Chapter 10
IRB Review of FDA-Regulated Research: Investigational Drugs, Devices, and Biologics

The Food and Drug Administration (FDA) is a component of the U.S. Department of Health and Human Services (DHHS) that is responsible for implementing and enforcing the Federal Food, Drug, and Cosmetic Act to regulate the safety and efficacy of these products for human use.

The FDA regulates clinical investigations that are conducted on drugs, biologics, and devices. All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review.

Clinical trials involving an investigational drug, device, or biologic that are supported by DHHS (e.g., the National Institutes of Health) fall under the jurisdiction of both the FDA and the DHHS Office for Human Research Protections (OHRP). Such trials must comply with both the FDA and the DHHS human subject regulations (including, of course, the Common Rule).

I. FDA vs Common Rule and DHHS Requirements. The human subject protection requirements found in FDA regulations and DHHS regulations are substantially the same as the Common Rule requirements. However, there are important differences:

A. FDA regulations contain no Assurance requirement;

B. Conditions for exemption, exception, and waiver of IRB review and Informed Consent requirements differ;

C. FDA regulations require specific determinations for the IRB review of device studies (see below);

D. FDA regulations include specific requirements for reporting adverse events that are not found in the Common Rule or DHHS regulations;

E. DHHS regulations include specific additional protections for pregnant women, fetuses, and human neonates (Subpart B) and prisoners (Subpart C) that are not contained in the FDA requirements; and

F. FDA regulations define “human subject” and “clinical investigation (research)” differently.

II. Investigational Drugs, Devices, and Biologics. Applications are submitted to FDA for approval of research involving investigational drugs, devices, and biologics as follows:
A. **Investigational New Drug Application (IND).** An IND is submitted so that an investigation can be conducted in support of a potential New Drug Application.

B. **Investigational Device Exemption (IDE).** An IDE supports research to be conducted for a Pre-Market Approval application. Devices that are substantially equivalent to other devices that are legally on the market are called 510(k) devices and can be marketed without clinical testing (see below).

C. **Biologics License Application.** A Biologics License Application is submitted to the FDA to receive approval for research on biological products that would support a Biologics License. Biologics include any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of human diseases or injuries.

III. **Clinical Investigator Responsibilities.** Under FDA regulations, the investigator in a clinical trial is responsible for the conduct of the study and for leading the team of individuals coordinating the study.

Each clinical investigator must accept specific responsibilities that include the following:

A. Ensuring conduct of the research according to the investigator agreement, investigational plan (protocol), and all applicable regulations

B. Protecting the rights, safety, and welfare of the research subjects

C. Training and supervising all members of the research team

D. Controlling access to and use of the test article (drug / biologic / device)

E. Monitoring and reporting adverse events

F. Maintaining and retaining accurate records

IV. **Sponsor Responsibilities.** The sponsor of a clinical investigation initiates and holds the IND or IDE for a clinical investigation, but may not actually conduct the investigation. Although the sponsor is usually a pharmaceutical, biotech, or medical device company, an individual or group of individuals can also be considered a sponsor for an investigation. An investigator is referred to as the sponsor-investigator when the individual investigator is also the initiator of the clinical investigation.

The responsibilities of sponsors and sponsor-investigators include the following:

A. Maintaining the IND, IDE, or Biologics License
B. Obtaining Qualified Investigators and Monitors

C. Providing Necessary Information and Training for Investigators

   A. Monitoring the Investigation
   B. Controlling the Investigational Agent
   C. Reporting Significant Adverse Events to FDA/Investigators
   D. Maintaining and Retaining Accurate Records

II. IRB Review of Medical Devices. In accordance with FDA requirements, it is the policy of HSS that a decision of Significant Risk (SR) or Non-Significant Risk (NSR) for a medical device is made prior to consideration of approval of the medical device study. The Significant Risk vs Non-Significant Risk determination must be made by the convened IRB. The criteria for approval of device studies are the same as for any FDA-regulated study.

   A. Significant Risk (SR) Device Defined. A SR device study presents a potential for serious risk to the 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. The FDA considers studies of all SR devices to present more than minimal risk; therefore, full IRB review for all studies involving SR devices is necessary. All devices with an IDE number require full Board approval.

   B. Nonsignificant Risk (NSR) Device Defined. A NSR device study is one that does not meet the definition of a SR study.

   C. Review Procedures. The following procedures govern review of investigational devices by the IRB.

   1. If the IRB determines, or concurs with the assessment of the sponsor that a device study involves a SR, then it would be governed by the IDE regulations at 21 CFR 812. The determination of the risk status of the device should be based on the proposed use of the device in the investigation. The IRB may review any of the following materials:

   a. A description of the device;
   b. Reports of prior investigations conducted with the device;
   c. The proposed investigational plan;
   d. A description of subject selection criteria;
   e. Monitoring procedures; and
f. The sponsor risk assessment and the rationale used to make the sponsor’s risk determination;

2. The IRB may also request additional information if necessary from the sponsor or investigator or ask the FDA to provide a risk assessment;
   a. A device study that is deemed to involve a NSR may begin immediately since it would not require the submission of an application to the FDA; and
   b. It is very important to note that the terms “non-significant risk” and “minimal risk” are defined separately, and are not synonymous.

D. 510(k) Devices. The review requirements for 510(k) devices are somewhat different. If FDA agrees that a new device is substantially equivalent to a device already on the market, it can be marketed without clinical testing. However, if clinical data are necessary to demonstrate equivalence, any clinical studies must be conducted in compliance with the requirements of the IDE, IRB review and informed consent regulations. Because 510(k) devices under clinical investigation fall under the IDE regulations, reporting of adverse or unanticipated 510(k) device effects follow the same requirements (see below).

E. Radiology Devices and Radioactive Materials. FDA is responsible for regulating radiology devices and radioactive materials used in health care and research. Oversight in this area is handled by the Radiation Safety Committee

### III. Investigators’ Responsibilities for Reporting to the IRB

FDA IND regulations require that the investigator report promptly to the Sponsor any “adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately” (21 CFR 312.64(b)). FDA IDE regulations require that the investigator notify the sponsor of any unanticipated adverse device effect within 10 days [see 21 CFR 812.150(a)(1)].

A. Investigators’ Duty to Report Unanticipated Problems. Investigators are required to report to the IRB (using the Internal Human Subjects Adverse Event Form) any unanticipated problems involving risks to subjects or others that occur in research conducted at facilities of this Institution or by its employees or agents.

B. Investigators’ Duty to Report Serious Adverse Events. Investigators are required to report to the IRB (using the Internal Human Subjects Adverse Event Form) any serious adverse event that occurs in research conducted at facilities of HSS or by its employees or agents.

C. Serious Adverse Event Defined. A serious adverse event is defined as any adverse experience occurring that results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of existing...
hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect [see 21 CFR 312.32(a) and 21 CFR 812.3(s)]

D. **Investigators’ Duty to Report Other Adverse Events.** Investigators are required to report to the IRB (using the Internal Human Subjects Adverse Event Form) any adverse event occurring in research conducted at facilities of HSS or by its employees or agent that is reported to the research sponsor or the FDA.

E. **Investigators’ Duty to Forward Sponsor or Cooperative Group Safety Reports.** Investigators are required to forward safety reports (or other information concerning adverse events) issued by sponsors or cooperative groups to the IRB within 5 working days of receipt. Each report should be accompanied by the completed IRB External Safety Report Form.

F. **Investigators’ Duty to Forward Data and Safety Monitoring Board (DSMB) Reports.** Investigators are required to forward DSMB reports to the IRB within 5 working days of receipt. When DSMBs are employed, 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. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to make its continuing review substantive and meaningful.

G. **Duty to Notify the IRB of Serious or Continuing Noncompliance.** Whether involved in the research or not, all employees and agents of this Institution are required to notify the IRB if they become aware of any serious or continuing noncompliance with human subject regulatory requirements or with the determinations of the IRB.

H. **Five (5) Day Requirement.** The IRB should receive the completed IRB Adverse Event/Unanticipated Problem Reporting Form, Safety Report, DSMB Report, or other report from the investigator within 5 working days of the investigator becoming aware of the event or report.

### IV. **Other Reporting Responsibilities.**

Investigators and sponsor-investigators have the following additional reporting responsibilities under FDA regulations:

A. FDA IND regulations require the clinical investigator to notify the sponsor of any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug.

B. FDA IND regulations require that the Sponsor notify the FDA and all participating investigators of any adverse experience associated with the use of a drug or biologic
that is both serious and unexpected as soon as possible but in no event later than 15 calendar days after the sponsor determines it to be reportable. The FDA should be notified by telephone, facsimile, or in writing as soon as possible but in no event later than seven calendar days of the sponsor’s receipt of the information of any unexpected fatal or life-threatening experience.

C. The Sponsor is required to evaluate the event and report serious, unexpected adverse device effects to the FDA, to all participating investigators, and to the IRB within 10 working days of the sponsor’s receipt of the information.

**TABLE 1 - Summary of Reporting Requirements for Manufacturers**

<table>
<thead>
<tr>
<th>REPORTER</th>
<th>WHAT TO REPORT</th>
<th>REPORT FORM #</th>
<th>TO WHOM</th>
<th>WHEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>30 day reports of deaths, serious injuries and malfunctions</td>
<td>Form FDA 3500A</td>
<td>FDA</td>
<td>Within 30 calendar days from becoming aware of an event</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>5-day reports on events that require remedial action to prevent an unreasonable risk of substantial harm to the public health and other types of events designated by FDA</td>
<td>Form FDA 3500A</td>
<td>FDA</td>
<td>Within 5 work days from becoming aware of an event</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Baseline reports to identify and provide basic data on each device that is subject of an MDR report. At this time, FDA has stayed the requirement for denominator data requested in Part II, Items 15 and 16 on Form 3417.</td>
<td>Form FDA 3417</td>
<td>FDA</td>
<td>With 30 calendar, and 5 work day reports when device or device family is reported for the first time. Interim and annual updates are also required if any baseline information changes after initial submission.</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Annual Certification</td>
<td>Form FDA 3381</td>
<td>FDA</td>
<td>Coincide with firm's annual registration dates.</td>
</tr>
</tbody>
</table>

**TABLE 2. - Summary of Reporting Requirements for User Facilities**
<table>
<thead>
<tr>
<th>REPORTER</th>
<th>WHAT TO REPORT</th>
<th>REPORT FORM #</th>
<th>TO WHOM</th>
<th>WHEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>User Facility</td>
<td>Death</td>
<td>Form FDA 3500A</td>
<td>FDA &amp; Manufacturer</td>
<td>Within 10 work days</td>
</tr>
<tr>
<td>User Facility</td>
<td>Serious injury</td>
<td>Form FDA 3500A</td>
<td>Manufacturer. FDA only if manufacturer unknown</td>
<td>Within 10 work days</td>
</tr>
<tr>
<td>User Facility</td>
<td>Annual reports of death &amp; serious injury</td>
<td>Form FDA 3419</td>
<td>FDA</td>
<td>January 1</td>
</tr>
</tbody>
</table>

V. **Off-Label (Unapproved) Use of FDA-Regulated Products in Medical Practice Versus Research.** 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 use of a marketed product in this manner when the intent is solely the practice of medicine does not require IRB review or the submission of an IND or IDE.

B. Off-label use of a marketed product in research (i.e., as part of a systematic investigation designed to develop or contribute to generalizable knowledge) does require IRB review.

C. Off-label use of a marketed product intended to support a change in labeling requires both IRB review and submission of an IND or IDE.

VI. **Treatment INDs and IDEs.** 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. Where necessary, this mechanism can be used even for providing such drugs to a single patient-subject. The Treatment IDE is a comparable mechanism for providing investigational devices to such patient-subjects.

The FDA regulations at 21 CFR 312.34 and 312.35 specify the requirements that must be satisfied before a Treatment IND can be issued. The FDA regulations at 21 CFR 812.36 specify the requirements that must be satisfied before a Treatment IDE can be issued.
Treatment IND and IDE studies require prospective IRB review and informed consent. Although the sponsor may apply for a waiver of local IRB review under a Treatment IND or IDE, such a waiver does not apply to the informed consent requirement. It is the policy of this Institution that all Treatment IND or IDE studies must be reviewed and prospectively approved by the IRB.

A. **Treatment IND.** During the clinical investigation of a drug, it may be appropriate to use the drug in treatment of patients not in the clinical trials. Such use requires FDA approval under a treatment protocol (21 CFR 312.35) or a treatment IND (21 CFR 312.34), as well as IRB review and approval and informed consent.

B. **Single Patient Treatment IND.** The Single-Patient Treatment IND is not described in regulations yet, but was added to the law under the FDA Modernization Act (FDAMA) in 1997. From an operational standpoint, the Single-Patient IND must meet the same requirements as a standard IND, and requires IRB review and approval and informed consent.

C. **Group C Treatment IND.** Group C drugs are Phase 3 study drugs that have shown evidence of efficacy in a specific tumor type. Group C drugs are distributed by the National Cancer Institute (NCI) with a Guideline Protocol and an informed consent document. Informed consent is required, and although FDA and NCI permit the use of Group C drugs without local IRB review, this Institution’s policy normally requires review and approval by the IRB. Investigators who are considering use of Group C drugs should contact the IRB Chairperson for guidance.

D. **Orphan Drugs.** The term "orphan drug" refers to a product that treats a rare disease affecting fewer than 200,000 Americans. The treatment use of orphan drugs requires prospective IRB review and approval and informed consent (21 CFR 316.40 and 312.34).

E. **Parallel Track Studies.** FDA also permits wider access to promising new drugs for HIV/AIDS related diseases under a “separate access” protocol that “parallels” the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. These so-called “parallel track” studies require prospective IRB review and informed consent.

F. **Treatment IDE.** Treatment use of an investigational device facilitates the availability of promising new devices to desperately ill patients as early as possible before general marketing begins. Such use may occur when: (i) the patient has a serious or immediate life-threatening condition; (ii) there is no comparable or satisfactory alternative available; (iii) the device is under investigation in a controlled trial for the same use (or such trials have been complete); (iv) the Sponsor is pursuing marketing approval/clearance; (v) the Sponsor has submitted and the FDA has approved an IDE.
under 21 CFR 812.36. Such use permits wide access to the device dependent upon patient need. IRB review and approval and informed consent are required.

| VII. Gene Transfer Research. | Gene transfer research involves the administration of genetic material to alter the biological properties of living cells for therapeutic use. Gene transfer activities in humans are investigational and are regulated by both the FDA and the NIH Office of Biotechnology Activities (OBA).

A. FDA regulations require the submission of an IND for human gene transfer research.

B. DHHS regulations specify that no individual may be enrolled in human gene transfer research until review has been completed by the Recombinant DNA Advisory Committee (RAC) at NIH; approval of relevant Institutional component-designated Committee(s) has been obtained; component IRB approval has been obtained; and the investigator has obtained all other regulatory authorizations (such as any consents required by regulations) from the subject (65 FR 196, October 10, 2000).

C. While the RAC is advisory to the Director of the National Institutes of Health (NIH), compliance with its guidelines is mandatory for all investigators at institutions that receive NIH funds for research involving recombinant DNA.

| VIII. Emergency Use of a Test Article without Informed Consent. | An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions.

A. Institutional Requirements. If at all possible, this Institution’s policy requires that investigators consult the IRB Chairperson for guidance when considering the emergency use of drugs or medical devices.

B. Required Conditions. All of the following conditions must be met for this type of emergency use:
   1. The subject is confronted by a life-threatening situation necessitating the use of the test article
   2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject
   3. Time is not sufficient to obtain consent from the subject’s legally authorized representative
   4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject’s life
   5. If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an independent physician within five working days
6. The emergency use must be reported to the IRB within five working days (such reporting must not be construed as IRB approval for the emergency use)