



CONTINUING REVIEW

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Introduction

Federal regulations require that DUHS has written procedures which the IRB will follow for (a) conducting its continuing review of research and for reporting its findings and actions to investigators and the institution, and (b) determining which projects require review more often than annually (45 CFR 46.103(b)(4) and 21 CFR 56.108(a)). Except when an expedited review procedure is used, the IRB reviews proposed research at convened meetings at which a majority of the members of that IRB are present, including at least one member whose primary concerns are in the nonscientific areas (45 CFR 46.108(b) and 21 CFR 56.108(c)). The IRB conducts continuing review of research at intervals appropriate to the degree of risk, but not less often than once a year (45 CFR 46.109(e) and 21 CFR 56.109(f)). Continuing review occurs as long as the research remains active for the collection or analysis of identifiable private information about participants, or for long-term follow-up of participants, even when the research is permanently closed to the enrollment of new participants and all participants have completed all research-related interventions.

In accordance with DHHS regulations at 45 CFR 46.108(b) and 46.115(a)(2), and FDA regulations at 21 CFR 56.108(c) and 21 CFR 56.115(a)(2), continuing review by the convened IRB, with a recorded vote on each study, is required unless the research is otherwise appropriate for review using the expedited procedure under 45 CFR 46.110 and 21 CFR 56.110. Furthermore, regulations at 45 CFR 46.111 and 21 CFR 56.111 set forth the criteria that must be satisfied in order for the IRB to approve research. These criteria include, among other things, determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for human subjects. The IRB must ensure that these criteria are satisfied at the time of both initial and continuing review. In particular, when conducting continuing review, the IRB determines whether any new information has emerged – either from the research itself or from other sources – that could alter the IRB’s previous determinations, particularly with respect to risk to subjects. Information regarding any unanticipated problems involving risks to subjects or others that have occurred since the previous IRB review will be pertinent to the IRB’s determinations at the time of continuing review.

The primary reviewer system is used for continuing review by the convened IRB. The primary reviewer uses the checklist titled “Primary Review Checklist for Continuing Review (Renewal) Protocols” and uses it as the basis for his/her presentation at the convened meeting. In deciding whether to approve research, the convened IRB uses the “Primary Review Checklist for Continuing Review

(Renewal) Protocols” and must decide as a committee that the regulatory criteria for approval (“boxed” items on the checklist) are met.

Conducting Continuing Review

Refer to the policy titled “Conduct of a Convened Meeting of the DUHS IRB” for a listing of the materials provided to the primary reviewer, and to all other board members, as they prepare to conduct continuing review of research not eligible for expedited review.

Upon request, any IRB member has access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting.

When reviewing the current consent document(s), the IRB ensures the following:

- The currently approved or proposed consent document is still accurate and complete;
- Any significant new findings that may relate to the subject's willingness to continue participation are provided to the subject in accordance with 45 CFR 46.116(b)(5) and 21 CFR 50.25(b)(5).

Review of currently approved or newly proposed consent documents occurs during the scheduled continuing review of research by the IRB, but consent documents are also reviewed whenever new information becomes available that would require modification of information in the consent document.

The minutes of IRB meetings document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

Investigators are expected to provide the IRB with all relevant information regarding the conduct of the research. This system is based on trust between the investigators and the IRB. In order to ensure that the research is conducted in compliance with all state and federal regulations for the protection of human subjects, the IRB may require verification of information from sources other than the investigator. Please refer to the DUHS IRB policy on “Determining Which Studies Need Verification from Sources Other Than the Investigator”.

DUHS investigators participating in multi-center clinical trials may be unable to prepare a meaningful summary of adverse events at the time of continuing review because study-wide information regarding adverse events is not readily available to them. In such circumstances, when the research study is subject to oversight by a monitoring entity such as the research sponsor, a coordinating or statistical center, or a DSMB/DMC, DUHS investigators are asked to submit a current report from the monitoring entity. Such reports include the following (where available):

- a statement indicating what information (such as study-wide adverse events, interim findings, and any recent literature that may be relevant to the research) was reviewed by the monitoring entity;
- the date of the review; and
- the monitoring entity's assessment of the information reviewed.

Determining the Frequency of Continuing Review

Please refer to the DUHS IRB "Policy on Determining Frequency of Continuing Review".

Conducting Continuing Review Using the Expedited Procedure

Please refer to the DUHS IRB policy on Expedited Review Procedures.

45 CFR 46.110(b) and 21 CFR 56.110(b) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364-60367, and to the review of minor changes in previously approved research during the period (of one year or less) for which approval is authorized. The IRB uses the expedited review procedure for the continuing review of research that involves solely one or more of the activities published at 63 FR 60364-60367.

The IRB Chair (or designated IRB member) who will conduct the continuing review receives the same documents that are received by the primary reviewer when the review involves the convened board (the documents are described in the policy "Conduct of a Convened Meeting of the DUHS IRB"). All of the relevant review procedures and considerations described for the primary reviewer and the convened board apply also to the reviewer who uses the expedited procedure. In addition, the reviewer records the protocol-specific category or categories (1-9) by which the continuing review is eligible for expedited review.

If research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review except in limited circumstances described by expedited review categories (8) and (9) at 63 FR 60364-60367. For Categories (8) and (9) to be used, the research has to meet all applicability criteria except for Category (8)(b) which only needs to meet the applicability criterion that the research is not classified research.

If research that previously qualified for expedited review in accordance with 45 CFR 46.110 and 21 CFR 56.110 is proposed to change to include new procedures not among those activities published at 63 FR 60364-60367, the continuing review of such research would no longer be permitted using the expedited procedure.

Under Category (8), an expedited review procedure may be used for the continuing review of research previously approved by the convened IRB as follows:

(a) Where:

- 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

(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.

The IRB recognizes that Category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure.

For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.

Under Category (9), an expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

The IRB Chair (or designated IRB member) using the expedited review procedure may make the determination that "no additional risks have been identified"; this does not need to be made by the convened IRB in the context of this use.

Determining the Continuing Review Date

DHHS regulations at 45 CFR 46.109(e) and FDA regulations at 21 CFR 56.109(f) require that an IRB conduct continuing review of research at intervals appropriate to the degree of risk, but not less frequently than once per year. The IRB decides the frequency of continuing review for each study necessary to ensure the continued protection of the rights and welfare of research subjects. The expiration date for an IRB protocol is the first date that the protocol is no longer approved.

Several examples illustrate how the expiration date is determined for studies approved for one year by the IRB at a convened meeting:

- The IRB reviews and approves a study without any conditions at a convened meeting on October 1, 2006. Continuing review must be completed within 1 year of the date of the meeting, that is, before October 1, 2007. The study will expire at 12:00 AM (midnight) on October 1, 2007. October 1, 2007 is the first date that the protocol is no longer approved.
- The IRB reviews a study at a convened meeting on October 1, 2006, and approves the study contingent on specific minor modifications to which the investigator can respond by simple concurrence and the IRB chair or his/her designee can verify. On October 31, 2006, the IRB chair or designee confirms that the required minor changes were made. Continuing review must be completed within 1 year of the date of the convened IRB meeting at which the IRB reviewed and approved the study, that is, before October 1, 2007. The study will expire at 12:00 AM (midnight) on October 1, 2007, which is the first date that the protocol is no longer approved.
- The IRB reviews a study at a convened meeting on October 1, 2006, and has serious concerns or lacks significant information that requires IRB review of the study at subsequent convened meetings on October 15 and October 29, 2006. At their October 29, 2006 meeting, the IRB completes its review and approves the study. Continuing review must be completed within 1 year of the date of the convened meeting at which the IRB reviewed and approved the study, that is, before October 29, 2007. The study will expire at 12:00 AM (midnight) on October 29, 2007, which is the first date that the protocol is no longer approved.

For a new study approved using the expedited review procedure, continuing review must occur within 1 year of the date the IRB Chair or IRB member designated by the Chair gives final approval to the study.

Review of only an amendment or change in a study does not alter the date before which continuing review must occur.

Since the regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval, continuing review and re-approval of research must occur before the date when IRB approval expires. In keeping with OHRP guidance (Guidance on Continuing Review, January 15, 2007), when continuing review occurs annually and the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must have been completed. This would be, for example, October 1, 2007, in the above examples 1 and 2, and October 29, 2007, in example 3, even if the continuing reviews took place within 30 days prior to these dates.

In the Event of a Lapse in IRB Approval

Please refer to DUHS policy on “Expiration of IRB Approval and Subsequent Notice to Cease Study Activity”.

Possible Actions by the IRB Following the Submission of Documents for Continuing Review

The IRB has a range of possible actions it may take for protocols undergoing continuing review:

- Approve, including the period of approval. The investigator is notified via the eIRB or in writing of this action by the IRB.

- Minor modifications required
A modification or change is minor if it does not represent a material change in the research, i.e.,
 - (a) the change does not adversely alter the overall risk/benefit ratio;
 - (b) the change will not potentially adversely affect the willingness of current participants to remain in the study or the willingness of potential participants to enroll in the study;
 - (c) the change will not diminish the scientific validity of the study,
 - (d) any added revision or procedure involves no more than minimal risk to subjects, and
 - (e) any added procedure falls into one of the categories (1)-(7) of research that can be reviewed using the expedited procedure.

A modification is also minor if the investigator is able to make the modification by simple concurrence. Examples of such a modification are specific wording changes to the consent form when the wording changes are provided by the IRB to the investigator, completion of ethics education requirements, adding a pediatrician specialist as a co-investigator for a study involving adolescents, and declaring which of two options, either of which is approved by the convened board, the investigator wishes to choose. The IRB also determines the period of approval should the minor modifications be made.

The investigator is notified via the eIRB or in writing of the action voted on by the IRB and, point-by-point, the required modifications to the research proposal. The investigator is asked to submit a point-by-point response as well as revised documents to the IRB within 60 days of the review date. Unless there are extenuating circumstances as determined by the IRB, at the end of that 60-day period, if the investigator has not submitted a response, the protocol is scheduled for review and consideration for disapproval at the next available convened meeting of the IRB.

When the investigator responds to the IRB’s request for minor modifications, IRB Chair/Vice-Chair and/or the Board Specialist review the response, including the revised documents, to determine if the investigator responded

by simple concurrence. The reviewer indicates whether the modifications required by the IRB have been made and whether the protocol can now be approved. If the modifications have not been made as required, and the investigator is unable or unwilling to make the required modifications, the protocol with the investigator's response is scheduled for review at the next available convened IRB meeting, where it is considered for disapproval.

- **Defer for more information**

When the IRB votes to defer pending receipt of additional information, the investigator is notified via the eIRB or in writing of the action approved by the IRB. Questions and concerns that need to be addressed as well as point-by-point modifications required to the research proposal are described. The investigator is asked to submit a point-by-point response and revised documents to the IRB within 60 days of the review date. Unless there are extenuating circumstances as determined by the IRB, at the end of that 60-day period, if the investigator has not submitted a response, the protocol is scheduled for review and consideration for disapproval at the next available convened meeting of the IRB.

When the investigator responds to the IRB's request for modifications, the investigator's response, including revised documents, are scheduled for review at the next available convened meeting of the IRB.

- **Disapprove**

When the IRB disapproves the research, the investigator is notified in writing of the basis for the disapproval. Disapproval means that the study as designed is inherently flawed, and the IRB can envision no straightforward modification or additional information that would likely result in an approval. The investigator is notified via the eIRB or in writing of this action by the IRB.

The decision of the IRB to disapprove human research cannot be overruled by any other institutional body or individual(s); however an investigator may appeal the decision of the IRB in writing directly to the Duke University School of Medicine Vice-Dean for Research (VDR). The VDR will review the appeal, if possible with the Chair/Vice-Chair who presided over the IRB meeting where the disapproval of the research occurred. This IRB Chair/Vice-Chair will schedule the appeal for review at the next available convened meeting of that IRB. If the review by the VDR with the Chair/Vice-Chair noted above is determined by the VDR to not be appropriate, the VDR will work with the IRB Executive Director to ensure that the protocol receives a complete re-review by a different convened IRB. At that time the range of possible actions described above will apply.