FRIENDS RESEARCH INSTITUTE, INC.
1040 Park Avenue, Suite 103
Baltimore, MD 21201

Subject: Post-IRB Approval Reviews
Division: IRB
Date: March 1, 2012

IRB Policy 111.5: CONTINUING REVIEWS

Policy

The IRB conducts continuing review of research taking place within its jurisdiction at intervals appropriate to the degree of risk, but not less than once per year. Generally, at FRI most 'minimal risk' studies are reviewed once a year, and most 'greater than minimal risk studies' are reviewed every six months. The study's risk level and review period will be noted in the original IRB approval letter.

The following factors are taken into consideration when determining the appropriate review interval, but are not limited to:

1. Involvement of vulnerable populations;
2. Research conducted internationally;
3. Use of waiver of informed consent procedures, (e.g. surrogate consent);
4. Research for which participants would be exposed to additional risks, e.g. breach of confidentiality, phase I studies, disproportionate number or severity of adverse events;
5. Previous Administrative Holds or Suspensions of the research due to compliance, record-keeping or other concerns;

Although the IRB Administrator will send out reminder notices when continuing reviews are due, it is the ultimate responsibility of the Investigator to submit progress reports to the IRB. Therefore, the investigator should not depend solely on IRB notification as a prompting for submitting all required information.

Continuing IRB review is required as long as individually identifiable follow-up data are being collected or analyzed. This remains the case even after a protocol has been closed at all sites and protocol-related treatment has been completed for all subjects. These renewal requests may qualify for expedited review.

If a Progress Report is not submitted in time for the IRB to review and approve the protocol for the next period, at the end of the current approval period the protocol will be ADMINISTRATIVELY SUSPENDED. The continuation of research after expiration of IRB approval is a violation of federal regulations [45 CFR 46.103(a) and 21CFR 56.103(a)]. Once it has been administratively suspended, all research activity on this protocol must stop and no new subjects may be enrolled in the study. Only upon receipt of a formal letter to the IRB requesting reactivation and submission of a completed Progress Report will the renewal of approval process be continued. After approval is granted at a convened meeting of the IRB, the use of that protocol may be continued.

IRB Continuing Review Considerations

Continuing review must be substantive and meaningful. In performing a continuing review, the IRB will look at an Application for Continuing Review, progress report, list of the adverse events over the past year, and previously approved protocol and consent form.

When considering whether or not to renew a study, the IRB revisits the same criteria used to grant initial approval. Therefore, it is the responsibility of the IRB to determine that:

1. Risks to subjects continue to be minimized and reasonable in relation to the anticipated benefits;
2. Selection of subjects continues to be equitable;
3. Informed consent continues to be appropriately obtained and documented;
4. Adequate provisions for monitoring the data collected to ensure the safety of the subjects is provided, when appropriate;
5. Adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, is provided, when appropriate; and
6. Appropriate safeguards for vulnerable populations are provided.

Additionally, the IRB will address the following during a continuing review:

1. Are the number of subjects accrued consistent with the IRB approved number?
2. Do the subject withdrawals indicate a problem with the protocol?
3. Does the progress report include study amendments and new AE information?
4. Are the risks and benefits as anticipated in the initial review?
5. Have any subjects been seriously harmed?
6. Has the IRB been informed of any unforeseen problems that may have occurred?
7. Since the last review, is there new risk or benefit information that might affect subjects' willingness to participate in the research?
8. Are there any new findings/knowledge/AEs that should be reported to subjects?
9. Does the progress of the research together with any new information indicate that the IRB should impose any new restrictions or relax any restrictions that were previously imposed?
10. Does the consent form require revision?
11. Are the procedures agreed upon at the beginning of the research still being used?
12. Are the procedures for data monitoring adequate?
13. If a study did not have a DSMB, should one be established?
14. How often should this study be reviewed by the IRB?

If the IRB determines that it needs verification from sources other than the Investigator, that no material changes have occurred since the previous IRB review, the IRB may request an independent assessment of information or data provided in the renewal application. The IRB will determine the need for verification from outside sources on a case-by-case basis and according to the following criteria:

1. Protocols randomly selected by the IRB office
2. Complex protocols involving unusual levels or types of risks to participants;
3. Protocols conducted by PIs who previously have failed to comply with Federal regulations or the requirements or determinations of the IRB; and/or
4. Protocols where concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.

The scope and extent of such an independent assessment is determined on a case-by-case basis. Sources for such outside information could include copies of FDA audits, literature searches, site visits conducted by authorized personnel, reports from subjects or study staff, or a directed audit at the direction of the IRB.

If Subparts B, C, or D are applicable to the research, the IRB will once again review the research under the appropriate subpart and determine if the requirements have been satisfied.

Continuing review of DSMB-monitored clinical trials

When a clinical trial is subject to oversight by a DSMB whose responsibilities include review of adverse events, interim findings and relevant literature (e.g., DSMBs operating in accordance with the National Cancer Institute Policy for Data and Safety Monitoring of Clinical Trials), the IRB may rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, interim findings and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. However, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to ensure that its continuing review is substantive and meaningful.

IRB Continuing Review Considerations: Consent Form

The purpose of this consent review is to continually improve the quality of the documents, ensure that the information is still accurate and complete, and to implement any changes newly required by the IRB.

When the IRB requests that routine changes be made to improve the quality of the consent document, it may only require that new subjects sign the revised consent document. However, in instances where the new consent document provides pertinent new information for all subjects and may affect/relate to the subjects' willingness to continue in the study, it may additionally require that current subjects (or only the ones who may be affected by the new information) be re-consented with the new document. If the IRB determines that the new information is important for all subjects, but it would not affect the subjects' willingness to continue study participation, the IRB may require that all subjects be provided with an information sheet, which provides them with the new information. An example of when an information sheet may be used is to provide subjects with new contact information for the Investigator or IRB Chairperson.

Possible Outcomes of Continuing Review

Given the authorities that IRBs have under HHS regulations at 45 CFR 46.109(a), when conducting either initial or continuing review of a research study, an IRB can take any of the following actions:

- Approve the research study either (a) as submitted without any conditions, or (b) with conditions;
- Require modifications to secure approval and defer the research study for further review at a future date after the required modifications are submitted by the investigator; or
- Disapprove the research study.

With respect to the first action listed above, by *IRB approval with conditions* (sometimes also referred to as "conditional approval" or "contingent approval") in the context of continuing review, OHRP means that at the time when the IRB reviews and re-approves a research study, the IRB as a condition of approval requires that the investigator:

(a) make specified changes to the research protocol or informed consent document(s),

(b) confirm specific assumptions or understandings on the part of the IRB regarding how the research will be conducted, or

(c) submit additional documents, such that, based on the assumption that the conditions are satisfied, the IRB is able to make all of the determinations required for approval under the HHS regulations at 45 CFR 46.111 and, if applicable, subparts B, C, or D of 45 CFR part 46.

With respect to research reviewed and approved with conditions by the IRB at a convened meeting, note that because the IRB is able to make all these determinations, the IRB may designate the IRB chairperson (and/or other individual(s) with appropriate expertise or qualifications) to review responsive materials from the investigator and determine that the conditions have been satisfied, and further review by the IRB at a subsequent convened meeting would not be necessary.

When approving research with conditions at the time of continuing review, the IRB should be careful to specify whether any conditions need to be satisfied before an investigator can continue particular 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 could approve the research with the following condition: 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. Note that OHRP would not consider such a suspension of subject enrollment at the time of continuing review to be a suspension of IRB approval that needs to be reported to appropriate institutional officials, the head (or designee) of the agency conducting or supporting the research, or OHRP under HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

IRB approval for the conduct of a study may be withdrawn 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 Institutional 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.

Once the IRB has voted to approve a study, the IRB will again make a risk determination for the study, and then determine the review period.

Determination of the Continuing Review Date

The following are several scenarios for determining the date of continuing review for protocols reviewed by the IRB at a convened meeting. (These examples presume the IRB has determined that it will conduct continuing review no sooner than within 1 year).

- Scenario 1: The IRB reviews and approves a protocol without any conditions at a convened meeting on October 1, 2002. Continuing review must occur within 1 year of the date of the meeting, that is, by October 1, 2003.

- Scenario 2: The IRB reviews a protocol at a convened meeting on October 1, 2002, and approves the protocol contingent on specific minor conditions the IRB Chairperson or his/her designee can verify. On October 31, 2002, the IRB Chairperson or designee confirms that the required minor changes were made. Continuing review must occur within 1 year of the date of the convened IRB meeting at which the IRB reviewed and approved the protocol, that is, by October 1, 2003.

- Scenario 3: The IRB reviews a study at a convened meeting on October 1, 2002, 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, 2002. At their October 29, 2002 meeting, the IRB completes its review and approves the study. Continuing review must occur within 1 year of the date of the convened meeting at which the IRB reviewed and approved the protocol, that is,

by October 29, 2003.

On occasion, the IRB may also determine that the PI should submit a periodic report prior to the next continuing review due date. Examples of these types of reports include an update regarding recruitment, an update regarding a new procedure, an update after the first subject has been medicated, etc. These types of reports will be requested when the IRB feels that it is necessary to be updated on specific information within a certain time frame, however, it does not deem it necessary to conduct a complete continuing review at this time. When this type of periodic report is requested, it will be stated in the approval letter, along with the due date of the report.

Extensions of Approval Period

There is no grace period extending the conduct of the research beyond the expiration date of IRB approval. Extensions beyond the expiration date will not be granted. If Continuing Review Report forms and other requested progress reports are not received as scheduled, the Investigator must suspend the study and study enrollment until reports are reviewed and approved.

However, if the Investigator is in communication with the IRB, the Continuing Review Report or other report is forthcoming, and in the opinion of the IRB, subjects participating in such a study would suffer a hardship if medical care were discontinued, appropriate medical care may continue beyond the expiration date for a reasonable amount of time. However, new subjects cannot be enrolled. The IRB will address on a case-by-case basis those rare instances where failure to enroll new subjects would seriously jeopardize the safety or well being of an individual. Prospective research data cannot be collected, and no procedures that are only being performed for the purposes of the protocol may be performed until a Continuing Review Report or other progress report is reviewed and approved.

Expedited Review For Renewal

A protocol with no major changes and minimal risk classification may be eligible to receive continuing review on an expedited basis. Additionally, a protocol that had no accrual during the previous period, or which has not been awarded funding, or which remains open only to data analysis may be reviewed using an expedited review.

When conducting research under an expedited review procedure, the IRB Chairperson or designated IRB member conducts the review on behalf of the full IRB using the same criteria for renewal as stated in this policy. If the reviewer feels that there has been a change to the risks or benefits, he or she may refer the study to the full IRB for review.

Responsibility

IRB Administrators are responsible for establishing and implementing processes for making research renewal decisions. IRB Reviewers are responsible for conducting a thorough review and making all appropriate approval recommendations for consideration by the IRB.

Applicable Regulations and Guidelines

21 CFR 56. 111
45 CFR 46.111
OHRP Guidance on IRB Continuing Review of Research (November 10, 2010)
FDA Information Sheets: Continuing Review After Study Approval