materials for continuing review:

- The initial IRB application document, updated with changes that were reviewed and approved during previous year.
- If amendments are being proposed, a separate Modification Request Form must be submitted and include
  - a highlighted or/track changed version of the revised documents/study materials
  - any new materials for IRB review.
- Currently approved consent document(s) and as well any proposed changes to the consent document(s).
- Any report of an unanticipated problem and relevant information received since the date of the last IRB review of the research project. This may include information from any monitoring entity (e.g., a data and safety monitoring board (DSMB), data monitoring committee (DMC), etc.)

Each continuing review request with supporting documentation will receive either full board or expedited review. Studies which have exempt status at Princeton are not required to undergo continuing review.

For full and expedited review, the IRB members will each receive the above documentation. IRB members will be given access to all IRB records related to the research, including those associated with the initial review and approval, and any other pertinent information associated with previous reviews. For continuing review of research at a convened meeting, IRB members should receive appropriate materials sufficiently in advance of the meeting to allow adequate time for review.

Continuing review requests reviewed through expedited review procedures must be minimal risk and fall into categories (2) through (7) of the categories for expedited review procedures (45 CFR 46.111).

Protocols that were not eligible for expedited review procedures during initial review will not qualify for an expedited review procedure at the time of continuing review, except in the following limited circumstances when the research involves only activities described by categories for expedited review procedures (8) or (9); that is,
Under category (8), an expedited review procedure may be used for the continuing review of research previously approved by the IRB at a convened meeting as follows:

- (a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; OR
- (b) Where no subjects have been enrolled and no additional risks have been identified; OR
- (c) Where the remaining research activities are limited to data analysis.

Under category (9), an expedited review procedure may be used for the continuing review of research previously approved by the IRB at a convened meeting that meets the following conditions:

- The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE);
- Expedited review categories (2) through (8) do not apply to the research;
- The IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk to the subjects; and
- No additional risks of the research have been identified.

It is also possible that research activities that previously qualified for expedited review may subsequently require full board review upon continuing review.

Key Considerations when Evaluating Research Undergoing Continuing Review

- Criteria for IRB Approval - In order to re-approve research at the time of continuing review, the IRB must determine that all criteria for approval have been met (45 CFR 46.111) See Initial Review Procedures.

- Risk Assessment and Monitoring - the IRB will consider whether there is any new information provided by the Investigator or available to the IRB, that would alter the IRB's previous conclusion that the criteria for approval have been met.
  - When appropriate, the IRB must confirm that provisions established for monitoring the research data ensure safety of subjects have been implemented and are working as intended.
• Adequacy of the Informed Consent Process - the IRB will review a copy of the informed consent document submitted by the Investigator to verify that the Investigator is using the most recently approved version and that the document contains the most accurate, up-to-date information about the research.

  o If the requirement for consent or documented consent has been waived, the IRB must assess the accuracy of the consent of the information being provided to subjects orally and of any written statement regarding the research that is being provided to subjects.

**Approving Research at the Time of Continuing Review:**
The Princeton IRB can take any of the following actions at Continuing Review:

- Approved
- Conditional Approval
- Approved with Stipulation
- Deferred
- Disapproved*
- Tabled**

(Note: See Initial Review Procedures for fuller description of IRB actions)

When approving research with conditions at the time of continuing review, the IRB will specify whether any conditions need to be satisfied before an Investigator can continue specific research activities related to those conditions. For example, if at the time of continuing review, the IRB requires the Investigator to change the research protocol to include a specific new procedure for screening prospective subjects, the IRB can approve the research with the condition that research activities involving currently enrolled subjects may continue, but no new subjects may be enrolled until a designated IRB member reviews a revised protocol and verifies that the protocol includes the new screening procedure.

The IRB may designate the IRB chairperson (and/or other individual(s) with appropriate expertise or qualifications) to review the Investigator’s response to modification requests during review and determine that the conditions have been satisfied. Further review by the IRB at a subsequent convened meeting would not be necessary.

* Research cannot be disapproved by expedited review
** Convened IRB review of the investigator’s response(s) is required
Lapses in Continuing Review:
As noted above, the regulations permit no grace period or extension of approval after approval has expired. Research that is conducted after the approval period has expired is conducted without IRB approval.

If a continuing review for a study is not approved by the expiration date IRB approval expires automatically:

- All research activities must stop, including recruitment, enrollment, consent, research interventions, data collection, etc., unless the IRB finds that it is in the best interests of individual subjects to continue participating in research interventions (such as in ongoing drug studies).
- The IRB administrative staff will immediately notify the Investigator of the approval expiration and that all research activities must stop.

Once approval has expired, IRB review and approval must occur prior to commencement of study procedures. If the study approval has lapsed more than 90 days and the Investigator has not provided the required continuing review information, the study may be administratively closed and the Investigator must submit a new IRB application for review. Such closure may require the Investigator to notify the research sponsor. If study approval has lapsed 30 days or less, the Investigator must provide the required continuing review information, as well as an assurance statement that no study procedures occurred during the period of expiration.

References
Princeton University - Initial Review Procedures
OHRP - Guidance on IRB Continuing Review of Research
OHRP - Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure
http://www.hhs.gov/ohrp/policy/expedited98.html
OHRP - Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events
http://www.hhs.gov/ohrp/policy/advevntguid.html
OHRP - Guidance on IRB Approval of Research with Conditions

Version History

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