FDA INSIGHTS

Providing a Reasonable Assurance of Safety and Effectiveness

Who is responsible?

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The mission of the Center for Devices and Radiological Health (CDRH) is to promote and protect the health of the public by ensuring the safety and effectiveness of medical devices and the safety of radiological products. Although we are the gatekeeper for medical devices, we share this responsibility as it relates to clinical studies with Institutional Review Boards (IRBs), device manufacturers, and those participating in clinical studies.

The evaluation of medical devices is unfortunately plagued with inherent biases. The types and sources of potential bias are innumerable. There are problems with both real and perceived bias. For example, a lack of randomization in a study introduces the potential for the comparison of patients with different risk levels. Covariate analyses and propensity score analyses may lessen the concern; however, the perception is likely to remain that the comparison may not be appropriate. Similarly, excessive lost-to-follow-up or missing data in a clinical study may bias the results.

Recently, there has been criticism of the conduct of studies used to evaluate new interventional devices. This article will discuss the responsibilities of various entities in minimizing bias and optimizing datasets to provide the best possible assurance of the safety and effectiveness of medical devices in the US.

FDA RESPONSIBILITIES

The Office of Device Evaluation (ODE) in the Center for Devices and Radiological Health is responsible for reviewing clinical study proposals under Investigational Device Exemptions (IDE) applications. In this capacity, the ODE determines whether adequate information has been provided to justify the initiation of the study, whether the study should result in the collection of valid scientific evidence, and if all required elements for the IDE have been provided, including written monitoring procedures and the investigator agreement. As such, the primary contribution of the ODE in minimizing bias is to help optimize the study design and to make sure that the written plans for the collection of data and monitoring of the study are adequate.

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Of note is that the ODE generally does not get involved in selecting investigators or investigational sites. Usually, a waiver is provided to the sponsor, which allows them to select and enroll a specified number of sites without the need for FDA approval of each site.

Part of the information the sponsor of the IDE collects from potential investigators is a disclosure statement that provides current and accurate financial information as it relates to the study or investigational device; however, this information is only submitted to FDA in a marketing application involving the subject device and not at the time of IDE submission. Sponsors of a Pre-Market Approval application are required to submit disclosures for all investigators participating in any study regarding the investigational device. If a conflict of interest is noted in the disclosures during the review of the Pre-Market Approval that may affect analysis of the clinical trial results regarding the device, sever-

al options may be considered. The sponsor of the Pre-Market Approval may be able to provide a rationale for why the study design or monitoring of the clinical trial mitigates perceived conflicts by any one investigator. Alternatively, the FDA may choose to conduct an analysis of the dataset without data collected by a conflicted investigator.

IRB RESPONSIBILITIES

An IRB monitors and reviews research involving human subjects prior to initiation of an investigation and throughout a clinical study. The IRB is a group formally selected to ensure that the rights, safety, and welfare of patients participating in a clinical study are protected. An IRB has the right to approve, disapprove, or modify proposed clinical studies.

A sponsor wishing to study a significant-risk device must have approval from both the FDA and the IRB prior to initiating the investigation. The FDA does not approve or endorse any specific IRB; however, they may inspect the records and procedures of an IRB to ensure that they are in compliance with FDA regulations. Although clinical investigators may be IRB members, the regulations prohibit anyone from participating in the review of any study in which they have a conflicting interest.

INVESTIGATOR RESPONSIBILITIES

Before participating in an investigational study, an investigator must sign an agreement. This agreement contains an explanation of the investigator's applicable experience, including a curriculum vitae as well as notification of any research that was terminated that included the investigators' involvement. By signing the agreement, the investigator agrees to conduct the study in compliance with the agreement, the investigational plan, applicable regulations, and conditions of approval specified by the IRB or the FDA. They also agree to oversee use of the device in all patients and make sure that informed consent is obtained appropriately.

A study investigator has many responsibilities to ensure the safety of patients enrolled in a trial, including keeping records and submitting appropriate reports to the sponsor and the IRB. FDA regulations specify that an investigator must maintain complete and accurate records related to the study. Such records should be current and include information pertaining to all correspondence with other investigators, the IRB, the study sponsor, monitor and the FDA; use and disposition of the investigational device; subjects' case histories and device use, including case report forms, medical records, evidence of informed consent, and all relevant observations; and documentation of any protocol deviations.

Investigators are also required to provide reports to the study sponsor, the IRB, and if the investigator is the sponsor of the study, the FDA. Reports are required to detail the progress of the study as well as to report unanticipated adverse device effects, deviations from the investigational plan, or withdrawal of IRB approval. When a study is completed or terminated, an investigator should also submit a final report.

In the end, the investigator is responsible for following the protocol, which includes following through with the written plan approved by the FDA and the IRB, and maintaining and providing appropriate documentation. By following the plan, the investigator minimizes biases associated with protocol deviations and optimizes the data available to demonstrate safety and effectiveness.

IDE SPONSOR RESPONSIBILITIES

The brunt of the responsibility in establishing an investigational plan that will develop data to provide a reasonable assurance of safety and effectiveness for a device resides with the IDE sponsor. It is the sponsor who defines the clinical study, with an emphasis on developing the least burdensome plan. For example, although randomized clinical studies are the most rigorous, they are also difficult to conduct. As such, if a reasonable assurance of safety and effectiveness can be obtained through the use of a concurrent control or another study design, the sponsor will propose the less burdensome design.

The responsibility of selecting investigators also falls to the sponsor. They are charged with selecting investigators qualified to participate in a specific study based on the clinicians' training and experience. As noted previously, investigators are required to report any conflict of interest in a disclosure statement, as well as sign an investigator agreement. With respect to conflicts of interest, sponsors must weigh their ability to encourage investigators to participate with the appearance of conflicts and potential for introducing bias in the study.

Sponsors are required to monitor the study to ensure that investigational sites are in compliance with the investigational plan. Although the FDA audits the data, this generally occurs late in the process (ie, too late to salvage the data if major problems are identified).

In summary, the responsibility of minimizing bias and the ability to optimize datasets lies primarily with the sponsor. However, all involved parties must fulfill their responsibilities in order to ensure that investigations are conducted appropriately. ■

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