

<b>University of Kentucky Office of Research Integrity and Institutional Review Board Standard Operating Procedures</b>			
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Approved By: ORI Director	Signature	Date	Date First Effective: 05-17-05
Approved By: Nonmedical IRB Chair	Signature	Date	
Approved By: Medical IRB Chair	Signature	Date	Revision Date: 02-18-2012

## **OBJECTIVE**

To describe the policies and procedures for conducting continuation review (CR)

## **GENERAL DESCRIPTION**

The Institutional Review Board (IRB) conducts substantive and meaningful CR at intervals appropriate to the degree of risk but not less than once per year. The research protocol must satisfy the criteria set forth in 45 CFR 46.111 and 21 CFR 56.111 for the IRB to approve the protocol for continuation. The IRB may only use expedited review procedures for CR under the following circumstances:

1. The study was initially eligible and continues to be eligible for expedited review procedures; OR
2. The research is permanently closed to the enrollment of new subjects, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; OR
3. Where study personnel have enrolled no subjects at UK and no additional risks have been identified either at UK or at any site if the research involves a multi-site study; OR
4. The only remaining research activities are limited to data analysis; OR
5. The research involves the study of drugs and/or medical devices AND either does not require an Investigational New Drug (IND) (21 CFR Part 312) and/or an Investigational Device Exemption (IDE) (21 CFR Part 812) and/or the device is approved for marketing and being used in accordance with the approved labeling. The IRB must also have determined and documented at a convened meeting that the research is no greater than minimal risk and no additional risks have been identified.

In accord with federal requirements, the IRB approval period can extend no longer than one year after the start of the approval period. (See Study Closure SOP for policy on expiration date.) The PI may not continue research after expiration of IRB approval; continuation is a violation of federal requirements specified in 45 CFR 46.103(a) and 21 CFR 56.103(a). If the IRB approval expires, the PI must cease all research activities and may not enroll new subjects in the study. However, if the IRB determines that there is an overriding safety concern and/or ethical issue or

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that it is in the best interests of the individual subjects to continue participating in the research activities, the IRB may permit the subjects to continue in the study for the time required to complete the CR process.

### **RESPONSIBILITY**

Execution of the SOP: Office of Research Integrity (ORI) Staff, IRB Members, IRB Chair, IRB Vice Chair, ORI Research Privacy Specialist (RPS), Principal Investigator (PI)/Study Personnel

### **PROCEDURES**

#### *CR Requests, Submissions, and Screening*

1. Using the forms and letters generated by the ORI database, ORI staff send CR requests and reminders to the PI before the IRB approval period expires (e.g., approximately 12 weeks, 8 weeks, and 4 weeks prior to expiration). The PI is responsible for responding to those requests in a timely manner.
2. The PI completes the application for CR according to the instructions on the form.
3. The PI must submit continuation review reports for studies as long as the research:
  - Remains open to enroll new subjects;
  - Remains active for long-term follow-up (even when the research is permanently closed to enrollment and all subjects have completed all research-related interventions); and/or
  - Requires analysis of data with identifiers.

See the Study Closure SOP for details on circumstances in which a PI may close a study.

4. Upon receipt of the CR materials, ORI staff screen to determine whether the study is eligible for expedited review.
5. ORI staff also screen the application to ensure compliance with selected federal requirements, such as need for prisoner representative review.
6. If the CR submission includes a new unanticipated problem/adverse event report, ORI staff separate the unanticipated problem/adverse event report from the CR materials and process it under separate cover. ORI staff write a note to accompany the separated problem/adverse event materials indicating that the PI originally submitted them with CR materials. The IRB Chair reviews the unanticipated problem/adverse event report using standard procedures. (See the Unanticipated/Anticipated Problem/Adverse Event Reporting SOP.)

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7. When the ORI receives the CR materials, ORI staff conduct a preliminary screening of the materials submitted and of the IRB's protocol records to ensure the materials are complete and consistent with IRB requirements.
8. During screening, ORI staff update the ORI database with requested extension dates, number of subjects enrolled, and other information provided by the PI in the CR materials. ORI staff compare answers in the CR materials with the data in the existing IRB file (i.e., physical file or database).
9. ORI staff screen for Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule and/or Family Educational Rights to Privacy Act (FERPA) concerns. If the PI includes a HIPAA form or checks "HIPAA" in the application or if there is a HIPAA or FERPA concern, ORI staff forward the application to the ORI Research Privacy Specialist (RPS) for review. The RPS reviews the application and submits suggestions in writing, which ORI staff forward to the expedited reviewer or the convened IRB for a final determination.
10. ORI staff code the CR in the database, assign a meeting date, and describe the extension/modification requests in the codes/events notes section.
11. ORI staff contact ad hoc and cultural consultants regarding issues for which the IRB does not have the appropriate expertise, using the procedures outlined in the Initial Full Review SOP.
12. The ORI may request additional information or materials from the PI if the application is not complete. If the PI does not respond, ORI staff make up to three attempts to contact the PI and/or research staff for additional information/materials, provided there is sufficient time before the end of the approval period.
13. If the ORI does not receive a response from the PI, the ORI sends the CR to the IRB. If the approval period limits the amount of time available to resolve outstanding issues, ORI staff may schedule the protocol for IRB review "as is" to avoid a lapse of approval. ORI staff forward notes detailing the missing or incomplete materials to the IRB.

#### *Medical and Nonmedical Full Continuation Review Procedures*

1. The Medical and Nonmedical IRB conduct full CR at regularly scheduled convened meetings.
2. The Vice Chair or designee serves as the primary reviewer for full CR IRB protocols. If the Vice Chair has a conflict of interest (e.g., is study personnel on a protocol for CR), is unavailable, or does not have the appropriate expertise to review the CR, ORI staff send the CR to the Chair, another Vice Chair, a voting member of the IRB, or a consultant with the appropriate expertise.

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3. Approximately 5-10 days prior to the convened meeting, the primary reviewer receives the following information, but not limited to:
  - A completed CR report form (progress report) for each study, which includes, when applicable, the number of subjects enrolled (including gender and minority status) and withdrawn from the study; summary of unanticipated problems/adverse events involving risks to the subject or others; recent literature; complaints about the research; and any new, significant findings (new findings and implications for subject participation described);
  - A protocol summary and status report on the progress of the research;
  - A copy of the currently approved sponsor protocol for externally funded research (including any prior IRB approved modifications) and/or research description (summary which addresses all elements of criteria for approval);
 and if applicable:
  - A cover memo if it contains pertinent information to review of protocol;
  - Attachments (e.g., updates/changes, explanations)
  - Summary data and safety monitoring reports;
  - A copy of the consent/assent form for which the investigator is seeking IRB approval (with changes underlined for the primary reviewer);
  - A revised grant application;
  - Copies of signed consent forms and if applicable HIPAA Authorizations for the two most recently enrolled subjects;
  - IRB Continuation Review: Primary Reviewer Checklist;
  - ORI staff recommendations including HIPAA comments.

See the CR form for a complete list of information and attachments the PI must submit.
4. Approximately 5-10 days prior to the meeting, the IRB members scheduled to attend the meeting receive the following items, but not limited to:
  - The completed CR report form;
  - A cover memo if it contains information pertinent to review of protocol;
  - Attachments (updates/changes, explanations);
  - A copy of the consent/assent/HIPAA form for which the investigator is seeking IRB approval;
  - A protocol summary and status report of the progress of the research;
5. All IRB members review information in the agenda packet in advance of the meeting (including those protocols for which the IRB member is not the primary reviewer) in enough depth to be familiar with the protocol, to be prepared to discuss the protocol at the meeting, and to be prepared to determine whether the research meets the regulatory criteria for approval.

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6. All IRB members are responsible for evaluating the information communicated to the subject during the consent process and on the form as outlined in the Informed Consent SOP. When documentation of informed consent is required, the IRB reviews the informed consent/assent/HIPAA document(s) submitted for re-approval to ensure accuracy and completeness.
7. ORI staff ensure that the complete IRB protocol record is available to all IRB members prior to and, if requested, during the convened meeting. All IRB members have the opportunity to discuss each research protocol during the convened meeting.
8. The convened IRB assesses the CR materials using the federal criteria for approval (i.e., 45 CFR 46.111 and 21 CFR 56.111).
9. When the IRB reviews research that involves categories vulnerable to coercion or undue influence, ORI staff ensure that adequate representation or consultation is present for discussions of research involving vulnerable human subjects. (See Protection of Vulnerable Subjects SOP and Membership of IRB SOP)
10. The IRB/ORI staff conduct the convened meeting in accord with the Conduct of IRB Meetings SOP. Members who have a conflict of interest follow procedures outlined in both the Conduct of IRB Meetings and IRB Member and Consultant Conflict of Interest SOP.
11. ORI staff serve as intermediaries between the PI and the IRB primary reviewer. However, the primary reviewer may contact the PI directly for clarification. The reviewer documents in the CR materials the issues discussed with the PI.
12. Primary reviewers provide recommendations to the IRB at the convened meeting on issues which they determine do not meet the federal criteria for approval, are controverted, need additional information, or concern compliance with the mandatory University of Kentucky human research training requirements.
13. If the primary reviewer is unable to attend the meeting, ORI staff provide his/her comments or recommendations in writing for presentation to the IRB at the convened meeting.
14. The IRB considers CRs scheduled for full review individually for approval. At the meeting, the IRB reviews the CR report and any controverted issues and their resolution prior to voting. During discussion, the IRB members only raise those controverted issues that the IRB determines do not meet the federal criteria for approval as specified in 45 CFR 46.111, 21 and CFR 56.111. IRB approval of the CR materials documents that the IRB agrees with the PI assessment of any specific findings included in the CR report that the IRB has not previously addressed.

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15. The IRB ensures that the PI provides any significant new findings that might relate to the subject's willingness to continue participation to the subject in accordance with regulations.
16. The convened IRB makes the final determination on the outcome of the review. The primary reviewer or designated IRB member documents the IRB's determinations on the IRB Continuation Review: Primary Reviewer Checklist.

*Medical and Nonmedical Expedited Continuation Review*

1. The Vice Chair or designee serves as the expedited reviewer for expedited CR protocols. If the expedited reviewer has a conflict of interest (e.g., is study personnel on a protocol for continuation review), is unavailable, or does not have the appropriate expertise to review the CR, ORI staff send the CR to the Chair, another Vice Chair, or a voting member of the IRB.
2. ORI staff send the expedited reviewer the following information, including, but not limited to:
  - A completed CR report form for each study, which includes, when applicable, the number of subjects enrolled (including gender and minority status) and withdrawn from the study, summary of unanticipated problems/adverse events involving risks to the subject or others, recent literature, complaints about the research, and any new, significant findings (new findings and implications for subject participation described);
  - A copy of the currently approved sponsor protocol (including any prior IRB-approved modifications) and/or research description (summary which addresses all elements of criteria for approval);
 and if applicable:
  - A cover memo if it contains pertinent information needed to review of protocol;
  - attachments (e.g., updates/changes, explanations);
  - A copy of the consent/assent form for which the investigator is seeking IRB approval (with changes underlined for the primary reviewer);
  - A revised grant application;
  - Copies of signed consent/assent forms and if applicable HIPAA Authorizations for the two most recently enrolled subjects;
  - IRB Continuation Review: Primary Reviewer Checklist;
  - ORI staff recommendations including HIPAA comments.
3. All expedited reviewers are responsible for reviewing information in the expedited review packet in enough depth to be familiar with the protocol, to determine whether the research is eligible for expedited review, and to determine whether the research meets the regulatory criteria for approval.
4. The expedited reviewer is responsible for making the final determination that the protocol meets the criteria for expedited review as outlined above. If the expedited reviewer determines full review is necessary, he/she documents this requirement in the *Reviewer's*

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*Recommendations* section of the IRB Continuation Review: Primary Reviewer Checklist. Upon receipt of the reviewer's recommendation, ORI staff implement full CR procedures.

5. The expedited reviewer applies the same criteria for approval as outlined above for full review (i.e., applies 45 CFR 45.111 and 21 CFR 56.111, and informed consent regulatory criteria), and completes the IRB Continuation Review Primary Reviewer Checklist as documentation of his/her determination. The expedited reviewer raises controverted issues he/she determines do not meet federal criteria and/or may request additional information.
6. When documentation of informed consent/assent is required, the expedited reviewer reviews the informed consent/assent document(s) submitted for re-approval to ensure accuracy and completeness.
7. ORI staff serve as intermediaries between the PI and the IRB expedited reviewer. However, the expedited reviewer may contact the PI directly for clarification. The reviewer documents in the CR materials the issues discussed with the PI.
8. The expedited reviewer documents in the CR materials any determination pertaining to specific findings, as mandated by federal regulations that were not previously addressed by the IRB. (Expedited reviewer approval of the CR materials documents that the reviewer agrees with the PI's assessment of the specific findings).
9. The expedited reviewer ensures that the PI provides any significant new findings that might relate to the subject's willingness to continue participation in accordance with regulations. The reviewer uses the IRB Continuation Review: Primary Reviewer Checklist as a prompt.
10. If the approval might lapse before completion of the CR, the expedited reviewer can make a determination to allow subjects currently participating to continue in accord with procedures described in the section below on lapses of approval.
11. ORI staff list expedited CRs on the IRB agenda to advise the IRB of the expedited CRs.

#### *Lapse of Approval*

1. If a PI fails to return the CR report form or the IRB has not completed review by the end of the approval period, ORI staff notify the PI in writing that the approval will lapse or has lapsed. ORI staff inform the PI that research must cease and no new subject enrollment may occur. ORI staff also inform the PI that he/she should, if appropriate, notify subjects that the study approval has lapsed and that, if applicable, it is his/her responsibility to notify the funding agency of the expiration of the IRB approval.
2. The PI may ask the IRB for permission to allow subjects currently participating to continue due to an overriding safety concern, ethical issues, or because it is in the best interest of the

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individual subjects. The IRB makes the final determination, if appropriate. The ORI or IRB notifies the PI in writing of that determination.

3. In the case of a study in which the PI is actively pursuing renewal, but he/she could not respond to the IRB request for changes before the end of the approval period, with the result that a lapse of approval has occurred, ORI staff send the resubmitted materials to the same IRB that requested the changes. The IRB may subsequently approve the study for continuation.
4. If a protocol approval has expired due to failure of the PI to submit a continuation review report or to respond to the IRB's request for revisions and the PI subsequently submits the CR materials/revisions after the end of the approval, the ORI requests from the PI either a written statement that verifies no research activities have occurred since the lapse, (i.e., recruitment or enrollment of new subjects, interaction, intervention, or data collection from currently enrolled subjects, or data analysis), or a written summary of events that occurred in the interim. If the PI submits the materials/revisions less than three months from the end of the approval period, ORI staff forward the PI's summary and the CR materials/revisions to the IRB. The IRB reviews the materials/revisions following procedures outlined in the Continuation Review SOP.
5. If a protocol approval has expired due to failure of the PI to submit a CR report or respond to the IRB's request for revisions and the PI subsequently submits the CR materials/revisions more than three months after the end of the approval, the IRB requires a new initial review application. If applicable, ORI staff link the new application to the previous protocol number and keep any previous CR materials with the new submission.
6. When continuing review and approval of a research study do not occur prior to the end of the approval period, the IRB does not report the expiration as a suspension of approval under Food and Drug Administration or Department of Health and Human Services regulations.

#### *Review Outcome(s)*

1. For full CR, an IRB member makes a motion, the motion is seconded, and then the IRB members vote for, against, or abstain from one of the following five actions:
  - APPROVED (Vote for a #1): IRB approval - A vote of #1 indicates that the IRB concluded that the research and, if applicable, consent forms meet the federal criteria for approval. The IRB's approval vote verifies that the IRB members agree with the information/materials submitted for continuation of the protocol and/or specific findings described in the CR report by the PI. ORI staff send the investigator an approval letter according to the guidelines in the ORI Customer Service Standard, if applicable, accompanied by an informed consent/assent document with the affixed "IRB Approval"

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validation stamp, which includes valid dates of IRB approval.

- **REVISIONS and/or ADDITIONAL INFORMATION REQUIRED (Vote for a #2):** A vote of # 2 indicates that the IRB has approved the protocol pending submission of minor revisions and that the IRB has given the individual chairing the meeting the authority to approve the minor revisions which do not involve substantive issues. In accordance with ORI Customer Service Standards, ORI staff send a letter to the PI describing the revisions requested by the IRB.

The PI responds to the IRB's suggested revisions in writing and sends the response to the ORI. ORI staff give those responses to the IRB member designated at the IRB meeting to review the requested revisions. That IRB member may forward the responses to the entire IRB for additional review, request additional information, or approve.

- **TABLED - Vote for a #3:** A vote of #3 indicates the IRB withholds approval pending submission of major revisions/additional information. ORI staff send the PI a letter according to the guidelines in the Customer Service Standard. The letter lists the reasons for tabling and includes a description of the revisions or clarifications requested. For some studies, the IRB may appoint one or more members of the IRB to discuss the reasons with the investigator. If the vote is for a #3, ORI staff schedule the PI's response to the requested revisions for review by the full committee. The IRB does not require the PI to attend.
  - **TABLED – Vote for a #4:** A vote of #4 follows the same procedure as a vote of #3 except the PI needs to attend the future IRB meeting at which the IRB reviews his/her response to discuss or answer IRB concerns or questions. ORI staff notify the PI of the request for him/her to attend that future IRB meeting.
  - **DISAPPROVED (Vote for a #5):** A vote of #5 indicates the IRB disapproves the protocol. ORI staff send the investigator a letter according to the guidelines in the ORI Customer Service Standard, describing the reasons for disapproving the protocol. This outcome usually occurs when the IRB determines that the risk of the procedures outweighs any benefit or if the research does not meet the federal criteria.
2. For expedited CR, the expedited reviewer may make the following determinations: 1) approved; 2) revisions and/or additional information required; 3) review by the full committee required. The expedited reviewer exercises all the authority of the IRB except he/she may not disapprove the CR. Only the convened IRB may disapprove the CR.
  3. During the convened meeting, the IRB determines the approval period as appropriate to the degree of risk but not less frequently than once per year. The IRB may set a shorter approval period (for CR to occur more often than annually) for high risk protocols or protocols with a

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high risk/low potential benefit ratio. No approval period extends beyond one year. When a protocol receives final approval, ORI staff document the approval period in the approval letter to the investigator. For full CR, ORI staff include the approval period in the meeting minutes.

4. For full CR, the date of the start of the approval period is the date of the convened meeting. When the outcome of the IRB vote is a “2” (approved pending submission of minor revisions), the ORI staff issue approval after the IRB Chair or the individual chairing the meeting reviews and approves the PI’s response. The approval period begins on the date on which the convened IRB reviewed the protocol. For expedited CR, the date of the start of the approval period is the date the expedited reviewer approves the study.
5. Upon request, ORI staff also send the PI a funding agency Certification of Approval form. (See the Mandated Reporting to External Agencies SOP.)
6. The ORI maintains a Statement of Compliance, signed by the IRB Chair, and provides that statement to PIs upon request if the protocol falls under the International Conference on Harmonisation guidance related to Good Clinical Practice.
7. If the PI has concerns regarding the IRB decision/ recommendations for changes in the study, he/she may submit his/her concerns to the IRB in writing with a justification for altering the IRB decision. The IRB reviews the request using the standard IRB review procedures.

## **REFERENCES**

21 CFR 56.108(a)(1)&(2)  
 21 CFR 56.109(f)  
 21 CFR 56.110  
 21 CFR 56.111  
 21 CFR 56.115(a)(3)&(7)  
 45 CFR 46.103(b)(4)  
 45 CFR 46.108(b)  
 45 CFR 46.109(e)  
 45 CFR 46.110  
 45 CFR 46.111  
 45 CFR 46.115(a)(3)&(7)  
 45 CFR 160  
 45 CFR 164

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