Food & Drug Administration Requirements for Research

A. Purpose

The purpose of this procedure on the Food and Drug Administration (FDA) requirements[1] for research is to delineate the regulatory stipulations for drugs and devices.

B. Protocol Design Requirements

FDA requires a protocol to contain the following elements (from Title 21 CFR 312.23 & 812.25):

1. A statement of the objectives, purpose and duration of the study.

2. Name, address and curriculum vitae of each investigator.

3. Criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

4. A description of the design of the study, including the kind of control group to be used, if any, and a description of the methods to be used to minimize bias on part of subjects, investigators and analysts. FDA outlines five different types of controls that can be used:
   a. placebo concurrent control
   b. dose-comparison concurrent control
   c. no-treatment concurrent control
   d. active-treatment concurrent control
   e. historical control

5. The method for determining the dose to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

6. A description of the observations and measurements to be made to fulfill the objectives of the study.

7. A description of the clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

8. If the drug is a radioactive drug, sufficient data from animal or human

studies to allow a reasonable calculation of radiation absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

9. Device trials require the following as well:
   a. A description and analysis of all increased risks to which subjects will be exposed by the investigation.
   b. The manner in which these risks will be minimized.
   c. A justification for the investigation.
   d. A description of the patient population including number, age, sex, and condition.
   e. A description of each important component, ingredient, property and principle of operation of the device and of each anticipated change in the device during the course of the investigation.
   f. A written procedure for monitoring the investigation.

C. Investigational Drugs

1. Drug Form for Clinical Investigations (Form 6)
   Investigators are required to complete "Form 6: Drug Form for Clinical Investigations" on all studies involving investigational drugs and submit the form as part of the application process.

2. Investigational New Drug Number (IND#)
   a. Investigational new drug means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous.
   b. IND means an investigational new drug application. A number is assigned for each application and must be included in the QMC RIRC application.

3. Investigator's Brochure
   The Investigator's Brochure contains a description of the drug substance and formulation, a summary of the pharmacological and toxicological effects, a summary of pharmacokinetics and biological disposition, a summary of information relating to safety and effectiveness in humans and a description of possible risks and side effects to be anticipated from prior experience with the drug. A copy of the Investigator's Brochure is required to be submitted with the RIRC application. **The Principal Investigator is responsible to forward updated Investigator Brochures as they are received, and include a determination whether the consent form should be updated.**

4. Emergency Use of an Investigational Drug or Biological (see SOP Review Procedure, Section 4)

5. Use of Treatment INDs
The treatment IND is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug may be effective and does not have unreasonable risks. Treatment IND studies require prospective RIRC review as outlined in this manual. There are four requirements that must be met before a treatment IND can be issued:
   a. The drug is intended to treat a serious or immediately life-threatening disease.
   b. There is no satisfactory alternative treatment available.
   c. The drug is already under investigation, or trials have been completed.
   d. The trial sponsor is actively pursuing marketing approval.

6. Use of Parallel Track Drugs
The FDA's Parallel Track Policy permits wider access to promising new drugs for AIDS/HIV related diseases under a separate expanded access protocol that parallels the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. It provides an administrative system that expands the availability of drugs for treating AIDS/HIV. Parallel Track Drugs require prospective RIRC review as outlined in this manual.

7. Drug Trial Phases 1-4

   a. Phase 1 Drug Trial – Phase 1 trials include the initial introduction of an investigational new drug into humans. These studies are typically closely monitored and conducted with healthy volunteers; sometimes, the drug is intended for use in patients with a particular disease, however, such patients may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled sufficiently valid Phase 2 studies. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.
   b. Phase 2 Drug Trial – Phase 2 trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and

to determine the common short-term side effects and risks associated with the drug. These studies are conducted with relatively small number of patients, usually involving no more than several hundred subjects.

c. Phase 3 Drug Trial – Phase 3 trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, effectiveness, and appropriate dosage. The are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to FDA for approval to market the drug. Phase 3 trials usually involved several hundred to several thousand patient-subjects.

d. Phase 4 Drug Trial – Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain post-marketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies should include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

e. Research concerning new treatments for certain life-threatening conditions (e.g., cancer, AIDS, emergency-room interventions) may progress differently through the four phases.

D. Investigational Devices

1. Investigational Device Form (Form 7)

Investigators are required to complete Form 7: Investigational Device Form on all studies involving investigational devices as part of the application process.

2. Medical device defined

A medical device is defined, in part, as any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and diagnostic aids (e.g. reagents and test kits for in vitro diagnosis of disease and other medical conditions like pregnancy).

3. Investigational Device Exemption Number (IDE#)

An investigational device is a medical device which is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the "Investigational Device Exemption (IDE)" regulation. Each IDE is assigned a number.

4. Class 1 to 3 Medical Devices
In 1976, Medical Device Amendments to the Federal Food, Drug and Cosmetic Act gave FDA the responsibility for assuring the safety and effectiveness of devices intended for human use (Title 21 CFR 812). Under these regulations, FDA has classified devices according to their level of risk.

   a. Class 1 Medical Device – Class I medical devices include those devices for which safety and effectiveness can be assured as long as there is compliance with provisions for notification of defects, repairs, replacement or refund, records and reports. Device manufacturers are required to also avoid distribution of adulterated, misbranded, or banned devices. Examples include: crutches, band aids, etc.
   b. Class 2 Medical Device – Class II medical devices are those that require something more than proper labeling and quality assurance to ensure their safety and effectiveness. Examples encompass apparatus like wheelchairs and tampons.
   c. Class 3 Medical Device – Class III medical devices are those that are life-sustaining, life-supporting, implanted in the body, or of substantial importance in preventing impairment. Examples consist of products like heart valves, pacemakers, surgical lasers, etc.

5. 510(K) Devices
When a new device is substantially equivalent to one marketed prior to enactment of the Medical Device Amendments (1976), it may be sold without additional proof of safety and efficacy, under Section 510(K) of the Federal food Drug and Cosmetic Act. These devices are thus commonly referred to as "510(K)" devices. Research activities involving a 510(K) do not require an FDA IDE, but do require RIRC approval and informed consent like other prospective human research studies (Full Committee Review).

6. Humanitarian Use Device (HUD)
A device that is designed to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 people in the United States per year fall under the definition of a HUD (Title 21 CFR 814). There cannot be a comparable device that is available to the intended population. The FDA approval of the HUD is a marketing approval and the device is not considered investigational. Under this designation, the product is exempt from obtaining

an IDE, but the utilization of the device requires RIRC approval and informed consent (if greater than minimal risk) with Full Committee Review. In addition to initial approval, the RIRC must perform "continuing review" at least yearly. The treating physician is not required to collect data as with regular IDEs, but adverse events are required to be reported.

A Humanitarian Device Exemption (HDE) enables the provision of HUDs in the population described above a faster than the traditional FDA approval process. A device manufacturer must submit an HDE application to the FDA that includes a description of the product, available non-clinical and clinical evaluation data, and experience with the product. FDA will only approve a HDE if the manufacturer proves that the device is safe ("will not expose patients to an unreasonable or significant risk of illness or injury") and that it has probable benefit ("probable benefit to health from using the device outweighs the risk of injury or illness from its use") in the intended patient population.

7. Significant and Non-significant Risk Devices
The IDE regulations describe two types of device studies, "significant risk" (SR) and "nonsignificant risk" (NSR). Both types of device studies require RIRC approval of the protocol and consent form prior to initiation of the trial. (Title 21 CFR 812)

The effect of the designation of a SR or a NSR status is very important to research sponsors and investigators. SR device studies are governed by the IDE regulations (Title 21 CFR 812). NSR device studies have fewer regulatory controls than SR studies and are governed by an abbreviated requirement (Title 21 CRF 812.2(b)). The SR/NSR decision is important to FDA because the IRB serves, in a sense, as the FDA's surrogate with respect to review and approval of NSR studies. FDA is usually not apprised of the existence of approved NSR studies because sponsors and IRBs are not required to report NSR device study approvals to FDA. To help in the determination of the risk status of a device, the RIRC should review information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria and monitoring procedures. The sponsor should provide the RIRC with a risk assessment and the rationale used in making its risk determination (Title 21 CFR 812.150(b)(10)).

a. Studies involving Non-significant Risk Devices
An SR device study is defined as a study of a device that presents a potential for serious risk to health, safety, or welfare of a subject and 1) is intended as an implant; or 2) is used in supporting or sustaining human life; or 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or 4) otherwise prevent a

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

If an investigator or sponsor proposes the initiation of a claimed NSR investigation to the RIRC, and if the RIRC agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA. Generally, RIRC review at a convened meeting is required when reviewing NSR studies. Some NSR studies, however, may qualify as minimal risk and the RIRC may choose to review the study under an expedited review procedure (Title 21 CFR 56.102(i) and 56.110).

b. Studies involving Significant Risk Devices

A NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in RIRC regulations to identify certain studies that may be approved through an "expedited review" procedure.

If the RIRC believe that a device study is a SR, an investigation may not begin until both the RIRC and the FDA approve the investigation. FDA considers studies of all significant risk devices to present more than minimal risk; thus, full RIRC review for all studies involving SR devices is necessary.

c. Device Risk Determination

The assessment of whether or not a device study presents a NSR is initially made by the sponsor. If the sponsor considers that a study is NSR, the sponsor will provide the RIRC with an explanation of its determination and any other information that may assist the RIRC in evaluating the risk of the study. The sponsor should provide the RIRC with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the RIRC deems necessary to make its decision. The sponsor should inform the RIRC whether other IRBs have reviewed the proposed study and what determination was made. The sponsor must inform the RIRC of the FDA's assessment of the device's risk if such an assessment has been made. The RIRC may consult with FDA for its opinion.

The RIRC may agree or disagree with the sponsor's initial NSR assessment. If the RIRC agrees with the sponsor's initial NSR assessment and approves the study, the investigation may be initiated. If the RIRC disagrees, the sponsor must notify FDA that a

SR determination has been made. The study may be conducted as an SR investigation only after FDA approves an IDE application.

The risk determination should be based on the proposed use of a device in an investigation and not on the device alone. In deciding if a study poses an SR, an IRB must consider the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical o r surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure should be considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the RIRC must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

FDA has the ultimate decision in determining if a device study is SR or NSR. If the FDA does not agree with the RIRC's decision that a device study presents an NSR, an IDE application must be submitted to the FDA. On the other hand, if a sponsor files an IDE with FDA because it is presumed to be an SR study, but FDA classified the device study as NSR, the FDA will return the IDE application to the sponsor and study would be presented to the RIRC as an NSR investigation.

Examples provided by FDA are found in Appendix III to assist the RIRC in making SR/NSR determinations (FDA Information Sheets Page 8). This list includes many commonly used medical devices. Inclusion of a device in the NSR category should not be viewed as a conclusive determination, because the proposed use of a device in a study is the ultimate determinant of the potential risk to subjects. It is unlikely that device listed in the SR category could be deemed NSR due to the inherent risks associated with most such devices.

8. Emergency Use of Unapproved Medical Devices

An unapproved medical device is defined as a device that is used for a purpose or condition for which the device requires, but does not have, an approved application for pre-market approval under section 515 of the Food Drug and Cosmetic Act (Title 21 USC 360(e)). An unapproved device may be used in human subjects only if it is approved for clinical testing under an approved application for an IDE under Title 21 CFR 812. FDA recognizes that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or

institution is not approved under the IDE. Using its enforcement discretion, FDA has not objected if a physician chooses to use an unapproved device in such an emergency provided that the physician later justifies to FDA that an emergency actually existed.

a. Requirements for Emergency Use

Each of the following conditions must exist to justify emergency use:

i. the patient is in a life-threatening condition that needs immediate treatment;
ii. no generally acceptable alternative for treating the patient is available; and
iii. because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for use.

FDA expects the physician to determine whether these criteria have been met, to assess the potential for benefits for unapproved use of the device and to have substantial reason to believe that benefits will exist. The physician may not conclude that an "emergency" exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available. Physician should be aware that FDA expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.

b. Subject Protection Procedures for Emergency Use of Unapproved Device

The RIRC expects the physician to follow protection procedures. These include:

i. obtaining an independent assessment by an uninvolved physician;
ii. obtaining informed consent from the patient or a legal representative;
iii. notifying the RIRC; and
iv. obtaining authorization from the IDE holder, if an approved IDE for the device exists.

c. After-use Procedures for Emergency Use of Unapproved Device

After an unapproved device is used in an emergency, the physician is required to:

i. report to the RIRC with 5 days (Title 21 CFR 56.104);
ii. evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain RIRC approval and an approved IDE

for the device's subsequent use; and

iii. if an IDE for the use does exist, notify the sponsor of the emergency use, or if an IDE does not exist, notify FDA of the emergency use (CDRH Program Operation Staff Phone # (301) 594-1190) and provide FDA with a written summary of the conditions constituting the emergency use and request an approved IDE for such uses.

Subsequent emergency use of the device may not occur unless the physician or another person obtains approval of an IDE for the device and its use. If an IDE application for subsequent use has been filed with FDA and FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist.

d. Exception from Informed Consent Requirements for Emergency Use of Unapproved Device

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and physician who is not otherwise participating in the clinical investigation certify in writing all of the following (Title 21 CFR 50.23):

i. The subject is confronted by a life-threatening situation necessitating the use of the test article.

ii. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.

iii. Time is not sufficient to obtain consent from the subject's legal representative.

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

E. Radiology Devices and Radioactive Material

1. Informed Consent Requirements

The consent form must clearly outline in lay language, the quantity, significance, and risk, if any, of the radiation absorbed dose. The dose is should be compared with background radiation (300 mrem per year), radiation doses a radiation technician receives each year (5000 mrem), or radiation doses received from familiar medical procedures (e.g., chest x-ray)

2. Positron Emission Tomography (PET)

Investigators using PET radiopharmaceuticals have the same review requirements as researchers using other radioactive radiopharmaceuticals.