Clinical Research Column

Research Compliance Q&A: Investigator-Initiated Clinical Research Studies

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In an investigator-initiated clinical research study, the investigator serves as both the sponsor of the research and the clinician-investigator. While investigator-initiated clinical research generally is governed by the same principles and regulations that apply to clinical research studies sponsored by a third party, such as a pharmaceutical company, some aspects of investigator-initiated research require special consideration. As investigator-initiated research becomes increasingly more prevalent, it is important to be aware of some common misconceptions and issues of concern in this area. The following questions and answers highlight some of these important issues.

Q: I overheard one of the members of our medical staff say that investigator-initiated drug studies are easier to manage because they are exempt from FDA regulations. Is it true that FDA requirements do not apply to investigator-initiated studies?

A: Clinical investigators who sponsor research studies 'sponsor-investigators' may not be well versed in FDA regulatory requirements and may mistakenly assume that these requirements do not apply to investigator-initiated drug studies. For example, some sponsor-investigators erroneously conclude that an investigator-initiated drug trial does not require an Investigational New Drug application (IND). Federal regulations require the sponsor of a study to obtain an IND not only for clinical trials involving drugs that are not yet approved for marketing, but also for trials involving a new indication, route of administration, or change in dosage for an approved drug. Drug trials involving the latter are exempt from IND requirements only if the study (1) is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use or other significant change in the labeling of the drug; (2) is not intended to support a significant change in the advertising for the product; (3) does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks, or decreases the acceptability of the risks, associated with the use of the drug product; (4) is conducted in compliance with federal IRB review and informed consent requirements; and (5) is conducted in compliance with the requirements for promoting and charging for investigational drugs found at 21 C.F.R. § 312.7. See 21 C.F.R. § 312.2(b).

Investigators who normally take part in studies sponsored by a pharmaceutical company or other third-party may be surprised to learn that in investigator-initiated studies the responsibility for obtaining an IND shifts to the investigator. Similar confusion may arise with respect to the Investigational Device Exemption (IDE) requirements that apply to device trials. While some device trials are exempt from IDE requirements, there is no blanket exception for investigator-initiated device trials. The fact that a study is investigator-initiated does not itself excuse the study from compliance with either the IND or IDE regulations; rather, the sponsor-investigator has a duty to obtain the IND or IDE if one is required.

Sponsor-investigators also sometimes believe that if a drug study does satisfy the IND exemption requirements, the study is not subject to IRB review or the FDA's informed consent requirements. In fact, a drug study that is otherwise exempt from IND requirements must comply with federal regulations regarding IRB review. In addition, sponsor-investigators of drug studies must document, via a signed informed consent form, the informed consent of each research participant or the participant's legally authorized representative. An IRB may waive the requirement for a signed informed consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. In very limited, life-threatening circumstances, an IRB may approve a waiver of informed consent in its entirety pursuant to 21 C.F.R. § 50.23. In short, it is erroneous to assume that an IND-exempt drug study is automatically exempt from other FDA regulatory requirements. If an otherwise IND-exempt drug study fails to obtain IRB review and/or informed consent in accordance with FDA regulations, it will no longer satisfy the IND exemption criteria and will lose its exempt status.

Q: I am a principal investigator looking to sponsor a study that will investigate a new indication for a drug that has already been approved by the FDA. The manufacturer has agreed to provide the study drug to me free-of-charge and might fund the study as well. The sales representative said the company wants to send me,
and my husband, on an all-expenses paid 10-day trip to Paris. They have an office there and have asked me to meet with company representatives to review my protocol. The company also wants me to meet other researchers based in Europe who are looking at new uses for the same drug they think we should meet to discuss our respective protocols and share ideas, increase efficiencies, and perhaps collaborate rather than run separate studies. The meeting with the company representatives and the researchers will only take two days to complete. Is it OK to accept the free study drug, funding, and trip to Paris?

A: The Office of the Inspector General (OIG) has indicated in its Compliance Program Guidance for Pharmaceutical Manufacturers that the provision of a study drug free-of-charge and/or funding for an investigator-initiated study is not permissible under federal fraud and abuse laws, so long as the study is for a legitimate scientific purpose and the funding is tied to legitimate study costs. See 68 Fed. Reg. 23731 (May 5, 2003). In other words, the study cannot be a sham such that it serves, for example, simply as a vehicle to reward either high-volume on-label prescribing practitioners or key opinion leaders on the off-label use of the manufacturer’s drug.

In the OIG’s view, the legitimacy of the study and the funding may be suspect if the marketing division of the pharmaceutical company is the driving force and decision-maker on whether to support the study. Consequently, you should ensure that your request for support is reviewed and approved by the medical/clinical component of the pharmaceutical company.

It may also benefit both you and the pharmaceutical company if the study undergoes scientific review by a third party; this will help support the legitimacy of the study. Many research institutions have a scientific review committee, so if you are affiliated with an institution that has such a committee, it may be worth pursuing. Indeed, some institutions require scientific review of investigator-initiated studies.

As for the trip to Paris, it too must pass the ‘legit’ test. As is true with respect to remuneration you receive from any entity to which you refer health care business, you must be very careful that the remuneration is not payment for referrals in fact or in appearance. You must ensure the remuneration is fair market value for legitimate services rendered or otherwise is a valid component of implementing a legitimate investigator-initiated research study. Consequently, if (1) you legitimately need to meet in Paris because it is a central location convenient for all of the other researchers and because it is where the company’s clinical/medical representatives are convening (not because you told the sales representative that you always wanted to go there); (2) you actually meet and discuss your protocol with company representatives and the other researchers; and (3) the expenses paid are reasonable and not lavish, it should be acceptable for the company to fund the portion of your trip related to the business conducted with the company and other researchers. This means it is not appropriate for the company to pay for lodging and expenses for 10 days when your meeting will conclude in two days, nor should you accept any payment to cover your husband’s expenses.

Q: The number of investigator-initiated studies at our institution has increased considerably in the past few years. We are preparing to audit our research compliance program to ensure that investigator-initiated research is adequately addressed. Are there any specific oversight mechanisms that institutions should consider implementing for this type of study?

A: Investigators who decide to become sponsor-investigators may be seasoned in administering the study protocol and other clinical aspects of the research endeavor; however, they are often less experienced, or not experienced at all, in taking overall responsibility for the study with respect to monitoring, data integrity, reporting obligations, and oversight of human subject protections. FDA regulations specify responsibilities for both sponsors and investigators, and in the case of an investigator-initiated study, the sponsor-investigator must comply with both sets of requirements. As investigator, he or she is responsible for: obtaining IRB approval; obtaining the informed consent of each study participant; implementing the protocol; oversight of study personnel; and reporting adverse events to the IRB. As the sponsor, he or she is responsible for developing and modifying the protocol, as necessary; ongoing monitoring of the study; reporting adverse events to regulatory authorities; interacting and responding to regulators; and suspending or discontinuing the study for safety or other reasons, as appropriate. In addition, as with any research endeavor, the sponsor-investigator must ensure compliance with applicable state laws, codes of conduct, and good clinical practices.

When wearing the hats of both sponsor and investigator, even the most diligent sponsor-investigator needs assistance juggling the patchwork of legal and institutional rules and requirements. Failure to comply with any of the governing authority can result in harm to human subjects, government sanctions, loss of research funding, civil lawsuits, and damage to the reputation and integrity of an institution’s research activities. Typically, sponsor-investigators are also able to secure only very limited indemnification, if any, from third parties who fund their research or donate a study drug for the research. For example, drug manufacturers who donate study drugs may agree to indemnify the sponsor-investigator or an affiliated institution only for manufacturing defects, if that. Consequently, the liability exposure in investigator-initiated studies may be greater due to limited contractual indemnification.

For all of these reasons, it is imperative that the institution invests sufficient resources to help sponsor-investigators understand their responsibilities as both the sponsor and investigator of investigator-initiated research studies. This includes extensive education and the development of policies and procedures that clearly define roles and responsibilities. The institution should also consider special oversight mechanisms and requirements for
review and approval of investigator-initiated studies, some of which are highlighted below.

1. Know When Research is Going On.

A significant risk for institutions regarding investigator-initiated studies is that research might occur on the institution’s premises, including use of the institution’s equipment and staff for research, without the institution’s knowledge. To minimize this risk, institutions should implement policies and procedures that require investigators to notify the institution of the investigator’s intent to conduct research and that prohibit investigators from conducting studies at the institution without prior written approval. The institution can give these policies and procedures “teeth” by making compliance a condition of granting, and keeping, staff privileges. The institution will also need to invest time in educating investigators because some may not understand fully what activities constitute research. In addition, consider requiring prior review of all publications. Designate an individual responsible for cross-referencing each proposed publication with IRB records to ensure any research reflected in the proposed publication was appropriately reviewed.

2. Require Scientific Review and Appropriate Pre-Implementation Planning.

An important issue for institutions is ensuring that investigator-initiated studies have scientific merit and are well planned and coordinated. Therefore, an institution might consider requiring scientific review of all investigator-initiated research studies before they are submitted to the IRB. Scientific review looks at appropriateness of the study design, use of accepted research techniques, evidence of proper safety oversight, adequacy of background literature review, and validity of the statistical analysis plan.

The institution should also require the sponsor-investigator to hold pre-implementation meetings with key representatives from the institution, including pharmacy, billing, clinical, lab, compliance, registration, and grants and contracts. If the study is subject to FDA oversight, require the sponsor-investigator to communicate and consult with the FDA early on about the study, before enrollment begins. Also, require the sponsor-investigator to notify the institution regarding any FDA or other regulatory audits or sanctions, including clinical holds or other problems.

3. Ensure the Study is Monitored Objectively.

An institution should consider implementing a process for review and approval of outside monitors and should also consider developing specific criteria for when investigator-initiated studies must be reviewed by a Data Safety Monitoring Board (DSMB). The DSMB is charged with monitoring data throughout the duration of a study to ensure the continuing safety of study participants. The method and extent of data safety monitoring should be tailored to the nature, size, and complexity of a particular study, the expected risks to the subjects involved, and the specific population being studied.

4. Implement Mechanisms to Ensure Adverse Event Reporting.

As noted above, reporting obligations that ordinarily apply to a third-party sponsor shift to the investigator in an investigator-initiated study. The sponsor-investigator must report safety information, including adverse events, to the FDA and/or other regulatory authorities as appropriate. It is important for institutions to implement mechanisms to ensure sponsor-investigators follow through with these reporting obligations.

The above represent some of the special areas to consider when reviewing investigator-initiated studies. Other important areas an institution should review in any standard research compliance audit include: informed consent documentation and the informed consent process; recruitment and enrollment; budgeting, billing, and grant management; pharmacy operations; conflicts of interest; data integrity; protocol compliance/deviations; and record retention and documentation.

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Strong reasons make strong actions.
— William Shakespeare