Becoming a principal investigator in FDA clinical trials: Legal and practical considerations

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With declining reimbursement rates from both public and private payors, physicians may be tempted to supplement their practice income with revenue from performing Phase II or III clinical drug or medical device studies. But should they? Such an undertaking requires consideration of both practical and legal issues.

Background. Most studies in which non-academic medical center physicians serve as principal investigators (each, a principal investigator) are studies of interventional medications or medical devices conducted under the authority of the U.S. Food and Drug Administration (FDA). Whether a drug or medical device manufacturer, the sponsor of a clinical trial (the sponsor), must both register the trial and submit information regarding study results to the ClinicalTrials.gov databank. Clinical trials also are conducted under the guidance of an institutional review board (IRB), which is charged with protecting the well-being of human study subjects. For example, the IRB must approve the informed consent document, the protocol for the study (the protocol), any study subject compensation and any investigator brochures or advertisements. The IRB interacts with the principal investigator, rather than the sponsor, although some communication between the sponsor and the IRB may occur to resolve issues that come up in studies.

Requirements of principal investigators. Typically, the principal investigator will contract with the sponsor or a clinical research organization (CRO) hired by the sponsor to assist in carrying out the study process. FDA regulations charge the principal investigator with protecting the rights, safety and welfare of study subjects by appropriately participating in and supervising each clinical trial and ensuring the accuracy and integrity of the data produced during the study.[1] A clinical trial agreement (the agreement) will usually require the principal investigator to carry out the following affirmative duties:

- Conduct the trial in strict accordance with the protocol (except as required to preserve the health and safety of a study subject, and only then with immediate notification to the sponsor) and in compliance with all applicable laws, FDA regulations and guidelines and conditions imposed by the IRB.
- Obtain the approval by the IRB (either designated by the sponsor or chosen by the principal investigator).
- Provide the qualifications of the principal investigator to conduct the clinical trial.
- Store and use the investigational study product (whether drug, biomedical or a device) (the product) as required by the protocol. Some products will require storage in specific temperature ranges and require the principal investigator's site to have refrigerators or freezers with extended capabilities to maintain those temperature ranges and electronic monitors to notify research staff if the temperature departs from the specified range.
- Recruit and screen subjects for the clinical trial. Some multi-site trials have competitive enrollment such that enrollment is closed after the desired number is reached, regardless of whether an individual site has reached its enrollment goals.
- Maintain the confidentiality of all trade secrets relating to the clinical trial.
- Prepare and maintain accurate, complete and up-to-date records regarding the clinical trial. Often, individual study records are submitted via an electronic Case Report Form (each, an e-CRF).
- Obtain from each study subject informed consent and a valid (HIPAA-compliant) authorization to allow the use of e-CRFs and other information for the purposes of the study.
- Carry sufficient professional liability insurance.

- Report any adverse events to the sponsor and/or the IRB.
- Refrain from publishing any articles, abstracts, or presentations regarding study results from their study site prior to the publication of the aggregate study results, and then only with sponsor approval.
- Sign over any and all patentable and unpatentable inventions, discoveries, improvements and ideas made in connection with the trial or product to the sponsor and require all staff to do so as well.

Protections for the principal investigator. The principal investigator will want to ensure that the agreement contains key terms to protect both the principal investigator and the practice serving as the site of the clinical trial. Most important is an indemnification provision pursuant to which the sponsor will hold harmless the principal investigator and practice in case a study subject is injured by the product. The sponsor will likely limit this indemnification to circumstances under which the product was administered in strict adherence with the protocol. In lieu of an indemnification provision, a sponsor may provide product liability insurance coverage that names both the principal investigator and the practice as additional named insureds. Independent insurance covering the activities of the principal investigator and the practice is available and should be considered. Working with an experienced insurance broker and a qualified attorney can help ensure appropriate coverage. In addition to one or more of these protections, the agreement also should provide for direct reimbursement of services provided by the principal investigator, the practice or a hospital for treatment of study subject injuries without the need for litigation.

Applicable law. In addition to the FDA regulations that describe the responsibilities of investigators, requirements of informed consent and other aspects of the clinical trial process, a prospective principal investigator should be aware of other statutes that are implicated by participation in clinical studies.

Federal Anti-Kickback Statute (AKS). The AKS prohibits knowingly offering, paying, soliciting, or receiving anything of value to induce or reward referrals of or otherwise generate Federal health care program business (including, but not limited to, Medicare and Medicaid). The statute, which has both criminal and civil/administrative penalties, ascribes liability to both sides of a transaction. Because of the breadth of the AKS, the U.S. Department of Health and Human Services Office of Inspector General (the OIG) has promulgated regulations, known as "safe harbors," that protect arrangements that meet all elements of the safe harbor from prosecution. Failure to meet all elements of a safe harbor, however, does not make an arrangement a *per se* violation of the AKS.

As a physician who may order the product, if approved, or other drugs or devices manufactured by the sponsor, a principal investigator must ensure that the agreement with the sponsor fits as much as possible within the personal services safe harbor, which requires, *inter alia*: a signed, written agreement that covers all services to be provided; compensation that is both consistent with fair market value and whose method of calculation is set in advance; aggregate services that are reasonably necessary to accomplish the commercially reasonable business purpose of the services; and services that do not involve the counseling or promotion of a business arrangement or other activity that violates any state or Federal law. However, intent also must be considered in certain circumstances. For example, if a pharmaceutical representative approaches a physician who is one of the sponsor's top prescribers in the area and states that, as a reward for those prescriptions, the physician will be offered the opportunity to make more money by conducting clinical trials for the sponsor, that is highly problematic, and a health law attorney should be consulted.

Physician Payments Sunshine Act (PPSA). The PPSA was passed as Section 6002 of the Affordable Care Act of 2010. It requires medical product manufacturers, including pharmaceutical companies and medical device makers, to disclose to the Centers for Medicare and Medicaid Services (CMS) certain information. Data regarding payments for research that must be submitted include: the physician's name and NPI; state professional license number; specialty; and principal business address. This information is submitted annually to CMS, which publishes the data on a public website that can be searched. Prior to publication, the physician is provided notice of the data and 45 days to review and correct it, if necessary. Because of the PPSA, a principal investigator will be asked to fill out forms prior to the commencement

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of the study so that the sponsor may properly report payments made. The purpose of the PPSA and the resulting database is to provide patients information with which they may assess whether their physician may be influenced by payments from medical product manufacturers.

Federal wire fraud statute (18 USC 1343). This statute and others in Title 18 of the U.S. Code may be used to prosecute principal investigators for falsification of data. The wire fraud statute is applicable because most study records submitted are in the e-CRF format and, thus, use interstate wire communications. In order to be convicted under this statute, it must be shown that: (1) the defendant voluntarily and intentionally devised or participated in a scheme to defraud another (i.e., the sponsor) out of money; (2) the defendant did so with the intent to defraud; (3) it was reasonably foreseeable that interstate wire communications would be used; and (4) interstate wire communications were in fact used.

Penalties for misconduct in FDA research activities. Principal investigators can feel a variety of pressures from the sponsor or study monitors hired by the sponsor: getting sufficient patients to enroll, following protocols precisely, filling out paperwork correctly, providing data in a timely manner and others. Those who fail to fulfill their responsibilities properly can be subject to consequences ranging from the sponsor's cancellation of the agreement to FDA enforcement action and even federal criminal prosecution.

The FDA looks at misconduct on different levels.[2] The lowest level is ignorance, which encompasses conduct that a principal investigator, especially a new one, may not realize is wrong, such as filling in a missing date on a consent form the day before the study monitor is supposed to come. The next level of misconduct is sloppiness, which involves inattention to detail, lack of supervision – in general, not acting as the *principal* investigator. The highest level is malfeasance, which often involves falsification of data. Obviously, falsification of data is the FDA's primary concern, as it can place study subjects in that trial at risk and, moreover, destroy the integrity and reliability of data submitted to the FDA.

The FDA has an arsenal of tools for dealing with serious misconduct, including: warning letters (which are publicly available); formal disqualification (meaning that the researcher is ineligible to receive products with which to conduct clinical trials (this occurs after an extensive regulatory hearing process); consent agreements (which contain no formal determination of guilt); voluntary agreements with restrictions (the eligibility to receive products may be retained, provided that studies are conducted in compliance with the restrictions specified and all applicable regulations); clinical hold (FDA orders the sponsor to delay the proposed study or suspend an ongoing one); criminal prosecution; and debarment (after an individual or entity is convicted of a crime related to the FDA drug approval process, a debarred person is prohibited from working for a drug firm in any capacity and from participating in preparing materials to be submitted to the FDA).

Data falsification/research misconduct is a high priority not only for the FDA, but also for the Department of Justice (DOJ). On March 22, 2021, the DOJ announced that a Florida medical doctor was sentenced to 63 months in prison after pleading guilty to participating in a scheme to falsify clinical trial data regarding an asthma medication for children. Her study coordinator was sentenced to prison as well. With respect to this case, Acting Assisting Attorney General Brian M. Boynton stated that the DOJ "will continue working with its partners at the Food and Drug Administration to investigate and prosecute anyone who endangers the public for personal gain."[3]

Takeaways. As clinical drug and device trials are projected to become more decentralized – that is, conducted away from academic medical centers and more accessible to potential study subjects in their own communities and even, in whole or in part, online – the opportunities for independent community physicians to become principal investigators are expected to increase. While many physicians successfully become involved in clinical trial research, becoming a principal investigator is not an enterprise to be undertaken lightly. Interested physicians should consider taking CME or other courses regarding conducting clinical trials, become very familiar with relevant regulations and expectations, hire an experienced clinical research nurse or research coordinator, determine whether current insurance coverage is adequate and have all contracts reviewed by an experienced attorney.

This is not something to be done just for the money, although proceeds from clinical research can boost a practice's revenue. Rather, a genuine desire to further knowledge in your specialty or to provide your patients with cutting-edge medications or technology, as well as having sufficient time, resources and expertise, are necessary to ensure that you can operate successful and compliant clinical trials.

DISCLAIMER: This article is for informational purposes only and does not constitute legal advice. You should contact your attorney to obtain advice with respect to your specific issue or problem.

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References

1. See 21 CFR Part 312 for the investigator's responsibilities in conducting clinical investigations for drugs or biologics; for medical devices, the responsibilities are set forth in 21 CFR Part 812. Prior to participating in a clinical trial, the investigator must complete, sign and submit to the sponsor a Form FDA 1572, which contains commitments of the investigator under Part 312. Nonbinding recommendations are included in "Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects," available online at: https://www.fda.gov/media/77765/download.

2. Information derived from Woollen, Stan W., "Misconduct in Research – Innocent Ignorance or Malicious Malfeasance?" available online at: http://www.fda.gov/files/science%20%26%20research/published/Misconduct-in-Research--Innocent-Ignorance-or-Malicious-Malfeasance-.ppt.

3. DOJ News Release, available online at: https://www.justice.gov/opa/pr/medical-doctor-and-study-coordinator-sentenced-prison-scheme-falsify-clinical-trial-data#:~:text=On%20March%205%2C%202021%2C%20Lisett,conducted%20at%20Unlimited%20Medical%20Research