CHAPTER 7

REQUIREMENTS FOR INVESTIGATORS

Chapter Overview

The Principal Investigator of a research study is ultimately responsible for assuring compliance with applicable Adventist HealthCare IRB policies and procedures, HHS federal policy (e.g., "Common Rule"), FDA regulations, and for the oversight of the conduct of the research study and the informed consent process.

The Principal Investigator must understand his or her role in conducting the research, as well as the appropriate interaction with the Adventist HealthCare IRB.

I. UNDERSTANDING THE IRB'S ROLE

See Chapter 1 for a more complete discussion of the IRB's purpose, function, and authority. Principal Investigators are advised to read the IRB Handbook and to be clear on their responsibilities before submitting a research protocol. These general principles will assist the Principal Investigator in minimizing delays during the review process:

1. When preparing submissions for the IRB, take the same care you would when submitting grant applications to funding agencies.

2. Be sure to use the correct form(s), follow the directions, and use the Adventist HealthCare Site Protocol Guidelines and IRB Handbook for guidance.

3. Answer <u>all</u> questions - if you are unsure how to answer a question, call the IRB office for assistance.

4. Timely communication helps speed the process along.

5. Be sure that contact information is complete with a phone number where you can be reached and an e-mail address.

6. Type all communications to the IRB - do not submit handwritten materials.

7. The IRB staff are available to guide you through the IRB process.

8. Plan to attend the IRB meeting to present the research to the Board and to answer questions.

II. SUBMITTING PROPOSED RESEARCH FOR IRB REVIEW

A. IRB Protocol

1. Initial IRB Review of Research

The starting point for projects that require IRB review is the Adventist HealthCare Site Protocol. Some projects use other types of forms and Principal Investigators should be clear about the nature of their project before submitting a package for review. Other types of initial submissions include Request for Expedited Review (an additional form that accompanies the protocol), or the Request for Exemption from IRB Review.

IRB Protocols are lengthy submission forms that require some attention to detail and considerable knowledge about the project in order for the protocol to be prepared correctly. It is the Principal Investigator's responsibility to ensure that the protocol is completed in its entirety and is accurate. The Adventist HealthCare Site Protocol Guidelines is a copy of the Adventist HealthCare Site Protocol form which contains additional directions and examples to assist in the preparation of the protocol. Principal Investigators who have questions about specific questions or sections of the protocol should call the IRB Staff for guidance when preparing the form.

In addition to completing and submitting the Adventist HealthCare Site Protocol, other attachments including the sponsor's protocol or research plan, consent forms, questionnaires, advertisements and other materials for subject recruitment, data collection forms, investigator's brochure, FDA assurances, and other materials must also be submitted.

The Principal Investigator is expected to attend the IRB meeting for the initial review of a project to present the research study and answer questions for the Board. Regardless of the submission date, initial review of a project may be scheduled for a later meeting depending on the Principal Investigator's availability.

The project must be reviewed and approved by the IRB before study commencement and before subjects may be screened for the study. Upon IRB approval, an approval letter will be issued indicating the date of approval, the expiration date of the approval, and any conditions of approval such as the total number of subjects approved for enrollment.

The approval date of protocols undergoing full committee review and requiring no revisions will be the date of the IRB meeting. In this case, the expiration date, or date by which continuing review must occur may be as late 364 days after the date of the IRB meeting at which the research project was initially approved. If initial review is conducted by expedited review procedures, the initial review approval date will be the date on which the IRB Chair or designee approved the protocol and will be stated explicitly in the approval letter.

Quite often, projects require revisions, changes, or corrections based on the initial review by the IRB. If the IRB requests modifications, the study may be given conditional approval, which means the study will be approved once the changes have been made and approved by the IRB Chair or designee. In this case, the effective date of the initial approval is the date on which the IRB Chair or designee reviews the revised documents and determines that all conditions set forth by the IRB have been satisfied. The expiration date of the initial approval period may be as late as 364 days after the date of the IRB meeting at which the research project was reviewed and conditionally approved. If the modifications are significant or substantive, the revised documents will require full committee review. In this case, the effective date of the initial approval will be the date of the IRB meeting at which the modifications are reviewed and approved. Any modifications requested by the IRB will be communicated to the Principal Investigator by letter or a Post Meeting Notification form. After the appropriate changes have been made and approved by the IRB, an approval letter will be issued and all IRB deliberations will be documented in the IRB minutes. The care that goes into the preparation of an IRB submission is often reflected in the amount of time it takes to receive IRB approval. Well prepared, complete submissions typically have shorter turn-around times and are easier for the IRB members to review.

2. Application for Expedited IRB Review of Research

As defined by federal regulations, expedited review allows the IRB Chair, or a specifically designated IRB member or subcommittee, to evaluate and approve specific categories of research outside the context of a full committee meeting. Expedited review may be appropriate (1) for initial and/or continuing review of certain types of research and (2) for minor changes in previously-approved research.

Research may qualify for expedited review if it involves no more than minimal risk and falls within one or more specific categories established by the Federal Government. The list of categories can be found at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.110.

The standard criteria for IRB approval, including the standard requirements for informed consent that apply to full committee review also apply to expedited review. A reviewer (or reviewing subcommittee) conducting expedited review may exercise all the authority of the IRB except that he or she (or they) may not disapprove a study. When a reviewer or subcommittee cannot approve the research under expedited review, the study will be referred to the full committee for review at the next scheduled meeting. The IRB will provide written notification to the investigator regarding the outcome of an expedited review, which may include approval or a request for further information. The convened IRB will be notified of all research approved under expedited review at the next convened IRB meeting.

B. Pre-Review

Time permitting, submitted protocol packages will first undergo a "pre-review." Investigators are reminded that the pre-review by IRB staff is not the same as the IRB review. Pre-review by staff is to identify missing items and any regulatory deficiencies prior to review by the IRB. The IRB staff conducts this pre-review process to help minimize the number of incomplete submissions that are forwarded to the IRB for review. It remains the investigator's responsibility to ensure that a complete application is submitted.

C. Deadlines for Review

All submissions including initial IRB review submissions, modifications, and continuing reviews must be received at least two weeks prior to the regularly scheduled meeting in order to be placed on the agenda for that meeting. Meeting schedules and deadlines can be obtained from the IRB Administrator or staff. Please also see Chapter 3 for more information regarding IRB meetings and procedural issues.

III. CONTINUING REVIEW OBLIGATIONS

A. General Background

Continuing Review is required at least every 364 days and sometimes more often depending upon the evaluation of risk/benefit ratios and other monitoring that may be requested by the IRB. The approval expiration date will be indicated in either the initial approval letter for a new study, or the continuing approval letter for an ongoing study. It is the responsibility of the Principal Investigator to submit a complete continuing review submission at least 45 days **prior to the expiration date** to ensure that the protocol can be reviewed at an IRB meeting before it

expires. The requirement for continuing review and the criteria are defined in two regulations: 45 CFR 46.109(e) and 21 CFR 56.111.

If the initial approval period is for less than a year, it is usually due to issues regarding risks to the subjects that the IRB chooses to monitor more closely or a lag in timing between the date of conditional approval and the time all deficiencies were corrected and final approval was granted (the one year requirement is measured from the date of the initial conditional approval). Sometimes an expiration date is shorter than one year when an investigator has had difficulty maintaining study compliance. The approval time period is determined by the IRB on a case-by-case basis.

IRB approval must be maintained as long as human subjects are involved in any way with the study, including long-term follow-up, long-term data collection, and analysis of identifiable data.

B. Lapses in IRB Approval

Federal regulations do not allow for any extension or "grace" period in the approval period project beyond the expiration date. After the IRB approval expiration date, all research activities involving human subjects must stop unless it is determined that it is in the best interest of the already enrolled subjects to continue participation in the research study. This determination may be made initially by the investigator and the IRB Chair, possibly in consultation with the subject's treating physician. Continuing participation of already enrolled subjects in a research project during the period when IRB approval has lapsed may be appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to the subjects. Enrollment of new subjects cannot occur when IRB approval has expired.

Failure to maintain current approval may disqualify data from being accepted by a sponsor or a publication. Further, the IRB may place sanctions on the study, including the use of data gathered after the expiration date. **If the study expires the project is effectively closed, whether or not a notice is received from the IRB. Subjects may not be enrolled and no research information or data may be collected from currently enrolled subjects until IRB approval is reinstated.**

If a project expires, the Principal Investigator must call the IRB for instructions on how to proceed. If the study is to continue, a complete continuing review submission must be submitted as soon as possible. Investigators may resume the research activity once IRB approval has been granted. Until that application is reviewed and approved, no further research may be done. For the safety of subjects receiving medications or other interventions, it is important that continuing approval be maintained.

Please note that allowing a project to expire places an additional burden on all concerned parties. Further, there is potential that studies that are abruptly closed may impact the health and safety, and the willingness of subjects to participate in research. Investigators must be vigilant and ensure that studies do not expire.

C. Deadlines

It is the responsibility of the Principal Investigator to submit the Continuing Review application at least 45 days before the expiration date. A complete packet must be submitted. If the project is submitted less than 45 days prior to expiration, there is a risk that the project may not receive approval before the project expires.

The IRB will make a reasonable effort to notify investigators 60 days prior to the expiration date that the project is due for review. These notifications are sent by email. Upon receiving the notification, investigators should prepare the Application for Continuing Review for submission. If there is no response to the first notice, the IRB will make a reasonable effort to send a second notice 30 days prior to the expiration date. These IRB reminders are a courtesy. It is the Principal Investigator's responsibility to submit a required report in a timely fashion.

Continuing review is a good time to ensure that study files are in order, including verifying that there are consent forms for each research participant. The Adventist HealthCare IRB requires investigators to update the informed consent form at least annually to bring it in concordance with the standard informed consent template. The informed consent template is updated periodically during the year due to changes in regulations and/or policy and the introduction of new topics.

D. Requirements for Submission

The Application for Continuing IRB Review outlines all the documents to be included in the continuing review submission. These include updated or current protocol(s), revised informed consent documents, data collection tools, recruitment materials, a summary of Adverse Events, Investigator's Brochure or Instructions for Use, Delegation of Authority Log, a listing of protocol violations, and documentation from any external auditing. In addition, investigators are asked to ensure that the personnel section of the Adventist HealthCare Site Protocol is current.

Federal guidelines recommend a "substantive and meaningful" review be undertaken at the time of Continuing Review. **A research project usually merits the same level of review at Continuing Review as at initial review.** Hence, most projects require full committee review. As in the initial review, the IRB may require revisions to the protocol or the consent documents. Refer to Chapter 4 for details regarding the criteria used for IRB review.

E. Determination by IRB

The Principal Investigator will be notified of the outcome of the review of an application for continuing review at an IRB meeting. Possible outcomes include continued approval without stipulations, conditional approval (pending response to stipulations), deferral or disapproval.

If conditional approval is granted, the Post Meeting Notification will be sent to the investigator detailing the stipulations that must be addressed. The notification will specify if the conditions need to be satisfied before an investigator can continue any research activities or if the conditions only apply to specific activities. For example, if the stipulations require revision to the informed consent document, the IRB may grant approval to continue follow-up of currently enrolled subjects but require the stipulations to be satisfied before enrollment may resume. Investigators should address the stipulations in a timely manner.

If the project is approved without conditions or when the stipulations have been satisfied, investigators will receive a letter with the new expiration date and a stamped consent form, if applicable. Study staff and investigators should begin to use the newly stamped consent form immediately upon receipt.

If no changes are made to the consent form, re-consent of subjects using the new consent form is not necessary. However, the research team should use the newly approved consent form when new subjects enter the study. If changes are made to the consent form, it may be necessary to re-consent subjects. Changes that describe new risks should be communicated to subjects within a short time-frame. Minor changes can be communicated (by re-consenting subjects) during the next study visit. The approval letter will indicate if the IRB requires the re-consent of subjects.

These decisions are documented in the IRB meeting minutes which are approved by the IRB, reviewed and approved by the Adventist HealthCare Human Research Protection Quality Committee (HRPQC) and sent to the appropriate Adventist HealthCare entity Medical Executive Committee (MEC).

IV. MODIFICATIONS TO APPROVED RESEARCH

A. Modification

A modification is any change in the research study as described in the protocol and consent form. When approval is given, it is given for the materials that were presented at the time of approval. Any proposed changes to the approved documents also be reviewed and approved by the IRB prior to implementation.

The requirement for reporting any proposed modifications in a research activity are defined in 45 CFR 46.103b(4)(iii), which states that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject. The Adventist HealthCare IRB requires any modifications made on an emergent basis due to safety concerns to be reported to the IRB immediately.

B. Submission to the IRB

Any proposed modification must be submitted on the Amendment Request Form. The proposed change(s) should be clearly described. The current procedure should be described together with the proposed change and the reason for the change. The revisions to the protocol and/or consent form must be highlighted in the documents.

When submitting amendments from sponsors, include the Summary of Changes Table provided by the sponsor, or provide an explanation of the changes with reference to the specific area(s) within the protocol that have been revised. Investigators are not required to copy the wording of the amendments into the form. Modifications will not be accepted without adequate explanation and highlighting.

C. IRB Review of Modifications

1. Expedited Review

Minor modifications to previously approved research may be eligible for review via expedited review procedures. A minor change is one which, in the judgment of the IRB Chair (or designated reviewer(s)):

- does not change the risk/benefit ratio for individual subjects;
- does not substantially alter the IRB's original conditions of approval; and
- would not be expected to impact a subject's decision to participate (or remain) in the research.

2. Full Committee Review

Modifications that require full committee review are those that raise new ethical concerns, alter the risk/benefit ratio, introduce new procedures, change dosages, and other similar types of changes. The addition of any vulnerable population, including children, must be considered by full committee review.

It is often difficult to judge what might alter the risk/benefit ratio. The IRB suggests that a good rule of thumb for investigators to use in understanding whether a modification will likely go to the IRB for full committee review is to consider whether the modification:

- requires revision to the consent form (other than minor corrections);
- adds a new or additional consent form;
- changes the protocol in a substantive way; or
- adds vulnerable populations to the research.

These types of modifications will likely result in full committee review by the IRB. The IRB Chair reserves the right to refer any modification for full committee review that he or she feels needs the consideration of the full board. Modifications may not be implemented until approved by the IRB, unless a protocol must be changed immediately to avoid harm to subjects. In this case, the modification must be submitted to the IRB immediately.

Modifications approved by the IRB under full committee review receive an approval letter and a newly stamped consent form, if appropriate. Investigators should note that a newly stamped consent form does not alter the annual review date for continuing review. The annual continuing review is the only time that the expiration date is altered. However, an amendment may be submitted and reviewed concurrently with a continuing review.

V. EDUCATIONAL REQUIREMENTS FOR INVESTIGATORS

Adventist HealthCare requires that all investigators and staff involved in human subject research complete training in human research protection and training on federal regulations governing the confidentiality of protected health information (known as the HIPAA Privacy Regulations). All research personnel who participate in the conduct of research with human subjects (i.e. are responsible for the study design, data or specimen collection, or who contribute to the scientific development or execution of the study in a substantive, measurable way) must complete the web-based modules available through the Collaborative Institutional Training Initiative (CITI) website (www.citiprogram.org) for certification in human research protection training. Please refer to the IRB Policy on Human Research Protection Training for more information.

Training must be current for the appropriate learning group (i.e. completed within the last three years) for final approval to be issued for an IRB submission.

VI. REPORTING REQUIREMENTS

As detailed in Chapter 11, Adverse Events and Protocol Deviations and Unexpected Problems in Research, and Chapter 8, IRB Management of FDA-Regulated Research, investigators are required to report various events and occurrences to the IRB. Researchers should familiarize themselves with these reporting requirements. Additionally, if any of the materials submitted for initial or continuing review change, such changes must be reported to and approved by the IRB. Investigators are further obligated to promptly report to the IRB any communications from a federal or state regulatory or oversight agency or group (including, but not limited to, the FDA, OHRP, OIG, CMS, DOJ, state attorney general, etc.), that in any way relates to or effects research performed at an Adventist HealthCare facility. Investigators are also obligated to promptly provide copies to the IRB of all written correspondence, reports, or other materials (including communications) from such agencies or oversight groups. The IRB reserves the right to request these reports at any time from investigators.

VII. RESEARCH CONFLICT OF INTEREST DISCLOSURES BY INVESTIGATORS

Investigators are required to file a Research Conflicts of Interest Disclosure Statement with each new protocol submission, according to the Adventist HealthCare Research Conflicts of Interest and Disclosure Policy. If an investigator's conflict of interest status changes during the course of the protocol, the investigator must promptly provide a new Research Conflicts of Interest Disclosure Statement to the IRB Administrator. The investigator will be prompted by the Adventist HealthCare Site Protocol form to consider his/her conflict of interest status with each new study submission. In addition, the IRB administrative staff will review the open reporting system with Centers for Medicare & Medicaid Services (CMS) at the time of each continuing review to verify that no new conflicts have been identified that need to be reported.

Based on this policy, the term "investigator" refers to the Principal Investigator, sub-investigator and any other person (i.e. research study coordinator, research nurse) who is responsible for the design, conduct, or reporting of research, including investigators working for subgrantees/contractors/subcontractors/collaborators. A Financial Interest of anyone in a

Covered Party's immediate family shall be considered to be part of the Covered Party's potential conflict of interest.

All declarations of a conflict of interest will be reviewed initially by the IRB Chair and/or the Chair's designee and the IRB Administrator to determine if the conflict of interest involving an investigator exists. If a conflict of interest exists the IRB Administrator will immediately forward the documentation to the Research Conflict of Interest (RCOI) committee for review. It is the IRB Administrator's responsibility to express the urgency of the review to the RCOI committee.

The RCOI committee will review the declared conflict of interest within a period not to exceed 30 days. No research investigator with a declared conflict of interest may conduct human subject research until the RCOI committee has made a determination if a conflict of interest exists and, if necessary, develops a management plan for the conflict of interest. Once a determination has been made by the RCOI committee it will be communicated to the IRB Administrator who will inform the IRB Chair. The IRB Chair or designee will then communicate the RCOI committee findings and management plan, if applicable, to the research investigator.

VIII. UNAFFILIATED INVESTIGATOR AGREEMENTS

As described in Chapter 1, Adventist HealthCare IRB Policies, every institution engaged in federally supported non-exempt human subject research must obtain a Federal Wide Assurance (FWA) of compliance with the regulations pertaining to the protection for human subjects (45 CFR 46.103(a) and 38 CFR 16.103(a)).

Adventist HealthCare maintains an FWA, which covers employees and agents of the institution. Any investigator who is not an Adventist HealthCare employee may be covered under the Adventist HealthCare FWA through an Unaffiliated Investigator Agreement (UIA). This agreement is research study specific and must be included with each new protocol submission.