17 Regulatory Pathway for Physician-Sponsored Studies Evaluating Endovascular Aortic Repair

Dorothy Abel, Karen Ulisney, Fabienne J. Santel, and Jose Pablo Morales

Introduction

Access to new technology in the US is often achieved through participation in clinical studies. 21 CFR Part 812, the Investigational Device Exemptions (IDE) regulations, applies to these clinical studies or investigations, with submission of an IDE application required for the study of a significant risk device. The purpose of these regulations is to encourage development of useful devices while providing protection of public health and safety. An approved IDE exempts sponsors from certain provisions of the Food Drug & Cosmetic Act for the purpose of conducting a clinical investigation, for example, the requirement to have premarket approval to allow for lawful shipment of a device for the purpose of conducting a clinical investigation.

An IDE can be sponsored by a manufacturer or by an individual physician (termed sponsor-investigator or SI). For an SI IDE, the physician usually authors and will assume the responsibilities of both the sponsor and the primary investigator. These responsibilities include submission of the IDE application, oversight of data collection and reporting, appropriate study monitoring, and obtaining regulatory approval (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046702.htm).

There are multiple advantages of conducting SI IDE studies. Compliance with FDA's IDE regulations provides enhanced protection of the rights, safety, and welfare of study subjects. SI IDEs often treat patients that are not included in industry-sponsored IDEs, and these studies can advance treatment by capturing information that can be used to improve procedures and encourage device innovation in collaboration with industry partners. Also, since SI IDE studies collect patient-level data, SI IDE studies may be used to develop performance goals for industry-sponsored studies or can provide supportive data for a marketing application.

This chapter provides a general overview of the IDE regulations and the processes for IDE preparation, application, and conduct for physicians who are considering sponsoring an IDE with the intent to: (1) explain when an IDE is needed; (2) assist in the preparation and submission of an IDE application, and (3) clarify the responsibilities of sponsor-investigators. The information included in this chapter reflects past and current experiences with endovascular graft SI IDEs and information regarding good clinical practices and human subject protections as applied to these studies. This chapter is not intended to provide official FDA regulatory guidance.

When Is an IDE Needed?

The IDE regulations apply to clinical investigations to evaluate the safety and effectiveness of medical devices. Submission of an IDE may be needed for a clinical study depending on the device's approval status; the intended clinical use; and whether it is a significant risk or non-significant risk device.

The clinical study of a legally marketed device (e.g., an approved device) *may be* subject to the IDE regulations; the study of a device that is not marketed in the US *is always* subject to the IDE regulations because an IDE is the primary

D. Abel • J.P. Morales (✉)
Division of Cardiovascular Devices, Office of Device Evaluation, Center for Devices and Radiological Health, United States Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA
e-mail: Dorothy.Abel@fda.hhs.gov; Jose.Morales@fda.hhs.gov

K. Ulisney
Clinical Trials Program, Office of Device Evaluation, Center for Devices and Radiological Health, United States Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA
e-mail: Karen.Ulisney@fda.hhs.gov

F.J. Santel
Office of Compliance, Center for Devices and Radiological Health, United States Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA
e-mail: Fabienne.Santel@fda.hhs.gov

G.S. Oderich (ed.), *Endovascular Aortic Repair*, DOI 10.1007/978-3-319-15192-2_17

mechanism to obtain access to a device that is not legally marketed in the US.

Some studies are exempted from the IDE regulations, for example, the study of a marketed device that is being used in accordance with its labeling. If a study is not exempted from the IDE regulations, a determination as to whether it is a significant risk device is needed, as non-significant risk (NSR) device studies do not need an IDE application submitted to FDA. A NSR device is considered to have an approved IDE after being granted Institutional Review Board (IRB) approval and the SI follows the abbreviated IDE regulations.

A significant risk device may be an implant; a life-supporting or life-sustaining device; or a device of substantial importance in diagnosing curing, mitigating, or treating disease, or in otherwise preventing impairment of human health. Thus, significant risk devices are those that present the potential for serious risk to the health, safety, or welfare of a subject. A clinical study of a significant risk device that is subject to the IDE regulations (i.e., that is not exempt) requires prior FDA approval, through the submission of an IDE application to FDA, and IRB approval before initiating study subject enrollment.

Figure 17.1 summarizes when an IDE is needed. Any time a physician is systematically collecting safety or effectiveness data on a device (i.e., conducting a clinical study), the applicability of the IDE regulations and the need for an IDE must be considered. The IDE regulations apply to clinical studies or investigations of safety and effectiveness of all devices that are not legally marketed in the US and studies of marketed devices that are not exempted from the IDE regulations. Submission of an IDE application to FDA is needed for all significant risk studies that are subject to the IDE regulations. With respect to endovascular grafts, by definition all are categorized as significant risk devices and their clinical investigation to evaluate safety and effectiveness in the US requires an approved IDE and IRB approval if the studies are not exempted from the IDE regulations [1].

Content of an IDE Application

In order to gain FDA approval of an IDE, an investigator must provide adequate information to justify the proposed study, including, but not limited to reports of prior investigations of the device and an explanation as to how risks to the subjects will be minimized. The clinical protocol should also be designed to collect valid scientific evidence. Additional information is needed to ensure that the investigator will generate appropriate records and reports, distribution of the investigational device will be controlled, the study will be adequately monitored, and informed consent will be obtained from all subjects participating in the clinical study.

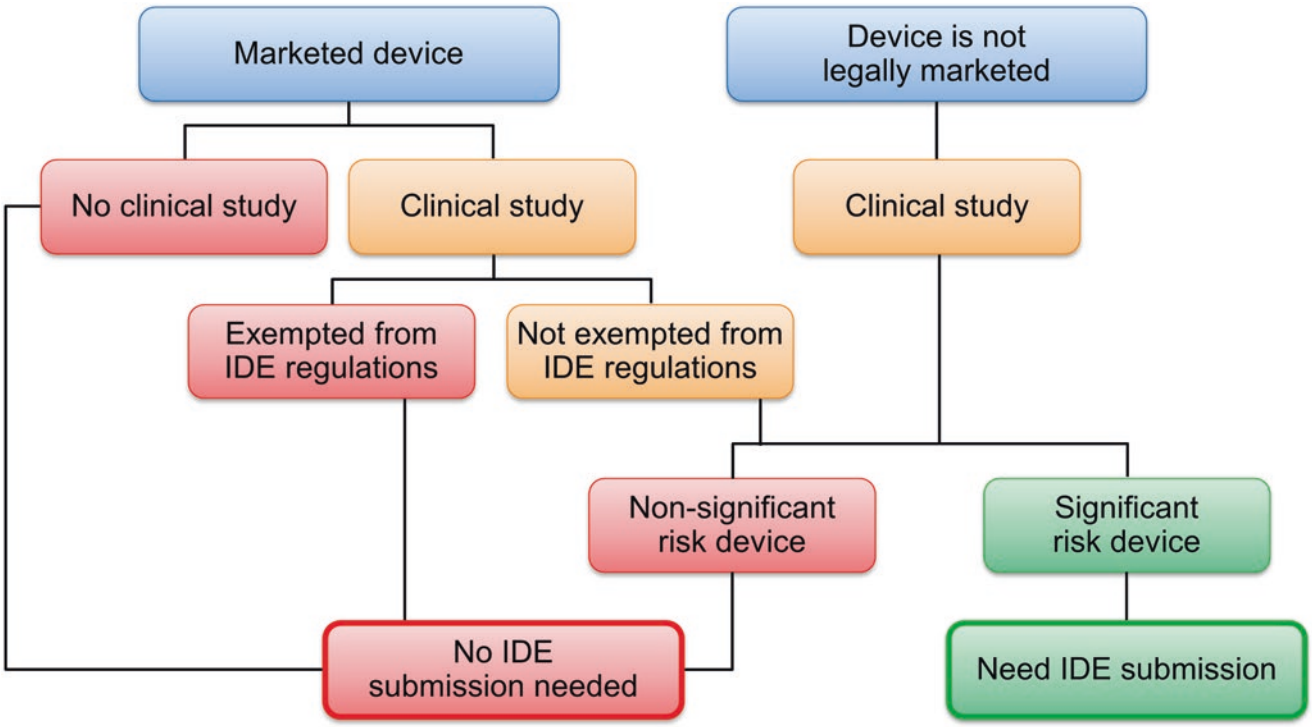

Fig. 17.1 When an IDE submission is needed

Table 17.1 Example of basic content for an SI IDE

1. Cover letter requesting to initiate a study
(a) Statement that it is an original IDE application
(b) Type of study
• Feasibility
• Pivotal
• Other study requiring IDE
(c) Study title
(d) Indications for use
• Type of lesions to be treated
• Extent of aorta to be treated
• Anatomical limitations
(e) Devices to be used
• Whether devices will be modified by the physician
• Manufacturer names and addresses
(f) Risk level of study subjects (e.g., standard risk, high risk)
(g) Number of sites and study subjects
(h) Pre-submission number (if applicable)
(i) Referenced files
(j) Contact information for all persons who may be contacted regarding the IDE (e.g., study sponsor, study coordinator, manufacturer representative)
(k) Attach the CDRH Premarket Review Submission Cover Sheet[a]
2. Table of contents
3. Cover sheet with basic information
(a) Study title
(b) Name and address of sponsor
(c) Contact information
(d) Investigational device(s)
(e) Intended use
(f) Study monitor
4. Report of Prior Investigations (§ 812.27)
5. Investigational Plan (§812.25)
6. Manufacturing information
7. Certification of investigators (or certification that all investigators will sign the investigator agreement)
8. Reviewing Institutional Review Board information
9. Device charges (i.e., the amount, if any, to be charged for the device and an explanation of why sale does not constitute commercialization)
10. Labeling (§ 812.5)
11. Appendices
(a) Copies of relevant references
(b) Test reports (if applicable)
(c) Investigator agreement (§ 812.43)
(d) Case report forms
(e) Draft informed consent form (21 CFR 50, Protection of Human Subjects)

[a]See the following link for a copy of the form: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM080872.pdf

The complete list of information that must be included in an IDE application for the investigation of a significant risk device is outlined in the IDE regulations (21 CFR 812.20, available on the FDA website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE). Table 17.1 provides an example of the basic contents for an SI IDE for the evaluation of an endovascular graft, based on prior IDE submissions.

Additional information regarding the key elements for an endovascular graft SI IDE follows.

The Report of Prior Investigations (RPI) includes reports of all relevant nonclinical and clinical testing of the device(s), and a description of any additional information intended to support study initiation and as outlined in the IDE regulations (21 CFR 812.27). Based on prior reviews of SI endovascular graft IDEs, the justification for the study may include the clinical expertise of the individual submitting the IDE, historical information on the development of the techniques proposed, and a description of the benefits and risks of alternative treatment options. Clinical mitigation strate-

gies (i.e., strategies included in the clinical protocol intended to minimize the frequency or severity of potential adverse events) have also been critical to support the study, particularly when limited nonclinical testing is available, consistent with the guidance provided in the Early Feasibility Study Guidance. As for all IDEs, the rationale for the conduct of the study should be tailored to the specific patient population to be enrolled, for example, patients at high risk for complications if treated with open surgical repair.

Examples of valuable information that has been submitted in the RPI specific to a proposed investigation include background information on the lesions to be treated and the alternative treatment options for the patients to be enrolled in the study, including the anatomy and pathophysiology and the benefits and risks of alternative treatments. As for all IDEs, the RPI should be specific to the patients to be enrolled, providing a justification for the subject selection criteria. An RPI for an SI IDE has historically included the investigator's experience and training, which can be described, along with the experience and support capabilities of the investigational site. A detailed description of the proposed device has helped to explain the applicability of any previous evaluations to the proposed study, with reference to regulatory submissions for nonclinical testing information and any prior clinical use of the device helping to describe the potential benefits and risks of the study device(s). This approach is consistent with the use of master files to support a study submitted by someone other than the owner of the master file. Particularly for early feasibility studies, and consistent with that guidance, clinical mitigation strategies have been described to help explain how the risks may be mitigated in the clinical study. It has been beneficial for the RPI to be wrapped up with a synopsis of the information available to support study initiation.

The clinical protocol for an SI endovascular graft IDE should contain information similar to that provided under manufacturer-sponsored IDEs. For an SI IDE, it has been helpful to be clear and consistent on the following aspects throughout the IDE submission:

- The patients to be enrolled in the study (e.g., suitable candidates for open surgical repair, at elevated risk of morbidity and mortality with open surgical repair);
- The lesion types to be treated (e.g., aneurysm, acute dissections, chronic dissections);
- The location and extent of aorta that may be treated (e.g., juxtarenal, pararenal, paravisceral, types of thoracoabdominal aneurysms);
- All devices to be used in the study (e.g., devices used in constructing the modified endovascular graft, covered stents, bare stents) and how the endovascular graft will be modified, if applicable;
- The anatomical limitations for the devices to be used (e.g., minimum length of landing zones, minimum and maximum vessel diameters, allowed angulation);
- The duration of the study (most endovascular graft IDEs specify 5-year follow-up for each patient);
- The potential risks that may be associated with the treatment and how the risks will be minimized; and
- The data to be captured, differentiating between protocol-required data and optional information.

The informed consent document for an SI IDE study as required by 21 CFR Part 50 Subpart B, Informed Consent of Human Subjects can be found in http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm. For these studies, it has been particularly important for prospective study subjects to be informed of potential benefits and risks that may be associated with study participation and that there could be unforeseeable risks due to limitations in available data and experience with the device. The benefits and risks associated with the standard of care (e.g., open surgical repair) should also be addressed.

Incorporation of appropriate monitoring and oversight will be important and may include the use of a clinical events committee and a data and safety monitoring board. Detailed information regarding the data monitoring committee may be found in FDA's Guidance for Clinical Trial Sponsors, The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors, published in March 2006 (http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm).

How to Apply for an IDE?

Information on how to prepare and submit an IDE application as outlined in the IDE regulations can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm. The preparation of an IDE application and the conduct of an IDE study can be challenging, requiring a skilled research staff. Consultation with the device manufacturer and physicians who have experience with the IDE process may be helpful. In addition, it is recommended that a sponsor-investigator interact with the FDA through the Pre-Submission process when preparing the IDE application. This process allows for discussion and feedback from FDA to address key components that need to be included or revised in the IDE submission regarding nonclinical and clinical testing strategies, study design, or application preparation. Information on the pre-submission process may be found in the guidance "Medical Devices: The Pre-Submission Program and Meetings with FDA Staff" at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.

Please note that an electronic copy (eCopies) will be required for a Pre-Submission or an IDE. See the following link for gen-

eral guidance on the preparation of eCopies: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/ucm370879.htm.

Common Mistakes Identified During Review of IDEs

Avoiding the frequently made mistakes in drafting an IDE can reduce delays in obtaining IDE approval. One of the most common mistakes is a lack of consistency throughout the IDE application (e.g., in the RPI, clinical protocol, and case report forms). For example, the RPI may support the use of the device in patients with juxtarenal aortic aneurysm; however, the eligibility criteria outlined in the investigational plan include patients with other aortic pathologies (e.g., dissections).

Sponsor-investigators often only identify the branched or fenestrated aortic component as the investigational device. For any IDE, however, devices not being used in accordance with their labeling need to be identified and addressed as investigational devices. As the use of multiple devices (e.g., renal or superior mesenteric artery stents) is required to complete an endovascular repair, all devices intended to be used during the procedure need to be specified as investigational devices. The use of each device needs to be justified in the RPI and appropriate information captured on the case report forms regarding the device use and performance.

Endovascular repair of complex aortic aneurysms often requires extensive aortic coverage and staged procedures may be used to decrease the incidence of paraplegia [2]; however, staging is often not addressed in the IDE. For any IDE, it is necessary to clearly describe the procedure and address any associated risks. Based on experience with previous SI IDEs, this would include staged procedures and therefore, to appropriately evaluate the potential benefits and risks associated with the endovascular treatment, considerations for staging and capturing data on the complete repair (i.e., both procedures) or incomplete repair (i.e., if the second procedure could not be performed) should be incorporated in the clinical protocol, case report forms, and informed consent form. Particularly for an early feasibility study, the use of staged procedures may also be identified as a risk mitigation strategy for paraplegia.

Another common mistake seen with SI IDEs is being too prescriptive which can lead to protocol violations. Since the devices used under SI IDE often have endovascular grafts tailored to the patient anatomy and pathology, and there is significant variability from patient to patient, it may be beneficial to be less prescriptive (e.g., include options when possible and appropriate for both the devices to be used and the procedures for placing the devices). For example, a sponsor could propose that the selection criteria allow for the use of a vascular conduit for access, rather than only requiring a specific access vessel size. As for any IDE, to avoid protocol deviations, it is helpful to distinguish between data that are required to monitor patient safety and device performance under the IDE from additional information that may be of interest to capture.

With the intent to offer patients specialized and personalized medical care, sponsor-investigators tend to be overly ambitious with their proposed clinical studies. For example, the IDE may request a large number of patients, when adequate information is only available to justify a smaller initial study. Commonly an SI will not propose to start with patients that do not have good treatment options or will not include strategies to minimize risks by starting with less complicated anatomies and expanding treatment to more complex anatomies after successful treatment of the first patients. As for any IDE, it is important for IDE applicants to be able to justify their proposed study, which may involve presenting a conservative approach to enrolling subjects under their IDE. Notably, supplements can be submitted to an IDE to modify or expand the clinical study (e.g., patient selection criteria and numbers) after information is available to support the proposal.

Finally, delays can be minimized when sponsor-investigators submit their IDE application after the spelling, grammar, formatting, and consistency are properly checked.

What It Takes to Run an IDE

Overview of Good Clinical Practices

FDA regulations that apply to the conduct of clinical investigations are based on the principles of Good Clinical Practices (GCP). Even beyond FDA, GCPs are the foundation upon which clinical investigations are developed and executed worldwide. Therefore, as a sponsor-investigator, a clear and thorough understanding of GCP and the practical implementation of these principles during the planning and conduct of the clinical investigation is just as important as possessing the scientific and clinical expertise in the disease or condition being investigated. It is, in fact, the combination of these two factors, scientific expertise and a thorough understanding of GCP that will help ensure that the clinical investigator will be successful in not only following FDA regulatory requirements, but most importantly help ensure the safety of the subjects enrolled in the investigation as well as provide valid and reliable data to FDA.

What Do We Mean When We Say GCP?

FDA regulations define GCP as "a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides

Table 17.2 Summary of GCP principles as per ICH E6

• Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s)
• Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks
• The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society
• The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial
• Clinical trials should be scientifically sound, and described in a clear, detailed protocol
• A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion
• The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist
• Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)
• Freely given informed consent should be obtained from every subject prior to clinical trial participation
• All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification
• The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s)
• Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol
• Systems with procedures that assure the quality of every aspect of the trial should be implemented

assurance that the data are credible and accurate and that the rights, safety, and well-being of trial subjects are protected" (21 CFR 312.120(a)(1)(i)). The principles of GCP can also be found in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E6 Good Clinical Practice [3]. In that document, commonly known as ICH E6, the principles of GCP are summarized in Table 17.2.

In addition to ICH E6, there are other globally recognized documents that further describe the importance, principles, and practices of GCP. These include:

- "***Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries***," published by the National Bioethics Advisory Commission, 2001
- "***International Ethical Guidelines for Biomedical Research Involving Human Subjects***," prepared by the Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization 2002
- ISO 14155:2011 "***Clinical Investigation of Medical Devices for Human Subjects-Good Clinical Practice***," issued by the International Organization for Standardization

It is important to note that ISO 14155:2011, unlike the other documents mentioned, is specific to medical devices and therefore it is intended to address the unique challenges that one may encounter when conducting a trial on medical devices that are not typically seen in trials of drugs and biologics.

The numerous documents and standards on GCP published by the various global health agencies and organizations give evidence to the fact that GCP is a critically important concept worldwide and is at the foundation of what it means to conduct a clinical investigation ethically by upholding the rights of study subjects and ensuring their safety and welfare. While it is not necessary for a clinical investigator to read and analyze all of these documents to remain in compliance with FDA regulations, it is important for him/her to recognize the importance of GCP and the general globally accepted concepts and principles that make up GCP.

Another reason why adherence to GCP is so important for FDA as well for regulators globally is because, in the not so distant past, the idea that human subjects in clinical trials should be afforded certain rights and protections was not given. As a result, there are numerous examples of clinical trials that were not conducted ethically and the rights of the human subjects were not considered. Not surprisingly, many of these trials resulted in significant injury or even the death of some of the human subjects involved. One of the earliest examples of violations of the rights of human subjects resulted in the Nuremberg War Crimes Trials.

During these trials, 23 physicians were charged with crimes against humanity due to their performing experiments on the prisoners in concentration camps without their knowledge and/or consent. These trials resulted in the formulation of the "Nuremberg Code" that effectively set basic rules for clinical trials. These are that consent should be voluntary; benefits should outweigh the risks, and that the subject should be able to terminate participation at any time. Unfortunately, despite the existence of the Nuremberg code,

there continued to be instances of human subject protection violations. Some of these include:

- The Thalidomide tragedy: The experimental drug, Thalidomide, was prescribed to thousands of pregnant women without informing them of the risks of the drug and the fact that it was experimental. The drug was found to be teratogenic, causing limb deformities in the fetus. Expectant mothers were not informed of the risks associated with thalidomide or that it was an experimental drug. Additionally, patients did not volunteer nor did they give consent to participate in the research. It is thought that some 12,000 babies were born with birth defects due to Thalidomide. In 1960, Dr. Francis Oldham Kelsey, a physician at FDA refused to approve Thalidomide for use in the U.S. due to reports of side effects, despite pressure from manufacturers. For her service to public health, Dr. Kelsey was awarded the President's Award for Distinguished Federal Civilian Service in 1962 by President John F. Kennedy (Fig. 17.2).
- The story of Henrietta Lacks: a 31-year-old African-American female from Maryland who sought treatment at Johns Hopkins for cervical cancer. She eventually died from the disease; however, during the course of her treatment before her death, her physicians at Hopkins had taken samples of her tissues, both healthy and malignant, to use for research purposes without her knowledge or consent. These cells would later be known as "HeLa" cells (Fig. 17.3) and they are referred to in more than 74,000 scientific publications and would eventually be used in the development of a number of medical advances, including the polio vaccine, tamoxifen, chemotherapy, gene mapping, in vitro fertilization, and treatments for influenza, leukemia, and Parkinson's disease. Her family became aware of this in 1973 and petitioned to have some say in the use of their relative's tissues. However, it was only recently in 2013 that the family regained some control over how Henrietta Lacks' genome is used [4] through an agreement reached with the National Institutes of Health.
- The Tuskegee Syphilis Experiment, 1932–1972 [5]: The experiment, sponsored by U.S. Public Health Service was proposed as an observational study of the effects of untreated syphilis. The clinical investigators recruited 600 poor, African-American males in Macon County, Alabama to participate in the study. Three hundred and ninety-nine (399) men had syphilis and 201 did not. These men's rights were violated from the very beginning. Some of the violations included the fact that the men were not told the purpose of the study; as a result no informed consent was obtained; they were lied to and were told that they were being treated for "bad blood"; they were offered free meals and payment of burial expenses as an incentive to participate; and finally the men who were known to have syphilis were not treated with Penicillin despite its availability in 1947. The Tuskegee Syphilis Study (Fig. 17.4) did set the stage for important U.S. legislation geared toward ensuring the protection of study subjects involved in clinical trials. Most specifically the Belmont Report [6] was drafted to provide important guidelines to help develop U.S. Regulations, including FDA GCP regulations, for the ethical conduct of clinical trials.

Fig. 17.2 Dr. Francis Oldham Kelsey receiving the President's Award for Distinguished Federal Civilian Service in 1962 by President John F. Kennedy

The Sponsor-Investigator and Good Clinical Practice

The clinical investigator of a trial has numerous responsibilities. The specific responsibilities as required by regulation will be discussed later in the chapter. If the clinical investigator is also the one manufacturing the device and/or initiating the clinical investigation, he/she therefore becomes the trial's sponsor-investigator (SI's). For those who choose to be SI's, the responsibilities increase significantly since they are accountable for following the FDA regulations that dictate both the sponsor's and the clinical investigator's responsibility. As stated earlier, FDA regulations for device trials are based on the principles of GCP—the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials. The SI's is ultimately responsible

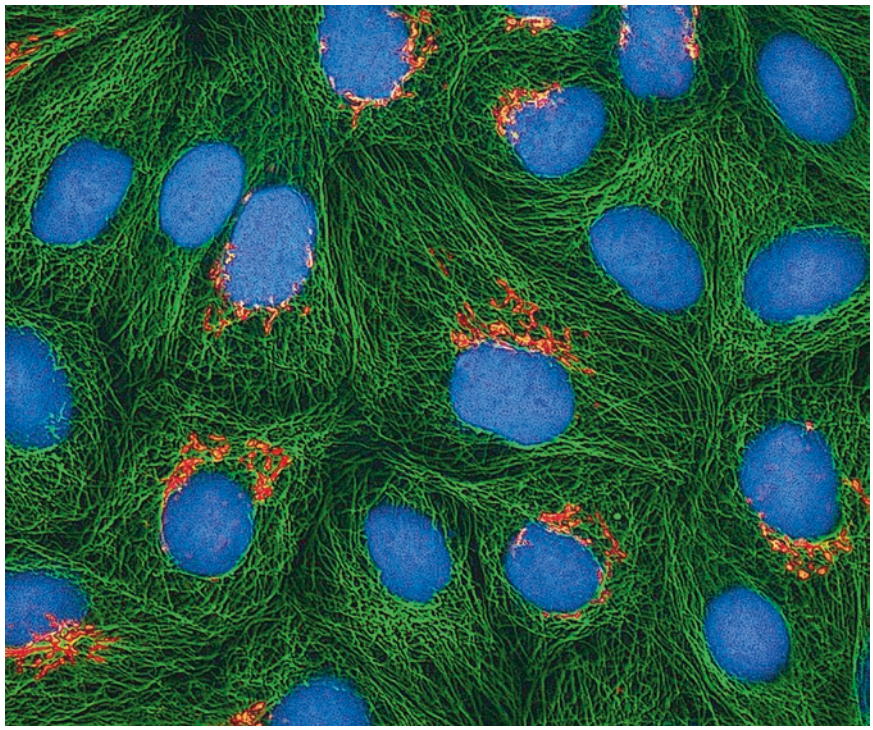

Fig. 17.3 Multiphoton fluorescence image of cultured HeLa cells *Tom Deerinck.* http://www.nih.gov/news-events/news-releases/nih-lacks-family-reach-understanding-share-genomic-data-hela-cells. NIH, Lacks family reach understanding to share genomic data of HeLa cells

Fig. 17.4 U.S. Public Health Service Syphilis Study at Tuskegee

for making sure that all of these principles are met. This may seem at first burdensome; however, in order to prevent any recurrences of the ethical violations presented earlier on in this chapter, it is essential that the SI acknowledges and accepts that the principles of GCP must be upheld through their understanding and compliance with FDA regulations. The NIH GCP training/certificate resource (http://www.cc.nih.gov/training/training/crt.html) is accepted by all IRBs and includes a module for FDA oversight of clinical research.

Adhering to GCP and conducting a trial successfully involves a team approach. For FDA, the trial's clinical investigator, sponsor, CRO, IRB, and FDA are all on the same team where communication is key and the responsibility to conduct the trial in accordance with GCP is shared.

Not unlike being the head of a surgical team, the SI should realize that successful conduct of a clinical trial at his/her site also involves a team approach where he/she is also the team leader. As the team leader, the SI's goal should be to recognize that each member of his/her team has their own set of responsibilities that must be fulfilled. Therefore, as the team leader the SI should make sure that, for example, his/her sub-investigators are properly trained and have knowledge of the protocol, including any amendments; that the person getting informed consent from subjects knows that they must use the most updated version and the form must be signed and dated in all of the required fields; and that the person reporting the adverse events is aware of when the report needs to be submitted if delineated by the protocol. In essence, the SI should ensure that members of the team are qualified to fulfill their role; are properly trained clinically, but also have knowledge of the protocol and what is required. The SI should also make it a practice to perform regular checks on the team members to ensure that they are performing their roles adequately. Regularly scheduled study team meetings are a great venue to communicate study updates and discuss study progress and challenges.

Overview of Sponsor-Investigator Roles and Responsibilities

The regulations define the dual role of the sponsor and investigator (SI's) as an individual who both initiates and actually conducts the study (21 CFR 812.3(o)). Examples of SI's include: inventor/innovator, academic researcher, sponsor sur-

rogate, physician/surgeon interested in a new use of an already approved device, or any combination of these examples. FDA regulations clearly define the role and responsibilities of those involved in FDA-regulated clinical investigations. It is important to have a full understanding of the SI role and associated responsibilities because this becomes a legal responsibility for which one is held accountable by regulatory authorities. Wearing both hats can be challenging and requires a skilled research team. Consultation with a device manufacturer with research experience and colleagues who have experience with the IDE application process and conduct of an IDE study can be helpful. Academic SI's may find it useful to consider the resources available within your institutions. For example, most academic institutions have regulatory resources available through the Research Department or Ethics Office of the University. Additionally, it is recommended that an SI interact with the FDA through the pre-submission process when preparing the IDE application. FDA also provides online resources that can assist the SI in their role and responsibilities. The following links will provide you with detailed information regarding device advice, basics of an IDE, and several case studies:

- http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm
- http://fda.yorkcast.com/webcast/Play/696d857b34334d5389364ed8c2db3ded1d
- http://www.fda.gov/Training/CDRHLearn/default.htm

As discussed earlier, the SI's are responsible for following the regulations of the Sponsor and Clinical Investigator (CI) as defined in the FDA IDE regulations (21 CFR 812.40 and 812.100). The clinical investigator conducts the investigation and oversees the use or administration of the investigational device in a patient. In the event of an investigation being conducted by a team of individuals, "investigator" refers to the responsible leader of that team. It is important to note that the FDA considers the principal investigator and the sub-investigators "investigators" who are held responsible for complying with the investigator responsibilities in the regulation.

The sponsor is an individual, company, institution, or organization that takes responsibility for the initiation, management, and may finance a clinical investigation. The sponsor-investigator responsibilities include all of those listed above for the investigator plus the sponsor responsibilities presented in Table 17.3.

Building Quality Into Sponsor-Investigator Clinical Studies of Medical Devices

There are resources available to assist SI's with incorporating quality early in the study design [7]. A well-designed and -executed study protocol is the most important tool for ensuring high-quality data and human subjects protections. Interactions with FDA during the design phase and throughout the study conduct is recommended as well as selecting qualified study personnel and working with a skilled research staff. It is advisable to consult with the device manufacturer when appropriate and other SI's who have experience with IDE studies. Additionally, obtain feedback from study staff early and often on the protocol requirements. Poorly designed or difficult to execute protocols and poor study monitoring can introduce errors leading to unreliable study data and may place study subjects at risk for harm. Study-specific training of site staff and the development of an adequate study monitoring plan is one of the best upfront investments to ensure data quality, integrity, and subject safety.

Site staff training is provided before study initiation and recommended when essential study staff are replaced, there are significant changes in the device or protocol, or monitoring visits reveal problems. Important areas to cover during training include: the study protocol, study expectations, procedures unique to the device or its use in the study, regulatory requirements, clinician vs. investigator responsibilities, and the importance of following the informed consent process, reporting of adverse events, and protocol deviations.

Clinical study monitoring is the development of a plan used to oversee the study conduct and reporting of data from a clinical investigation. The focus of study monitoring should be on the processes that are critical to protecting human subjects, maintaining the integrity of study data and compliance with applicable regulations.

Monitoring is intended to identify and correct practices that could result in inadequate patient protections and poor data quality. Regular data audits also avoid numerous site queries and costly late database cleanup.

FDA regulations are not specific about how sponsors are to conduct monitoring of clinical investigations. The regulations do require the selection of qualified, trained, and experienced monitors to monitor the study in accordance with the IDE and other applicable FDA regulations (21 CFR 812.43). For example, a medical monitor can be a physician independent of the study team who routinely provides this service through the university or academic research office. It is not advisable to select a colleague or physician who is not experienced in the role of a study monitor or able to commit to the study monitoring responsibilities. Monitoring services can also be provided through qualified third-party contract research organizations (CROs). Although sponsors can transfer responsibilities for monitoring to a third party, they are ultimately responsible for ensuring adequate study monitoring. The monitor assists the SI in study activities such as the development of the study monitoring plan, adverse event adjudication, data and site audits and initiation of corrective action early in the study conduct to catch problems before they become repetitive and data integrity is compromised.

Table 17.3 Summary of key components of an IDE as per CFR

21 CFR Part	Area	Description
812.40	General	Select qualified investigators and provide them with the information needed to conduct the investigation properly. Ensure proper monitoring of the investigation and IRB review and approval, submit an IDE application to FDA for significant risk device studies, and inform the IRB and FDA promptly of any significant new information about the investigation
812.42	FDA and IRB approval	Cannot begin an investigation or any part of an investigation until an IRB and FDA have both approved the application or supplemental application
812.43	Selecting investigators	Select qualified, trained, experienced investigators to investigate the device
812.43	Selecting monitors	Select qualified, trained, experienced monitors to monitor the investigational study in accordance with the IDE and other applicable FDA regulations
812.43	Device control	Can ship investigational devices only to qualified investigators participating in the investigation
812.43	Investigator agreements	Must obtain a signed agreement from each participating investigator as required by the regulation
812.45	Informing investigators	Must supply all participating investigators with copies of the investigational plan and a report of prior investigations of the device
812.46	Monitoring	Must secure investigator compliance, evaluate unanticipated adverse device effects, and follow-up on subsequent actions as required. Must seek IRB and FDA approval for the resumption of terminated studies
812.140	Sponsor records	Must maintain accurate and complete investigation records
812.150	Sponsor reports	Must provide reports in a timely manner to FDA, the IRB, and/or investigators
812.5	Labeling	An investigational device or its immediate package must bear a label with the prescribed information
812.7	Promotion of investigational devices	A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator cannot promote, test market, commercialize, etc., investigational devices

Source: U.S. Food and Drug Administration—Case Study (2014). http://www.fda.gov/downloads/Training/CourseMaterialsforEducators/NationalMedicalDeviceCurriculum/UCM404249.pdf

Typically, monitoring visits occur early to ensure site readiness and as frequent as necessary (i.e., every 4–8 weeks) to meet the needs of the specific study. Monitoring should focus on activities related to evaluation of study data and study conduct or processes. Suggestions for what should be monitored in an IDE study include:

- Data critical to the reliability of the study findings (i.e., source to case report form verification of data that support primary and secondary endpoints);
- Data critical to subject safety (i.e., protocol deviations/violations, subject eligibility criteria, serious and unanticipated adverse events, deaths and withdrawals particularly when related to an adverse event);
- Processes critical to subject safety and ethical treatment (i.e., verification that proper informed consent is obtained, appropriate medical consultation for significant clinical or lab findings and documentation of device accountability and administration of the investigational product); and
- Processes critical to data integrity (i.e., timely review of specified events for adjudication).

The goal at the end of the study is to have accurate and reliable clinical data and assurance that the rights, safety, and welfare of the subjects participating in the clinical investigation were protected.

FDA conducts on-site inspections to assess the protection and safety of subjects participating in clinical investigations and to determine the integrity and quality of data submitted to the agency. FDA's inspection program includes inspections of Sponsors, Clinical Investigators, CROs, and Institutional Review Boards (IRBs). An SI can be cited for non-compliance of both the sponsor and investigator regulations. Based on data from FDA inspections [8], some of the more common SI citations or deficiencies include:

- Failure to follow the investigational plan, investigator agreement or protocol (e.g.., changes made to the study without amending the protocol);
- Failure to obtain adequate informed consent (e.g., not re-consenting subjects when substantive revisions were made to the initial approved protocol and informed consent or consenting subjects with the incorrect version of the informed consent document);

- Not submitting an IDE application to FDA (e.g., SI not aware their study required an IDE);
- Inadequate study Monitoring (e.g., SI served as their study monitor and failed to catch many of their own mistakes);
- Not providing adequate progress reports to FDA and IRB (e.g., IRB halted the SI IDE study and the SI did not report to FDA); and
- Not having accurate, current, and complete records (e.g., SI focused on the science of the study and not enough on the importance of good documentation).

Historically, studies that have been initiated and conducted by physician-scientists or physician-inventors have been at the cornerstone of medical device innovation and development. We recognize that physicians and/or scientists who wish to pursue SI IDEs are required to take on a significant amount of responsibly as there are many rules and regulations to follow. However, FDA is committed to supporting and guiding those who wish to pursue SI IDEs in order to improve the public health by getting safe and effective medical devices to those who need them.

References

1. Abel D, Farb A. Application of Investigational Device Exemptions regulations to endograft modification. J Vasc Surg. 2013;57:823–5.
2. O'Callaghan A, Mastracci TM, Eagleton MJ. Staged endovascular repair of thoracoabdominal aortic aneurysms limits incidence and severity of spinal cord ischemia. J Vasc Surg. 2015;61(2):347–54. e1. doi: 10.1016/j.jvs.2014.09.011. Epub 2014 Oct 23.
3. http://www.fda.gov/downloads/Drugs/…/Guidances/ucm073122.pdf. Note: the ICH E6 currently published is being revised
4. Zimmer C. A family consents to a medical gift, 62 years later. The New York Times. 7 Aug 2013.
5. http://www.cdc.gov/tuskegee/timeline.htm
6. http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html
7. http://www.ctti-clinicaltrials.org/toolkit/qbd/learn-about-qbd
8. http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm261409.htm

Resources/Useful Links

Device Advice: Investigational Device Exemption (IDE). http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm

Selected FDA GCP/Clinical Trial Guidance Documents. http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219433.htm

2015 Case Studies. http://www.fda.gov/Training/CourseMaterialsforEducators/NationalMedicalDeviceCurriculum/ucm404245.htm

Building Quality Into Clinical Trial Design. http://www.ctti-clinicaltrials.org/toolkit/qbd/learn-about-qbd

Clinical Trials and Human Subject Protection. http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htmPre-Submission Program. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

Ecopy. http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm313794.pdf

Early Feasibility. http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf

CDRH Learn. http://www.fda.gov/Training/CDRHLearn/