Continuing Review

Introduction
The Department of Health and Human Services (DHHS) has specific regulations regarding IRB continuing review of ongoing research to ensure that the rights and welfare of human subjects are protected. They require both that the IRB conduct the continuing review at intervals appropriate to the degree of risk, but not less than once per year (45 CFR 46.109(e)), and for the review to be substantive and meaningful.

The aims of continuing review are to reappraise the research to:

- consider whether the risk/benefit ratio is still acceptable;
- determine if the measures taken to safeguard subjects are adequate;
- assess whether the approved protocol is being followed;
- verify that the protocol reflects changes in the regulations for human subjects’ research that have been implemented since the last approval;
- review the progress of the protocol since last review and the plans for the future based on the progress to date;
- review adverse events or unanticipated problems that occurred since the last review; and
- evaluate new significant findings that might relate to a participant’s willingness to continue and which should be disclosed to participants.

Although the IRB is required to perform a continuing review at least annually, the IRB can require a continuing review more frequently and at any time.

Definitions

Continuing Review is periodic review of research activities necessary to evaluate the progress of the study and to determine whether the risk/benefit ratio has changed, whether there are unanticipated findings involving risks to participants or others, and whether any new information regarding the risks and benefits should be disclosed to participants. Continuing Review includes, for example, regularly scheduled review before study expiration as well as reviews of amendments, unanticipated problem reports, and reports from audits and data safety monitoring boards.

Full Board Review is review of research involving human subjects conducted by the full IRB Board at a convened meeting where quorum is present and is in accordance with the requirements set forth in 45 CFR 46.108.

Expedited Review is review of research involving human subjects by the IRB Chair, a Vice Chair, or by one or more experienced IRB members. Expedited Review can only be used for protocols that meet the criteria for expedited review and approval as defined in the federal regulations.
**Experienced IRB Member** is an IRB member who has actively served for at least 6 months, is certified in Human Subjects’ Protections under the CWRU Continuing Research Education Credits program and demonstrates a high level of understanding of the human research protection regulations with an ability to appropriately apply the regulations to research involving human subjects and is sensitive to the range of IRB discussions and resolution of controversial issues related to IRB reviews.

**Administrative Hold**: An IRB protocol is on Administrative Hold if the continuing review materials or required revisions are not approved by the expiration date determined by the IRB. Per 45 CFR 46, no further work on the protocol may take place after the expiration date unless the appropriate materials are submitted to, and approved by the IRB.

**Minimal Risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves that those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102 (i)).

**Expiration date** is the last day that a protocol maintains its IRB approval. For example, an IRB approval letter that indicates that a protocol expires on “2/1/2015” is active until 11:59 on 2/1/2015 and no longer has IRB approval on 2/2/2015 if continuing review has not been obtained.

**Policy Criteria for IRB Review Process**
All ongoing research protocols are periodically re-reviewed in accordance with federal regulations. The continuing review is conducted no later than 364 days after the previous approval unless the research has been determined to be Exempt from IRB review.

All ongoing research must receive continuing review even when the research remains active only for long-term follow-up of participants (even when the research is permanently closed to the enrollment of new participants and all enrolled participants have completed the research-related interventions) and when the remaining research activities are limited to data collection.

Continuing review must occur until all data are de-identified. This includes destroying the master list.

**Full Board Review**
*Research protocols that were initially or previously reviewed by a convened meeting*
All IRB members will have access to all the study documentation, including: the continuing review application, the current informed consent document, any newly proposed consent documents and revised research plan, the complete protocol including any protocol modifications previously approved by the IRB and a status report on the progress of the research.

Access to additional information in the IRB protocol file is available either in hard copy or in the iRIS electronic IRB system. The IRB Director or designee will make these items available for review upon their request. In addition, all IRB members may come to the IRB office at any time
before and after the meeting, to review the complete IRB protocol file, meeting minutes, and any other study information.

The Board may require certain projects, as determined by an evaluation of the risk-benefit ratio, to be reviewed more frequently than yearly. For example, this can be either after a fixed period of time such as at six months or after a certain number of subjects have been enrolled or studied (an expiration date will also be set). The expiration date for an IRB approved study is clearly indicated on the IRB approval letter and is the last day that the study is approved.

The minutes of the IRB meetings will document separate deliberations, actions, and votes for each protocol undergoing continuing review. The rationale for any requested revisions must be documented. The minutes of IRB meetings will reflect the IRB’s determination regarding which protocols require continuing review more often than annually. The minutes will reflect any change in the level of risk (e.g., minimal or greater than minimal). All requested changes and/or requests for additional information will be communicated to the principal investigator.

**Expedited Review**
Research protocols that were initially reviewed using the expedited review process may receive continuing review on an expedited basis, unless the previously met criteria in 45 CFR 46.110 has changed. The expedited review procedure is conducted by the IRB Chair, Vice Chair or an experienced member of the IRB designated by the IRB office, with the assistance of the IRB Manager. When reviewing research using the expedited procedure, the reviewers utilize the same information provided at Full Board review, as outlined above.

**Protocols that Originally Underwent Full Board Review but Qualify for Expedited Continuing Review**
Research protocols initially reviewed by a convened IRB but meeting one of the following criteria may also qualify for expedited review at continuing review:

- **Subject Follow-up Only**: The research is permanently closed to enrollment of new participants, all participants have completed all research-related interventions, and the research remains active only for long-term follow-up of participants.
- **Delayed Start**: When no subjects have been enrolled at CWRU and no additional risks have been identified.
- **Data Analysis Only**: The remaining research activities are limited to data analysis.
- **Prior Board Approval for Expedited Continuing Review**: Studies that met the criteria for expedited review but, by the option of the IRB Chair, were initially reviewed at a Board meeting or are minimal risk but not clearly in one of the approvable expedited review categories can receive expedited continuing review if expedited continuing review was approved by the Board at the time of the convened Board review and documented in the minutes (Category 9).

**Criteria for Continuing Approval**

**IRB Responsibilities**
Continuing review must be substantive and meaningful and must follow the same approval criteria as that for initial review. The IRB must determine that all of the following requirements are satisfied (45 CFR 46.111):
Risks to subjects are minimized (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; and (ii) whenever appropriate, by using procedures already being performed on subjects for diagnostic or treatment purposes.

Risks are reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result.

Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it is conducted.

Informed consent will be sought from each prospective subject or the subject’s legally authorized representative in accordance with 45 CFR 46.116.

Informed consent will be appropriately documented in accordance with 45 CFR 46.117.

The research plan appropriately monitors the data collected to ensure safety of subjects.

The subject’s privacy is appropriately protected and confidentiality of the subject’s data is maintained.

Appropriate safeguards are included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, decisionally impaired, mentally disabled persons, or economically or educationally disadvantaged persons.

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires independent verification that no material changes or other problematic events have occurred during the IRB-designated approval period. In these situations, the IRB will utilize sources other than the investigator.

The IRB will consider the following factors in determining which studies require such independent verification:

- The probability and magnitude of anticipated risks to subject
- The likely psychological condition of the proposed subjects
- The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed
- Prior experience with the Responsible Investigator and research team
- Any other factors that the IRB deems relevant

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review.

When reviewing the continuing review submission, the IRB ensures the following:

- That all informed consent document(s) are still accurate and complete.
- All significant new findings that arose from the continuing review process and relates to a participant’s willingness to continue participation, are provided to participant by the Responsible/Principal Investigator.

**Investigator Responsibilities**

Research approved by the IRB may only continue for the approved duration set by the IRB. The Continuing Review submission must include detailed information about the progress of the
study, the number and type of participants enrolled since the last approval, a summary of protocol events and deviations (if any), a report of subject complaints (if any), and a review of any significant, relevant literature published since the last approval. If any changes are proposed since the last IRB review, the amendment should be described and the revised documents submitted.

All significant new findings that arise from the continuing review process and relates to a participant’s willingness to continue participation must be provided to participant by the Responsible/Principal Investigator.

**Continuing Review**

Continuing review must occur until data collection and data analysis on identifiable data are complete. However data analysis (not data collection) can continue after study termination if the data are de-identified. The continuing review form must be complete, informative, succinct, and must address the following:

- Summary of enrollment activity
- The total number of participants
- The number of participants enrolled since the last review.
- The number of participants to be enrolled in the coming year.
- The number of participants that have withdrawn from the study and the reason for their withdrawal.
- A summary since the last IRB continuing review of all adverse events; unanticipated problems involving risks to participants or others; and protocol deviations.
- For adverse events, the description should also include:
  - The seriousness of the events, i.e., death, serious, or non-serious.
  - Whether the events were expected or unexpected.
  - Whether the events were study related, possibly study related, not study related, or unknown relation to the study.
  - Whether the frequency, severity or specificity of adverse events has changed.
  - For external adverse events, a statement regarding whether the events affect the conduct of the research (e.g. risks; benefits; alternatives).
- A summary of subject complaints.
- Problems associated with the recruitment of participants.
- A summary of the study findings, including results and publications; and an assessment as to whether the risks and benefits of the research have changed.
- Any relevant publications/data that would affect the risk/benefit ratio.
- A change in investigator conflict of interest.
- A description of approved amendments since the last review.
- A description of the plans for the coming year.

**Informed Consent Documents**

The current approved informed consent documents, along with any revisions submitted at the time of continuing review, will be reviewed by the IRB to ensure that the information is still accurate and complete, and that subjects are fully informed of the risk and benefits associated with the research. Any significant new findings that may affect the participants’ willingness to continue to participate must be disclosed in an updated informed consent document.
Amendments to Protocol Submitted at the Time of Continuing Review

Amendments or revisions to a research protocol, including informed consent documents, may be submitted at the time of continuing review. All the appropriate documentation addressing the amendment must accompany the submission. The IRB must review and approve an amendment prior to its implementation.

Expiration of IRB Approval

The federal Regulations (45 CFR 46.109(e)) and the CWRU IRB do not allow for the conduct of research beyond the protocol expiration date. The investigator is responsible for ensuring that the research is submitted to the IRB for continuing review in an appropriate time frame, in order to avoid a lapse of IRB approval. The continuing review deadline and the protocol expiration dates are listed on the protocol approval letter and in iRIS. In order to avoid a lapse in IRB approval, the investigator is encouraged to plan ahead to meet the deadline specified by the IRB.

The iRIS system will indicate when a protocol is ready to expire and will automatically send courtesy notices at 90-day, 60-day, 30-day, and 14-day intervals alerting the investigator to submit a continuing review. If no continuing review is received before the expiration date and the protocol expires, iRIS will send an Administrative Hold/Protocol Expiration notice to investigators on the protocol’s expiration date. The Administrative Hold/Protocol Expiration notice informs the investigator that all research activities must cease and, if federally funded, the Office of Sponsored Projects will be notified and asked to cease all federal funding activities (i.e., reimbursement) related to the study. Further, investigators must inform the IRB if any research activities have occurred after the expiration date (a non-compliance issue, which will be processed as described in the CWRU IRB Non-Compliance policy).

If a protocol has been placed on Administrative Hold, the investigator has thirty (30) days from the protocol expiration date to submit a continuing review form. Within the Administrative Hold period, no research activity, including data analysis may occur. If a continuing review submission is not received for review within the 30-day Administrative Hold period, the protocol will be terminated. If an investigator wishes to resume his or her research protocol, the investigator must submit a termination form to properly close out the terminated protocol and submit a new protocol application to resume the research.

Research activities include but are not limited to the following:

- recruitment;
- enrollment;
- study interventions and subject interactions (i.e. any involvement of current participants including the scheduling of study visits); and
- identifiable data analysis, this also includes looking at new subject information

The IRB has the authority to allow the continued participation of subjects in research for which IRB approval has lapsed while the continuing review process occurs, only if there are overriding safety concerns or ethical issues that indicate it is in the best interest of the participants to continue, for example when the research interventions have the prospect of direct benefit to subjects or when withholding the study interventions poses an increased risk to subjects. In such
cases, the study will be closed to new enrollment and all data analysis must stop until the IRB completes the review process.

If an investigator makes a determination that immediately stopping all or some of the research activities would not be in a subject’s best interest, the investigator must inform the IRB via iRIS. This formal request must be made as an Amendment Form and must include the rationale and justification as to why the research activities should be allowed to continue. It should also include a confidential list of the research participants (identified by study number or initials only) for whom suspension of the research would potentially increase risk or deny benefits. The determination by the IRB may be made by the IRB chairperson, by another IRB member or group of IRB members designated by the IRB chairperson, or at a convened meeting of the IRB. Furthermore, this determination may be made for all enrolled subjects as a group or for each individual subject. If the investigator or IRB determines that it is not in the best interests of already enrolled subjects to continue to participate, investigators must stop all human subjects research activities, including intervening or interacting with subjects and obtaining or analyzing identifiable private information about human subjects (45 CFR 46.109(a) and (e)).

The IRB will acknowledge the closure of a study by sending a letter via iRIS. After a protocol has been closed the IRB does not accept reports of adverse events unless they impact the rights and welfare of participants enrolled or the integrity of the data. The investigator should keep all non-reported adverse events on file for review by regulatory agencies as required.

After a study has been permanently closed, signed consent forms should be available for IRB inspection for three years. In the event the principal investigator departs from CWRU, copies of signed consent forms should be given to a CWRU co-investigator or archived in accordance with the Records SOP. Closures/Terminations are included in the Notice of Committee Report to the IRB and those reports will maintained by the CWRU IRB office.

If the investigator continues to conduct the research after the study has expired (without prior approval from the IRB that it is in the best interest of the current subjects to continue activity), this becomes an issue of non-compliance and will be processed as described in the CWRU IRB policy and is reportable to the IRB via the electronic IRB system. The matter may also be reportable to the CWRU Compliance Officer, and to applicable regulatory or funding agencies.

References or Regulatory Citations

45 CFR 46.109(e)
45 CFR 46.110
Office for Human Research Projects (OHRP)
OHRP Guidance on Continuing Review, November 10, 2010