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Navigating the intricacies of medical device clinical research compliance: A primer

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The U.S. Food and Drug Administration (FDA) regulation of medical devices is quite complex. With the evolution and emergence of newer technologies, determining how these devices will be regulated and navigating the regulatory pathways are difficult tasks. In addition, during the past decades, the number and complexity of clinical trials have grown dramatically. These changes have created new challenges to clinical trial oversight. Effective monitoring of clinical investigations by sponsors is critical to the protection of human subjects and the conduct of high-quality studies. Protecting the rights, safety, and welfare of people who participate in clinical research is a critical aspect of the FDA's mission. In this article, we provide a top-level discussion on the basics of medical device clinical research compliance.

Regulatory authority over clinical investigations

In 1976 Congress enacted the Medical Device Amendments, which expanded the FDA's statutory authority over medical devices and established three regulatory classes for medical devices based on the degree of control necessary to assure that the various types of devices are safe and effective.[1] Since then Investigational Device Exemption (IDE) statutory provisions and implementing regulations have encouraged discovery and development of medical devices while protecting public health and safety. In particular, the FDA IDE regulation is intended to oversee clinical research involving "investigational" medical devices.[2] Using this tool, the FDA oversees clinical trials to ensure they are designed, conducted, analyzed, and reported according to federal law and good clinical practice. In addition, FDA guidance documents for clinical trials also provide a good road map for efficient medical product development while ensuring that trials generate the robust evidence needed to ascertain product safety and efficacy.[3] Most notably, the FDA's Center for Devices and Radiological Health has issued multiple device-specific guidance documents that contain explanations of the requirements for clinical trials as well as data and other information to be included in the different types of marketing submissions for medical devices. These should be consulted frequently as they are added to the FDA's website.

Investigational device exemptions

Devices meant to be used on human subjects in order to investigate the device's safety and effectiveness for a particular intended use, which are not cleared or approved by the FDA, are considered "investigational devices"

under Section 520(g) of the Federal Food, Drug, and Cosmetic (FD&C) Act.[4] These devices are not approved for commercial distribution by the FDA for their investigational use. Compliance with the IDE regulations allows an investigational device to be shipped lawfully through interstate commerce for the purpose of conducting the required clinical research without having to comply with other requirements set forth in the FD&C Act that would apply to devices in commercial distribution.

In this manner, an IDE allows for the investigational device to be used in a clinical study while safety and effectiveness data are being collected in order to support a marketing application (e.g., premarket notification, or 510(k), submission or a premarket approval application).[5]

Risk-based scheme

The FDA takes a risk-based approach to monitoring clinical study compliance, which focuses on sponsor and clinical investigator oversight activities, to prevent or mitigate risks to data quality and protect human subjects and trial integrity. The IDE regulations describe three types of medical device studies: (1) significant risk (SR), (2) non-significant risk (NSR), and (3) exempt. A study's classification will determine whether FDA approval of an IDE application is required before starting a clinical study. Sponsors are responsible for making the initial risk determination and presenting it to the institutional review board (IRB). The FDA is the final decision-maker as to whether a device study presents a significant risk or non-significant risk. It is important for study sponsors and investigators to be familiar with the IDE regulations and understand FDA considerations about risk determination so that their classification is aligned with how FDA reviewers assess the study.

SR and NSR devices

An SR device is considered an investigational device that (1) "is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;" (2) "is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;" (3) "is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or" (4) "otherwise presents a potential for serious risk to the health, safety, or welfare of a subject."[6] Some examples include sutures, cardiac pacemakers, and orthopedic implants. An NSR device is one that does not meet the definition of an SR device. Examples include daily-wear contact lenses, lens solutions, and Foley catheters.

The major difference between an SR and an NSR study mainly lies in the IDE approval process and the requirements, as outlined below. For instance, an SR device must meet all the regulatory requirements set in 21 C.F.R. Part 812 , including the requirements establishing that the sponsor obtain IDE approval for its study from the FDA.[7] Meanwhile, an NSR device study does not require IDE approval from the FDA and is subjected to an abbreviated set of requirements. Nonetheless, both types of studies are subject to the informed consent and IRB regulations as established in 21 C.F.R. §§ 50 and 56 .

A study determined to pose "non-significant risk" can begin without FDA review but still requires compliance with a set of abbreviated IDE requirements.[8] These include: (1) having appropriate labeling, (2) obtaining and maintaining IRB approval as an NSR study throughout the course of the investigation, (3) obtaining informed consent from study participants, (4) monitoring and ensuring compliance with protocols, (5) maintaining records of a participant's case history and exposure to device, and (6) submitting appropriate reports in case of an adverse event or withdrawal of IRB approval, among other requirements.

Exempted investigations

Generally clinical investigations of devices to support a market application are subject to the IDE requirements. However, there are certain limited exemptions from the IDE regulations. Some of these are for (a) devices "undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk"; (b) "shipped solely for research on or with laboratory animals" and labeled accordingly; and (c) diagnostic devices, if the sponsor complies with requirements in 21 C.F.R. § 809.10(c) and if the testing is noninvasive, "does not require an invasive sampling procedure that presents significant risk," "does not by design or intention introduce energy into a subject," and "is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure."[9]