CHAPTER 8

IRB MANAGEMENT OF FOOD AND DRUG ADMINISTRATION REGULATED RESEARCH

I. BACKGROUND

The Food and Drug Administration (FDA) regulates clinical investigations conducted on drugs, biologics, devices, diagnostics, and in some cases, dietary supplements and food additives (collectively referred to as "test articles"). Regardless of funding source or sponsor, all studies governed by FDA regulations must satisfy meet the IRB requirements described in the Adventist HealthCare IRB Handbook and comply with the applicable FDA regulations.

The FDA's mission is to promote and protect the public health by helping safe and effective products reach the market, and then monitoring these products for continued safety. FDA regulated test articles include:

1. Products that are not generally recognized as being safe and effective for any use under the conditions prescribed, recommended or suggested by the FDA; and

2. Products already approved by the FDA as safe and effective for specific indications that are being studied for new indications (or doses, strengths, or frequency) other than those that have been approved.

When submitting a research study to the IRB for approval, the investigator should indicate whether an Investigational New Drug (IND) or Investigational Device Exemption (IDE), as defined below, has been obtained from the FDA by completing the Adventist HealthCare Investigational Drug and/or Device form. With few exceptions, clinical research involving FDA-regulated test articles will require full committee review.

II. INVESTIGATIONAL NEW DRUG (IND)

With certain exceptions, clinical investigations involving the administration of a drug to human subjects must be conducted under an IND in accordance with 21 CFR 312. There are two categories of clinical investigations that do not require an IND: certain research involving marketed drug products and bioavailability or bioequivalence studies.

The FDA assigns an IND number to an investigator/sponsor upon receipt of an IND application. The FDA will notify the sponsor in writing of the date it receives the IND. An IND goes into effect and the sponsor may ship an investigational new drug to investigators named in the IND thirty days after the FDA receives the IND, unless the FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold or upon earlier notification by the FDA that the clinical investigations in the IND may begin..

A. Research Involving Marketed Drug Products

An IND is not required for research involving marketed drugs if all of the following criteria are met (21 CFR 312.2(b)):

1. The drug product is lawfully marketed in the United States.

2. The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in labelling of the drug.

3. In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.

4. The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of risk) associated with the use of the drug product.

5. The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR 56) and with the requirements of informed consent (21 CFR 50).

6. The investigation is not intended to promote or commercialize the product.

B. Bioavailability or Bioequivalence Studies

An IND is not required for bioavailability or bioequivalence (BA/BE) studies if all of the following criteria are met (21 CFR 320.31(b) and (d)):

1. The drug product does not contain a new chemical entity, is not radioactively labeled, and is not cytotoxic.

2. The dose (maximum single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the product.

3. The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR 56) and with the requirements of informed consent (21 CFR 50).

4. The sponsor meets the requirements for retention of test article samples (21 CFR 320.31(d)(1)) and safety reporting (21 CFR 320.31(d)(3)).

C. Adverse Events and Reporting Requirements

Chapter 11 of the Adventist HealthCare IRB Handbook outlines when a researcher must

report an adverse event to the IRB. In addition to the requirements outlined in Chapter 11, FDA investigational new drug regulations (for both drugs and biologics) require that the investigator immediately report to the sponsor all serious adverse events, regardless of whether the investigator believes that they are drug related, including those events listed in the protocol as anticipated to occur in the study population or in the Investigator's Brochure as predicted to occur with the drug (21 CFR 312.64(b)).

D. Emergency Use of an Investigational Drug or Biologic

The emergency use of an investigational drug requires an IND. However FDA regulations allow an emergency use exception to the requirement of an IND and IRB approval in certain circumstances. Emergency use is defined as the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)).

The term "Life-threatening" includes both life-threatening and severely debilitating as defined below:

- Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted, and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the patients must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

- Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

FDA regulations include provisions for expanded access to investigational drugs and biologics for treatment use, including emergency use.

The FDA may permit an investigational drug to be used by a licensed physician for the treatment of an individual patient (21 CFR 312.310). The licensed physician under whose immediate direction an investigational drug is administered or dispensed for expanded access use in an emergency context is considered an investigator, and must comply with the responsibilities set forth for investigators. Although treatment use of an investigational drug is not considered research, FDA regulations refer to this use as a clinical investigation.

In situations where prospective IRB review and approval is not feasible, the regulations allow for one emergency use of an investigational drug, which must be reported to the IRB within five working days. Any subsequent use is subject to prospective IRB review and approval. The IRB must prospectively review and approve all clinical investigations in which there is non-emergency use of an investigations drug.

1. Criteria for Emergency use of an Investigational Drug

The emergency use must meet the above definitions and the FDA must determine that (21 CFR 312.305(a):

a. The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

b. The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and

c. Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

The following determination must also be made (21 CFR 312.310(a):

a. The physician must determine that the probable risk to the individual from the investigational drug is not greater than the probable risk from the disease or condition; and

b. The FDA must determine that the patient cannot obtain the drug under another IND or protocol.

2. Process for Emergency use of an Investigational Drug

The following steps are required in order to use an investigational drug under the emergency use provisions:

a. **Contact the Sponsor** – Determine if the sponsor will provide the investigational drug under an existing IND or through an emergency IND.

b. **Contact the FDA** – If an emergency IND is necessary (i.e., a situation that requires the patient be treated prior to an expanded access submission/emergency use submission), the FDA may authorize the expanded access use to begin by telephone.

- Emergency use may be requested by telephone, facsimile, or other means of electronic communications. For investigational biological drug products regulated by the Center for Biologics Evaluation and Research, the request should be directed to the Office of Communication, Outreach and Development, Center for

Biologics Evaluation and Research, 240-402-8010 or 1-800-835-4709, e-mail: ocod@fda.hhs.gov. For all other investigational drugs, the request for authorization should be directed to the Division of Drug Information, Center for Drug Evaluation and Research, 301-796-3400, e-mail: druginfo@fda.hhs.gov. After normal working hours (8 a.m. to 4:30 p.m.), the request should be directed to the FDA Emergency Call Center, 866-300-4374, e-mail: emergency.operations@fda.hhs.gov.

- The investigator or sponsor must explain how the expanded access use will meet the requirements of 21 CFR 312.305 and 21 CFR 312.310, and must agree to submit an expanded access submission within fifteen working days of the FDA's authorization of the use.

c. **Contact the IRB –** Contact the Adventist HealthCare IRB office for assistance and to confirm that the proposed emergency use complies with FDA regulations.

- If time allows, submit an Emergency Use of an Investigational Drug, Biologic, or Device Form to the IRB;

- If the patient's condition allows, the IRB will convene an ad hoc meeting to review the treatment protocol prior to administration of the investigational drug. FDA regulations do not allow expedited review/approval of clinical investigations. Therefore, terms such as "interim approval," "compassionate approval," and "temporary approval" are not used for requests for emergency use of FDA regulated products. The IRB must either grant approval at a convened IRB meeting, or if the conditions of 21 CFR 56.104(c) are met and it is not possible to convene a quorum within the time available, the emergency use may proceed without IRB approval.

d. **Obtain Informed Consent –** Informed consent must be obtained from the patient or the patient's legally authorized representative, unless the requirements for an exception from the informed consent requirement (21 CFR 50.23(a) are met (see the Emergency Use Informed Consent template).

e. **Emergency Use Without Informed Consent -** FDA regulations (21 CFR 50.23) permit emergency use of an investigational drug without informed consent where the investigator and an independent physician, who is not otherwise participating in the clinical investigation, certify in writing all of the following:

- The patient is confronted by a life-threatening or severely debilitating situation necessitating the use of the investigational

drug;

- Informed consent cannot be obtained from the patient (because the patient cannot communicate or is incompetent to give consent);

- Time is not sufficient to obtain consent from the patient's legally authorized representative; and

- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the patient's life.

If there is not enough time to obtain the independent physician determination prior to use of the investigational drug, the investigator should make the determination and, within five working days following use of the investigational drug, have the determination reviewed and evaluated in writing by an independent physician.

3. Reporting/Notification Requirements

Following the emergency use of an investigational drug, the investigator must:

a. Submit the following documents to the IRB within five working days:

   - An Emergency Use of an Investigational Drug, Biologic, or Device Form (if not submitted prospectively);

   - Confirmation of the FDA authorization for emergency use (if not covered/included under an existing IND); and

   - A copy of the informed consent form used to obtain consent OR the documentation described above if administered under an exception of informed consent requirement.

b. If no IND exists, the investigator or sponsor must submit an expanded access submission to the FDA within 15 working days of the FDA's authorization of the emergency use in accordance with the requirements outlined in 21 CFR 312.305(b).

c. Report any adverse events to the sponsor.

d. Maintain accurate case histories and drug disposition records and retain records in a manner consistent with the requirements outlined in 21 CFR 312.62.

III. MEDICAL DEVICES

Similar to investigational new drugs, most clinical investigations of investigational devices to determine safety and effectiveness must be conducted under an Investigational Device Exemption (IDE) in accordance with 21 CFR 812.

A. Categories of Devices Exempt from the IDE Requirement

An IDE is not required for clinical investigations of the following categories of devices:

1. A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

2. A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that the FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used in accordance with the indications in the labeling the FDA reviewed in determining substantial equivalence.

3. A diagnostic device, if the sponsor complies with the applicable requirements in 21 CFR 809.10(c) and if the testing: (i) is noninvasive; (ii) does not require an invasive sampling procedure that presents significant risk; (iii) does not by design or intention introduce energy into a subject; and (iv) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

4. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

5. A device intended solely for veterinary use.

6. A device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c).

7. A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

B. Risk Determination

When reviewing a study involving a medical device, the IRB must review and assess the risk to the subject. Such determination of the risk level is based on the proposed use of the device and not just the device itself. FDA device regulations differentiate between significant

risk and non-significant risk devices. The definitions of a significant risk device and a non-significant risk device are provided below:

1. A significant risk (SR) device is an investigational device that (21 CFR 812.3(m)):

    a. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

    b. Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

    c. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

    d. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

2. A non-significant risk (NSR) device is one that does not meet the definition of a significant risk device.

If a sponsor/investigator determines that an investigational device is a non-significant risk device, the protocol may be submitted to the IRB for review without an IDE. The sponsor/investigator must provide the IRB with the rationale used in making the risk determination. The IRB will review the information provided and make an independent determination concerning whether the device is a significant risk or non-significant risk device. Minutes of the IRB meeting will document the rationale for significant risk/non-significant risk and subsequent approval/ disapproval decisions for a study.

A significant risk device must have an IDE, while a non-significant risk device is considered by the FDA to have an approved IDE if certain conditions are satisfied as outlined below unless the FDA has notified the sponsor that approval of an application is required:

1. The device is labeled in accordance with 21 CFR 812.5.

2. IRB approval of the investigation is obtained and maintained.

3. Each investigator participating in an investigation of the device obtains informed consent from each subject under 21 CFR 50 and documents it, unless documentation is waived by an IRB under 21 CFR 56.109(c).

4. The investigation is monitored in accordance with the requirements outlined in 21 CFR 812.46.

5. The sponsor maintains records as required under 21 CFR 812.140(b)(4) and (5) and makes the reports as required under 21 CFR 812.150(b)(1) through (3) and (5) through (10).

6. Participating investigators maintain records as required by 21 CFR 812.140(a)(3)(i) and makes the reports required under 21 CFR 812.150(a)(1),(2),(5), and (7).

7. All parties involved comply with the prohibitions in 21 CFR 812.7 against promotion and other practices.

C. Adverse Event and Unanticipated Adverse Device Effects Reporting Requirements

In addition to the adverse event reporting requirements outlined in Chapter 11 of the Adventist HealthCare IRB Handbook, unanticipated adverse device effects must be reported. Unanticipated adverse device effects are defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. The unanticipated adverse device effects reporting requirements are as follows:

1. Investigator to Sponsor and IRB - FDA IDE regulations require that the investigator notify the sponsor and the IRB of any unanticipated adverse device effect within 10 days of discovery (21 CFR 812.150(a)(1)).

2. Sponsor to the FDA, Investigator, and IRB - The sponsor is required to evaluate the event and report it to the FDA, to all participating investigators, and to all reviewing IRBs within 10 working days of the sponsor's receipt of the information (21 CFR 812.150(b)(1)).

D. Humanitarian Device Exemption

A Humanitarian Use Device (HUD) is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year (21 CFR 814.3(n)). A Humanitarian Device Exemption (HDE) means that certain statutes and regulations need not be followed in order to legally market a HUD. An HDE approval is based on safety and probable benefit; HDEs are exempt from the requirement to provide a reasonable assurance of effectiveness and can only be used in a facility after an IRB has approved their use in that facility, except in certain emergencies.

1. IRB Review of a HUD

When a HUD is used in accordance with the HDE approved indication(s) and safety and effectiveness data will not be collected, the use is not considered a clinical investigation; however, IRB approval is required before a HUD is used at a facility.

An investigator wishing to use a HUD must submit the following items to the IRB:

a. An Adventist HealthCare Site Protocol describing the plan to use the device;

b. A description of the device;

c. A copy of the HDE approval order (from the FDA);

d. The product labeling;

e. All information to be provided to the patient; and

f. The informed consent form for the use of the HUD (a sample HUD consent form is included in the IRB Handbook).

2. What adverse event reporting requirements apply to HUDs?

Investigators must submit reports to the FDA, the IRB, and the manufacturer whenever a HUD might have caused or contributed to a death, and must submit reports to the manufacturer whenever a HUD might have caused or contributed to a serious injury (21 CFR 803.30 and 814.126(a)). Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a body function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure (21 CFR 803.3).

E. Emergency Use of an Unapproved Medical Device

The IDE regulation recognizes that emergency situations might arise in which there will be a need to use an investigational device in a manner inconsistent with the approved investigational plan or by a physician who is not part of the clinical study. Therefore, the regulation permits deviations from the investigational plan when necessary to protect the life or physical well-being of a subject in an emergency (21 CFR 812.35(a)). Prior FDA and IRB approval for emergency use of the investigational device is not required, but the use must be reported to the IRB and the FDA within five working days from the time of use. The AHC Emergency Use of an Investigational Drug, Biologic, or Device Form is included in the AHC IRB Handbook. The report should contain a summary of the conditions constituting the emergency, the patient protection measures that were followed, and patient outcome information.

Emergency use of an unapproved device might also occur when: (i) an IDE for the device does not exist, (ii) when the physician wants to use the device in a way not approved under the IDE, or (iii) when the physician is not an investigator under the IDE.

A physician who intends to treat a patient with an unapproved medical device in an emergency situation should conclude that:

1. The patient has a life-threatening condition that needs immediate treatment.

2. No generally acceptable alternative treatment for the condition exists; and

3. Because of the immediate need to use the device, there is no time to use existing procedures to get IRB and FDA approval for the use.

The physician is expected to make the determination that the patient's circumstances meet the above criteria, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. In the event that a device is used in circumstances meeting the criteria listed above, the physician should follow as many patient protection procedures as possible. Such patient protection procedures include obtaining:

1. Informed consent from the patient or a legal representative (a sample template is included in the Adventist HealthCare IRB Handbook);

2. Clearance from the institution;

3. Concurrence of the IRB chairperson;

4. An independent assessment from an uninvolved physician; and

5. Authorization from the IDE sponsor, if an approved IDE exists for the device.

IV. OFF-LABEL (UNAPPROVED) USE OF FDA-REGULATED PRODUCTS

Good medical practice and the best interests of the patient require that physicians use legally available marketed drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not included in the approved labeling (i.e., off-label), 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.

A. Off-Label (Unapproved) Use of FDA-Regulated Products in Medical Practice

Off-label or unapproved use of a product when the intent is the practice of medicine does not require the submission of an IND or IDE.

B. Off-Label (Unapproved) Use of FDA Regulated Products in Research

An IND or IDE might be required for the off-label use of an approved, marketed product for research (i.e., a clinical investigation intended to develop information about the product's safety or efficacy) unless the criteria for exemption outlined above for INDs and IDEs are satisfied.