CHAPTER 12

INVESTIGATOR - INITIATED RESEARCH

Adventist HealthCare supports investigator-initiated research for its ability to advance modern science and enrich our collective understanding of disease and potential cures. While **all** human subject research conducted at any Adventist HealthCare facility requires Adventist HealthCare IRB review (regardless of whether it is investigator-initiated, conducted by a part-time faculty member or approved by another IRB), Adventist HealthCare recognizes there are challenges associated with complying with the federal and state laws governing research and the requirements of the Adventist HealthCare IRB Handbook, especially for those researchers working through the processes without the assistance and guidance of an industry sponsor. As such, this chapter offers guidance to investigator-initiated researchers by defining "research" and providing guidance regarding the requirement for IRB review, offering examples of challenges associated with investigator-initiated research, and providing a list of resources available to investigators.

I. TYPES OF INVESTIGATOR-INITIATED RESEARCH

Investigator-initiated research not only includes research in which an investigator receives no external funding (unfunded or funded by an Adventist HealthCare grant), it also includes research supported (in whole or in part) by funding provided to the Principal Investigator through a grant from organizations such as the American Cancer Association, Alzheimer's Association the American Heart Association, the National Institutes of Health (NIH) and the United States Public Health Service. Additionally, industry supported research (e.g., research sponsored by a pharmaceutical or device company) can be investigator-initiated if the researcher is listed as the sponsor.

II. ACTIVITIES THAT CONSTITUTE RESEARCH

A project is subject to the applicable laws, regulations and Adventist HealthCare policies for the protection of human subjects if it is research and involves human subjects as defined below.

A. Is It Research?

Federal regulations define *research* as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

B. Does the Research Involve Human Subjects?

Federal regulations define a *human subject* as a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

- *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

- *Interaction* includes communication or interpersonal contact between the investigator and the subject.

- *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be **individually identifiable** (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Investigators do not have the authority to make an independent determination of "Not Research" or "Research Not Involving Human Subjects." This determination is made by the IRB Administrator in consultation with the IRB Chair (or his or her designee). The investigator will be notified of the determination in writing and informed that any revisions to projects determined to be "not research" or "research not involving human subjects" that could affect the initial determination must be reviewed by the IRB Administrator or Chair (or his or her designee) prior to implementation.

C. Practice of Medicine

It is important to clarify that the "practice of medicine" is not considered research and does not require IRB review. Good medical practice and the best interests of a patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling (off-label use), they have the responsibility to be well-informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner when the clear intent is the "practice of medicine" does not typically require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by the IRB. However, the IRB reserves the right to require that a particular activity be reviewed by the IRB or to require some other institutional oversight.

On the other hand, the investigational use of approved, marketed products differs from the situation described above. When the physician's principal intent for the use of a test article is to develop information about a product's safety or efficacy, or test a hypothesis, or develop data for preparing an article for publication, the use is considered a clinical investigation and thus, will require review by the IRB. In other words, when an activity does not fall within the "practice of medicine" it must be submitted to the IRB for review. For more information on IND and IDE requirements, Off Label Use and other Investigator/Sponsor requirements, please read Chapter 8, IRB Management of FDA Regulated Research.

III. APPLICABILITY OF THE ADVENTIST HEALTHCARE IRB HANDBOOK AND FEDERAL AND STATE LAWS TO INVESTIGATOR-INITIATED RESEARCH

A. Applicability of the Adventist HealthCare IRB Handbook

All investigator-initiated human subject research conducted at an Adventist HealthCare institution or facility must be conducted in accordance with applicable federal and state laws, good clinical practice, other applicable codes of conduct and the requirements and principles established in the Adventist HealthCare IRB Handbook. It is important for those engaging in investigator-initiated research to understand that they will be held to the same requirements as those engaged in other types of human subject research.

Among the requirements such Investigators must adhere to are the IRB's requirements related to the submission of a completed protocol package. Unlike most industry-sponsored research, investigator-initiated research may not have benefited from peer review before submission to the IRB and may not include external review of the ongoing research process such as that provided by a Data Safety Monitoring Board. For these reasons and others, it is particularly important that the Principal Investigator clearly identify the methodology to be employed in the research, the scientific merit and the overall appropriateness of the chosen scientific design of the proposed research study. Doing so will assist the IRB in understanding and assessing the scientific merit of the research in conjunction with the IRB's focus on ethical issues regarding human subject protection.

B. Applicability of Federal and State IRB Laws

All research, as defined above, is subject to federal requirements governing research. A Principal Investigator engaged in research on a test article regulated by the FDA (see Chapter 8, IRB Management of FDA Regulated Research) who is the individual who both initiates (plans and designs) and conducts the investigation and under whose immediate direction the test article is administered or dispensed, is considered to by a "sponsor-investigator" and has absolute responsibility for the study, including those obligations generally assigned to the sponsor (e.g., reporting of Adverse Events). Refer to Chapter 8 for additional information on these responsibilities.

Additionally, except for those specifically enumerated categories of activities exempt from the federal regulations (see Chapter 3), Maryland law requires that ALL of the applicable provisions of the federal regulations governing research apply to research in Maryland. This means that the restriction in the federal regulations limiting the federal regulations to human research conducted or supported by federal regulation does NOT exclude the regulations from applying to any activity that would otherwise meet the definition of research described above. In other words, it does not matter whether the research is funded by the Federal Government - if it meets the definition of "research," the federal regulations apply to research in Maryland.

IV. OTHER CONSIDERATIONS

When Investigators undertake investigator-initiated research, they undertake the same responsibilities as non-investigator-initiated research. However, the Investigator engaging in investigator-initiated researcher does not have an industry-sponsor to guide him/her through the IRB and regulatory processes or to assist in identifying potential risk areas. The following are a few examples of such obligations:

- **Billing.** It is the Investigator's sole responsibility to determine the appropriateness of billing federal healthcare programs for items or services furnished as part of the research. The Investigator must ensure compliance

with all such applicable coverage and payment rules and to clearly identify any items or services that are furnished as a part of a research activity.

- **Documentation.** Federal regulations impose certain documentation requirements related to research studies. Additionally, Investigators may be responsible for complying with special documentation requirements associated with federal grants (e.g., time and effort reporting).

- **Conflicts of Interest.** it is important for Investigators to be particularly cognizant of potential conflicts of interest that could arise due to potential added vulnerabilities associated with the investigator's research on his or her own patients, and/or existing relationships (e.g., financial) between the investigator and the funding source.

V. AVAILABLE RESOURCES

Complying with the Adventist HealthCare IRB Handbook and federal and state research related laws is an obligatory and important process. The IRB has an administrator available to assist all researchers, including those contemplating or engaged in investigator-initiated research. If an Investigator has a question related to the requirements he or she should contact the IRB Administrator. In addition to the Adventist HealthCare IRB Handbook, there are a number of web sites that provide helpful guidance as well as access to applicable regulations. These websites include the following:

- FDA Guidance for IRBs and Clinical Investigators - http://www.fda.gov/oc/ohrt/irbs/default.htm

- Office of Human Research Protections (OHRP) - http://www.hhs.gov/ohrp/

- NIH Grant and Funding Guide - http://grants1.nih.gov/grants/index.cfm