CHAPTER 4

CRITERIA FOR IRB REVIEW

In order to approve research, an IRB must evaluate numerous aspects of a proposed study. This Chapter identifies the criteria that must be considered by the IRB when reviewing protocols and provides guidance for the IRB in making determinations (45 CFR 46.111, 46.204-207, 46.404-409). The criteria apply to both initial and continuing review of research. Each principal investigator seeking approval of a research project from the Adventist HealthCare IRB must submit the Adventist HealthCare Site Protocol, which will be used by the IRB to evaluate the research.

I. SCIENTIFIC MERIT AND STATISTICAL ASSESSMENT

It is the responsibility of the IRB to ensure a thorough assessment of each protocol's scientific merit and statistical assessment at both initial review of the protocol and when conducting continuing review. When assessing the scientific merit and statistical assessment, the IRB should consider the following: (1) the significance of the research study; (2) the proposed approach of the research study; (3) the innovation of the research study; (4) the investigators involved with the research study; and (5) the environment in which the research study will be conducted.

A. Significance. When reviewing the significance of the proposed research study, the IRB should consider whether the study addresses an important problem. Further, the IRB should consider whether the study, if successful, will advance knowledge.

B. Approach. When reviewing the approach of the research study, the IRB should consider the form of statistical assessment that will be used by the researchers to determine the results of the study. Further, the IRB must consider whether the methodology, the proposed form of analysis, and the sample size to be used by the researchers are appropriate to address the study question. Likewise, the IRB should consider whether the investigator has demonstrated his/her ability to implement the proposed approach.

C. Innovation. When reviewing whether the research study is innovative, the IRB should consider whether the project is novel and whether it will challenge existing ideas or develop new methodologies or technologies.

D. Investigators. It is important that the IRB assess whether it finds the investigator(s) appropriately trained and well-suited to carry out the proposed research study. Specifically, the IRB should consider whether the work proposed is appropriate for the experience level of the Principal Investigator and other researchers (if any) involved.

E. Environment. In reviewing the proposed research study, it is also important for the IRB to consider the research setting in which the work will be done to ensure that it is sufficient and logical for the completion of the proposed research study.

II. RISK/BENEFIT ASSESSMENT

Another of the primary functions of the IRB is to assess the risks of proposed research compared to the anticipated benefits of the research. The evaluation of risks and benefits often can be complicated by subtle distinctions between therapeutic and research activities and by the challenges of assessing the "standard" risks in the lives of normal and vulnerable classes of subjects. Also, the "risks" that must be considered by the IRB are not limited to the specific clinical risks identified for an investigational drug or device. The IRB must consider all risks, including physical, psychological, social and economic risks that are assumed by enrolling in a trial.

III. IRB REVIEW AND APPROVAL CONSIDERATIONS

Pursuant to federal regulations, an IRB is required to determine that each of the requirements specified below has been satisfied in order to approve proposed research (45 CFR 46.111(a); 21 CFR 56.111(a)). These requirements also are identified in the Adventist HealthCare IRB Protocol/Study Review Checklist; investigators are encouraged to use the Protocol Review Checklist as a guide when preparing submissions for IRB review. The IRB cannot approve proposed research until it concludes that all these requirements have been met. The IRB will use the Checklist to document its findings. The standard requirements listed below apply to both initial and continuing review of research.

A. Standard Requirements

1. **Risks to subjects must be minimized.** The IRB must determine that risks are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk and, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes (45 CFR 46.111(a)(1)).

   The IRB will consider the research plan, including the research design and methodology, to determine if it includes components that would place subjects at unnecessary risk. If the research design presents unnecessary or unacceptable risks to subjects without commensurate benefits to the subjects or to others, the research cannot proceed. In order to determine whether research is adequately designed and that subjects are protected, the IRB may seek opinions from consultants on proposed research and its design. The IRB may determine that proposed research must be redesigned to enhance subject autonomy, maximize benefits, reduce risks, select subjects equitably, minimize undue influence or coercion, or for other reasons.

   The IRB will also consider the qualifications, professional credentials and licensing privileges of the research team. The investigators and the research team members must possess the professional and educational qualifications, as well as the resources, to conduct the research project

and to protect the rights and welfare of subjects.

2. **Risks must be reasonable in relation to anticipated benefits.** The IRB must find that the risks to subjects are reasonable in relation to anticipated benefits (if any) to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy); these are outside the scope of the IRB's responsibility (45 CFR 46.111(a)(2)).

3. **Selection of subjects is equitable.** The IRB should carefully examine the inclusion/exclusion criteria of a study and the recruitment procedures in order to determine that the burdens and benefits of the research are distributed equitably. In making this assessment, the IRB should take into account the purpose of the research and the setting in which the research will be conducted (45 CFR 46.111(a)(3)).

   The IRB should be mindful of the importance of including members of minority groups in research, particularly when the research holds out the prospect of benefit to individual subjects or the groups to which they belong. Similarly, the IRB will be mindful of the desirability of including both women and men as research subjects and should not arbitrarily exclude the participation of persons of reproductive age. Excluding such populations must be justified and based on sound scientific rationale. The IRB will be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, and economically or educationally disadvantaged persons.

4. **Informed consent must be sought consistent with FDA and/or OHRP regulations.** The IRB must find that prospective informed consent will be obtained from each subject (or the subject's legally authorized representative) in accordance with, and to the extent required by, 45 CFR 46.116 and 117; and 21 CFR 50.20 and 25. The specific elements required for legally effective informed consent are discussed in detail in Chapter 5 of the IRB Handbook. The following informed consent procedures apply to all research conducted at Adventist HealthCare or by Adventist HealthCare employees or agents:

   - informed consent may only be sought under circumstances that provide the subject (or the legally authorized representative) with

sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence;

- informed consent information must be presented in language that is understandable to the subject (or the legally authorized representative); and

- informed consent must be obtained prior to the initiation of any screening procedures that are performed solely for the purposes of determining eligibility for research.

5. **Informed consent must be documented appropriately per FDA and/or OHRP regulations.** The IRB must find that informed consent will be documented in accordance with, and to the extent required by, 45 CFR 46.117 and 21 CFR 50.27. There are only two appropriate methods for documenting informed consent:

   - using a written consent document that contains all of the required elements of informed consent; or

   - using a short form consent document (and the related short form consenting process) which states that all the elements of informed consent have been presented orally to the subject (or his/her legally authorized representative).

   These two methods are explained in greater detail in Chapter 5 of the IRB Handbook.

6. **Adequate data safety monitoring processes must exist, when appropriate.** The IRB will assess the research plan to make sure it provides for adequate monitoring of the data collected to ensure the safety of subjects. A general description of the data and safety monitoring plan should be submitted to the IRB for consideration at time of initial review (45 CFR 46.111(a)(6)).

   Adequate monitoring provisions for research might include:

   - The type of data or events that are to be captured,

   - The entity responsible for monitoring the data collected, including data related to unanticipated problems and adverse events, and their respective roles,

   - The time frames for reporting adverse events and unanticipated problems to the monitoring entity,

- The frequency of assessments of data or events captured by the monitoring provisions,

- Definition of specific triggers or stopping rules that will dictate when some action is required, and

- Procedures for communicating to the IRB, Sponsor, the Investigator, and other appropriate official the outcome of the reviews of the monitoring entity.

In general, it is desirable for a Data and Safety Monitoring Board (DSMB) or a Data Monitoring Committee (DMC) to be established for research that is blinded, involves multiple sites, targets vulnerable subjects, or employs high-risk interventions.

The IRB has the authority to require a DSMB as a condition for approval of research where it determines that such monitoring is needed. When DSMBs are utilized, IRBs conducting continuing review of research 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.

7. **Adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data must exist, when appropriate.** The IRB will consider the nature, probability, and magnitude of harms that are likely to result from an unauthorized disclosure of collected information outside the research (45 CFR 46.111(a)(7)). It should evaluate the effectiveness of proposed anonymizing techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections. IRBs and investigators must keep in mind that this privacy/confidentiality requirement is in addition to similar requirements imposed under the HIPAA Privacy Rule. There may be occasions when the HIPAA privacy/confidentiality requirements do not apply but these human research rules do apply.

   Investigators conducting research involving highly sensitive information must consider whether it is appropriate to apply for a Federal Certificate of Confidentiality. Certificates of Confidentiality are discussed in greater detail later in this Chapter.

B. Specific Criteria for Continuing Review. In addition to the standard requirements listed above, the following additional requirements must be **considered** at time of continuing review.

1. Risk Assessment and Monitoring

   One of the most important considerations for the IRB at the time of continuing review is whether there is any new information provided by the investigator, or otherwise available to the IRB, that would alter the IRB's previous conclusion that (1) the risks to subjects are minimized, and (2) the risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(1) and (2)). Information regarding any unanticipated problems that have occurred since the previous IRB review in most cases will be pertinent to the IRB's determinations at the time of continuing review regarding the risk:benefit ratio of the research. It also may be appropriate for the IRB at the time of continuing review to confirm that any provisions under the previously approved protocol for monitoring the research data to ensure safety of subjects (45 CFR 46.111(a)(6)) have been implemented and are working as intended (e.g., the IRB could require that the investigator provide a report from the monitoring entity described in the IRB-approved protocol).

2. Evaluating the Adequacy of the Informed Consent Process

   At the time of continuing review, the IRB should review a copy of the informed consent document submitted by the investigator to verify that the investigator is using the most recently approved version and that the document contains the most accurate, up-to-date information about the research.

   Likewise, if the IRB waived the requirement for the investigator to obtain a signed consent form for some or all subjects (45 CFR 46.117(c)), the IRB will assess the accuracy of the content of the information being provided to subjects orally and of any written statement regarding the research that is being provided to subjects.

   When reviewing an informed consent document, the IRB will ensure that the currently approved or proposed consent document adequately addresses the elements of informed consent required under 45 CFR 46.116(a) and (b). The IRB should be particularly attentive to whether the informed consent document provides an accurate and up-to-date description of the reasonably foreseeable risks and discomforts of the research to the subjects (45 CFR 46.116(a)(2)) and any appropriate alternative procedures or courses of treatment that might be advantageous to the subject (45 CFR 46.116(a)(4)).

The IRB will also assess whether there is any new information presented by the investigator or others (for example, subjects or other individuals who have observed the investigator obtaining subjects' informed consent) that raises concerns about the circumstances under which informed consent is being obtained. The IRB will assess whether there is any new information indicating that the investigator may not be obtaining informed consent under circumstances that provide subjects with sufficient opportunity to consider whether or not to participate or that minimize the possibility of coercion or undue influence (see 45 CFR 46.116).

Continuing review provides the IRB with an opportunity to determine whether there is any new information that should be considered to represent such a significant new finding and that it must be communicated to subjects who have already enrolled in the research (e.g., important new toxicity information or new adverse event information related to the research interventions that is identified during analysis of the research data; or new information regarding alternative treatments that have become available and may be advantageous to the subjects).

3. Investigator and Institutional Issues

The IRB will consider issues regarding the investigator and the institution(s) where the research is being conducted during its continuing review, such as the following:

- Changes in the investigator's situation or qualifications (e.g., suspension of hospital privileges, change in medical license status, or increase in number of research studies conducted by the investigator);
- Evaluation, investigation, and resolution of any complaints related to the investigator's conduct of the research;
- Changes in the acceptability of the proposed research in terms of institutional commitments (e.g., personnel and financial resources, adequacy of facilities) and applicable regulations, State and local law, or standards of professional conduct or practice; and
- Reports from any third party observations of the research carried out under 45 CFR 46.109(e).

4. Research Progress

- Confirmation that Continuing Review Information is Consistent with the IRB-approved Protocol. The IRB will confirm that the information provided by the investigator at the time of continuing review is consistent with the research protocol previously approved by the IRB. If this information suggests that the investigator is not conducting the research in accordance with either the IRB-approved protocol or the requirements or

determinations of the IRB, the IRB will either defer re-approving the research or re-approve the research for a limited period of time (e.g., one month) and seek an explanation from the investigator regarding the apparent discrepancies.

- Total Subject Enrollment. As part of its initial review of a research project, the IRB typically will have approved a protocol that includes the expected total number of subjects to be enrolled by the investigator and the expected rate of enrollment. Evaluating information about the number of subjects enrolled in the research at the time of continuing review may allow the IRB to ascertain whether enrollment is consistent with the planned number of subjects described in the IRB-approved protocol.

- Subject Withdrawals. Subjects may discontinue their participation in research at any point for various reasons (e.g., serious adverse events, conflicts with the investigators, transportation problems, etc.). The IRB's continuing review procedures will review the number of subjects who discontinued their participation, and a summary of the reasons for the withdrawals, if known.

  IRB review of this information may shed light on problems related to the conduct of the research.

C. Additional Safeguards for Vulnerable Subjects

The IRB must determine that additional safeguards are in place in order to protect subjects likely to be vulnerable to coercion or undue influence (45 CFR 46.111(b); 21 CFR 56.111(b)). Vulnerable subjects include many groups of people, such as children, prisoners, pregnant women, persons with mental disabilities and economically or educationally disadvantaged persons. When the research involves pregnant women, fetuses, or neonates; prisoners; or children, the research must satisfy additional requirements for IRB approval under HHS regulations at subpart B, C, or D, respectively, of 45 CFR 46. Each research proposal will be reviewed to determine whether some or all of the subjects are likely to be vulnerable to coercion or undue influence to participate. These vulnerabilities may be subtle but may limit the ability of certain subjects to refuse to participate or to continue to participate in the research.

Research studies that plan to involve any potentially vulnerable populations must have adequate procedures in place for assessing subjects' capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable subjects, the IRB will verify that such procedures are a part of the research plan.

In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples include the inclusion of a consent monitor and/or subject advocate, translation of informed consent forms into languages and grade levels the subjects understand, and reading the consent form to subjects slowly to gauge their

understanding paragraph by paragraph. Also, the IRB may require that the investigator submit each signed informed consent form to the IRB, that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

Persons with acute and/or severe physical or mental illness may be overly compliant with requests to participate in research due to the effects of their illness or due to the prospect of relief from suffering. Clinical studies must be specially designed to assure that patients are able to consent freely. Additional safeguards may include such requirements as the co-consent of relatives, parents, or impartial observers. In acute illness, patients may need to be treated before being entered into research protocols as subjects. This may mean that "qualified" potential subjects are sometimes unable to be enrolled in a research study.

Occasionally, the institutional setting in which the consent is sought will pose the possibility of coercion. Conducting research at institutions that provide services to subjects may be perceived as implying that continued service is dependent upon participation in the research. These institutional pressures should be addressed in the research design. The protocol must adequately preserve the right to refuse participation.

There are many other examples of possible sources of undue influence on subjects. It may not be possible to remove all sources of influence, but the IRB must examine each project to assure the elimination of coercion and minimization of other influences. The research design must adequately address how informed consent will be obtained and what information will be given to prospective subjects. IRBs must look at the coercion issue in each proposal and insist on experimental designs that protect against undue influence to participate.

IV. ONGOING OVERSIGHT OF RESEARCH

As part of its clinical study oversight and monitoring responsibilities, the IRB is required to conduct substantive and meaningful "continuing review" of research not less than once per year. Please refer to Chapter 3 for details regarding the continuing review process. Per federal regulations, IRBs must have policies in place for determining which studies warrant continuing review more frequently than once per year and for determining which studies require verification by someone other than the researchers that no material changes have occurred since the previous IRB review. These issues are discussed below.

A. Determining if a Study will be Reviewed More Often than Annually (45 CFR 46.103(b)(4); 21 CFR 56.108(a)(2))

When an IRB approves a study, it also must determine the duration of the approval. While the maximum approval period is one year, the IRB may determine that more frequent review is appropriate (and thus may issue IRB approval that is valid for a period shorter than one year). In fact, federal regulations require IRBs to establish and follow policies for determining if a study should be reviewed more often than annually.

Adventist HealthCare IRB uses the following factors when making such determinations:

- the probability and magnitude of anticipated risks to subjects;

- the likely medical condition of the proposed subjects;
- the overall qualifications of the principal investigator and other members of the research team;
- the specific experience of the principal investigator and other members of the research team in conducting similar research;
- the nature and frequency of adverse events observed in similar research at this and other institutions; and
- any other factors that the IRB deems relevant.

Issues discussed and final determinations are recorded in the IRB minutes, and the IRB's decision is reflected in the IRB approval letter issued to the investigator.

B. Determining Which Studies Need Independent Verification that No Material Changes Have Occurred Since Previous IRB Review (45 CFR 46.103(b)(4); 21 CFR 56.108(a)(2))

Protecting the rights and welfare of subjects sometimes requires that the IRB independently verify information about various aspects of the study using sources other than the investigator on the research team. The IRB may do this in a number of ways, including monitoring adverse event reporting, tracking information in the scientific literature, assessing reports of drug toxicity, and confirming that no material changes occurred during the IRB-designated approval period. Additionally, an IRB may observe (or have a third party observe) the consent process and/or the research itself, as it deems appropriate. IRBs must follow written policies for determining which studies require independent verification.

Adventist HealthCare IRB uses the following factors when making such determinations:

- the probability and magnitude of anticipated risks to subjects;
- the likely medical 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 principal investigator and research team; and
- any other factors that the IRB deems relevant.

In making determinations about independent verification, the IRB may prospectively require that verification occur at predetermined intervals during the approval period, or it may retrospectively require such verification at the time of continuing review. Issues discussed and final determinations are recorded in the IRB minutes. Also, results of any monitoring efforts are maintained in the IRB files.

V. CERTIFICATES OF CONFIDENTIALITY: PROTECTION AGAINST COMPELLED DISCLOSURE

When research involves the collection of sensitive information about individually identifiable subjects, researchers and/or the IRB may conclude a "Certificate of Confidentiality" should be obtained from the Department of Health & Human Services (HHS). A Certificate of Confidentiality protects the investigator and anyone else who has access to research records from being compelled to disclose identifying information in any civil, criminal, administrative, legislative or other proceedings whether federal, state, or local. **Protection is available whether or not the research project has federal funding.**

Certificates can be used to promote participation in studies by assuring anonymity to participants when the research is of a sensitive nature and where protection is judged necessary to achieve the research objectives. The Certificate will help researchers avoid involuntary disclosure which could expose subjects and their families to adverse economic, psychological, and social consequences. A Certificate does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities of child abuse or of a communicable disease. In addition, a Certificate does not protect against the release of information to HHS or FDA for regulatory purposes.

A. Sensitive Research

Examples of sensitive research include (but are not limited to) that which involves the collection of information in any of the following categories:

- information relating to sexual attitudes, preferences, or practices;
- information relating to the use of alcohol, drugs or other addictive products;
- information pertaining to illegal conduct;
- information that if released could reasonably be damaging to an individual's financial standing, employability, or reputation within the community;
- information that would normally be recorded in a patient's medical record, and the disclosure of which could reasonably lead to social stigmatization or discrimination;
- information pertaining to an individual's psychological well being or mental health; or
- genetic information or tissue samples.

B. Obtaining a Certificate of Confidentiality

Researchers contemplating research on a topic that might qualify as sensitive should contact the IRB Administrator for help in applying for a Certificate. Additional information

concerning Certificates of Confidentiality can be obtained from the NIH website at: http://grants.nih.gov/grants/policy/coc/index.htm.