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# Investigator-Initiated Research

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## Commercial vs. Non-Commercial Clinical Research

Between 1986 and 2006, pharmaceutical and biotech companies submitted 8,759 commercial investigational new drug applications (INDs) to the FDA. During the same years, academic institutions and individuals submitted 26,941 non-commercial INDs, over triple the number of commercial INDs.[1]

Although a high percentage of IND research is non-commercial, government regulations and guidelines are geared toward INDs for commercial marketing purposes. In contrast, in academia, the primary objectives are patient care and contributing to medical knowledge, regardless of commercial implications. While commercial research may create new products that generate billions of dollars in revenue, non-commercial research is more likely to lead to only a small increase in the use of a drug, or even a decrease. In both cases, all the IND regulations in 21 CFR §312 must be followed.

## Investigators and Sponsors

An investigator is an individual who actually conducts a clinical investigation. The operative word here is "individual." A "sponsor" is an individual or organization that takes responsibility for and initiates a clinical investigation. The sponsor does not actually conduct the investigation unless the sponsor is a "sponsor-investigator."

A sponsor-investigator is an individual who both initiates and conducts an investigation, taking on the regulatory obligations of both. The term refers only to an individual. A pharmaceutical company, hospital, or an academic institution cannot be a sponsor-investigator because it is not an individual person. An "investigator-initiated trial" (IIT) is a clinical research study initiated and conducted by a sponsor-investigator. "Investigator-initiated research" (IIR) consists of one or more investigator-initiated trials.

## Clinical Research vs. Medical Practice

As shown in Table 1, there are many differences between conducting research and practicing medicine. Clinical trials do not evaluate medicines under real-life medical practice conditions, but rather under structured and often artificial conditions designed to best answer the trial's experimental questions. In contrast, doctors provide medical care to their patients every day, testing different treatments, observing the results, and learning from the experience. Conducting clinical research vs. providing clinical care has important implications for regulatory requirements.

**Table 1. Differences between Clinical Research and Clinical Care**

| Clinical Research | Clinical Care |
|---|---|
| Primary goal is to create generalizable knowledge | Primary goal is to provide medical care to patients |
| Systematic investigation with uniform treatment of subjects and few options | Individualized treatment of patients, with many options |

| | |
|---|---|
| Subjects meet eligibility criteria | All comers |
| Protocol and investigator's brochure | If anything, standard-of-care guidelines |
| Testing an experimental drug or new dosage, population or indication | Using a proven drug for a proven indication or off-label |
| Extensive documentation in case report forms | Brief notes on medical chart |
| Sponsor pays for test article and non-standard-of-care treatment | Patient or third-party payor pays for drug and treatment |
| Double blind | Unblinded |
| Randomized assignment of subjects to treatment | Treatment tailored to patient |
| Potential for publication of scientific articles | Potential for publication, if anything, of a case study |

**When Is an IND Required?**

Before a drug can be marketed, it must be approved by the FDA. Otherwise, an exemption must be obtained for experimental use. An IND (often referred to as Form FDA 1571, the IND application form) is a request for this exemption. An IND is required for drugs, biologics and botanicals. The counterpart to Form 1571 is Form 1572 – Statement of Investigator, which a sponsor-investigator must also sign. To use a new drug in research, filing both forms is required by law (Food, Drug, and Cosmetic Act, Section 505) and regulation (21 CFR §312).

Section 201 of the Food, Drug, and Cosmetic Act defines the terms "drug" and "new drug." Marketed drugs are recognized in the United States Pharmacopeia – National Formulary or the Homeopathic Pharmacopeia. A drug is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease. A dietary supplement or cosmetic, for example, can be categorized as a drug if it is intended for the same uses.

There are many types of new drugs. For example, a new drug can be a new chemical substance. An investigator obviously needs an IND to use a drug that is a new substance. A new drug can also be a new combination of drugs, for example, two marketed drugs that are put together in one tablet. Changing the proportions of active ingredients in a combination drug also creates a new drug. A new dosage form, such as changing an immediate-release tablet to an extended-release tablet, requires an IND. A new route of administration, such as intramuscular administration for an intravenous drug, requires an IND.

A new use, e.g., for a different disease or a different stage of the same disease, may require an IND, depending on the risk to subjects and whether there are data to support the new use. Testing an existing drug in a new population, e.g., children, may also require an IND.

There are some exemptions from INDs, as outlined in 21 CFR §312.2(b). If a drug is lawfully marketed in the United States and meets all of the following requirements, no IND is needed:

- The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.

- The investigation is not intended to support a significant change in the advertising for the product.
- The investigation 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.
- The study will be conducted in compliance with institutional review board (IRB) and informed consent requirements.
- The study will comply with the requirements for promotion of and charging for investigational drugs.

When the requirement for an IND is unclear, the sponsor-investigator has two alternatives:

- Play it safe by investing the time to file an IND and letting the FDA determine if the study meets the IND exemption requirements.
- Do not file an IND, proceed with the study, and hope that the right decision was made when the FDA investigates, for example, the death of a study subject.

**Form FDA 1572**

The sponsor-investigator accepts the obligations of a clinical investigator. When an investigator signs a Form FDA 1572, whether the investigator is conducting the research on his/her own IND or through a commercial IND, the investigator commits to many requirements, including conducting the study according to the protocol, personally conducting or supervising the investigation, informing the subjects of the investigational status of the test article, and reporting adverse events to the sponsor, who in turn notifies the FDA. (A sponsor-investigator must notify the FDA of adverse events, like any other sponsor.)

The investigator must read and understand the Investigator's Brochure. However, for an investigator-initiated IND, an Investigator's Brochure is not necessary, since the investigator wrote the IND. In either case, the investigator must inform all support personnel of the requirements of the investigation, and maintain adequate records and make them available for inspection.

**Form FDA 1571**

The IND regulations (21 CFR §312) set forth procedures and requirements governing the use of investigational new drugs, biologics and botanicals. The regulations apply to all clinical investigations of products that are subject to Section 505 of the Food, Drug, and Cosmetic Act.

Regarding IND contents, the FDA essentially wants to know everything there is to know about the drug. If it is a new drug that has never been on the market before, there will be a great deal of new data, especially pharmacology and toxicology data. Chemistry, manufacturing and control data are very important because the drug has never been made before for clinical use. An IND for a new substance will be much larger and complex than an IND for a marketed product that is being used for a different indication. IND contents are listed on the FDA's website at http://www.fda.gov/cder.

Many investigators who are also IND sponsors do not read Form FDA 1571 (the IND application) before they sign it; in fact, many do not even recall having signed the form. When a sponsor signs a Form FDA 1571, he/she agrees to the following requirements:

- To wait 30 days before beginning the study

- To not begin or continue the study if it is placed on clinical hold
- An IRB will be responsible for review and approval of the study
- To conduct the study in accordance with all applicable regulatory requirements

Many investigators do not know which regulatory requirements are applicable. Ignorance of the law is no excuse. An investigator who signs the form has signed a legal contract with the FDA to conduct the study in accordance with all applicable regulatory requirements. The bottom of the second page of Forms FDA 1571 and 1572 states in bold print, "WARNING: A willfully false statement is a criminal offense." Willful ignorance is not much of a defense in human experimentation.

The study sponsor submits the IND application to the central document room at the FDA. Once received, the FDA assigns an IND number and the 30-day safety review begins. The review has three possible outcomes:

- The IND is accepted as submitted and the study may proceed.
- There is not enough information to determine safety, so the FDA puts the IND on clinical hold and asks the sponsor-investigator to provide additional information.
- The FDA determines that the study is exempt from IND requirements.

It is important to note that the term "sponsor" may mean different things to different people. The entity responsible for compliance with the IND regulations and who is named in Form FDA 1571 is the "regulatory sponsor." The entity providing the funding to conduct the study is the "financial sponsor." In most commercial IND studies they are one and the same. In most investigator-initiated IND studies they are not the same.

The FDA's website (http://www.fda.gov/cder or http://www.fda.gov/cber) contains a lot of good information about how to file an IND. At http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm, there are guidance documents, regulations and forms. There is information specifically for sponsor-investigators submitting an IND at http://www.fda.gov/cder/forms/1571-1572-help.html.

**Compliance and Consequences**

Sponsor-investigators must ensure that the study's IRB is in compliance with the regulations and conducts initial and continuing reviews. They must promptly report study changes and unanticipated risks to the IRB, and not make any changes to the protocol without IRB approval and, under certain circumstances, FDA notification.

Sponsor-investigators sometimes forget that they are conducting research. For example, they may make changes to the protocol without telling the IRB, notifying the FDA, or even formally documenting the changes. Non-compliance with the regulations is a criminal violation of federal law. It can jeopardize the safety and welfare of the research subjects. It may damage the public's trust in the investigator, the institution, and clinical research in general. It may deprive the public of important scientific evidence for medical decisions. The investigator may be disqualified or debarred from involvement in future clinical research, fined, and incarcerated. Legal expenses and distractions from productive work for the investigator and the institution can be formidable. Bad press can affect the investigator and institution for decades. Entire careers can be ruined.

**FDA Inspections: Implications for Sponsor-Investigators**

The FDA's Bioresearch Monitoring Program (BiMo) conducts inspections of clinical investigators. From 1998 to 2004, BiMo inspectors conducted 4,700 inspections of clinical

investigators (2,400 for drug studies, 800 for biologics studies, and 1,500 for device studies).[2]

The most common violations are failure to follow protocol requirements, failure to obtain proper informed consent, lack of supporting data, discrepancies between source documents and CRF entries, inadequate drug accountability records, and failure to notify the IRB of adverse events, deaths and protocol changes.[3] When a pharmaceutical company sponsors a study, it sends site monitors to find these types of problems and prevent their reoccurrence. However, many sponsor-investigators do not monitor their studies, substantially increasing the risk that these problems will occur and not be corrected. If an FDA inspection takes place, the FDA inspector will probably find them.

Adequate funding for investigator-initiated research is a real concern. For example, not having staff on duty to execute a specific protocol instruction is a protocol violation. The sponsor-investigator should either modify the protocol (and obtain IRB approval) to allow for compliance with current staff or obtain funding to hire additional staff. The FDA does not accept inadequate funding as justification for regulatory noncompliance.

For investigator violations, the FDA can issue a warning letter and later disqualify, debar, or criminally prosecute an investigator. Warning letters inform the recipient of objectionable conditions found during the inspection and are available on the FDA's website at http://www.fda.gov/foi/warning.htm. The investigator must respond within 15 days.

If there is evidence that the clinical investigator repeatedly or deliberately violated FDA's regulations or submitted false information, the FDA may issue a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE). These notices are listed on the FDA's website at http://www.fda.gov/foi/nidpoe/default.html.

The level of disqualification or debarment is determined by the FDA depending on the severity of the failure to comply with the applicable regulatory requirements. After debarment or permanent disqualification, the investigator may not have any involvement with clinical trials. Although any violation of the Food, Drug, and Cosmetic Act is a criminal offense, the FDA typically reserves prosecution for material falsifications and other significant violations. The usual prison terms and fines for criminal offenses apply.

**Key Points to Remember**

Sponsor-investigators must remember:

- Clinical research investigators and sponsors have different, albeit overlapping, responsibilities.
- Sponsor-investigators must comply with the applicable laws and regulations for both roles.
- If an individual is conducting a clinical trial with a substance that the FDA regulates, the FDA has jurisdiction over that trial, even if the trial meets all the criteria for IND exemption.
- Lack of familiarity with the applicable laws and regulations is no excuse for non-compliance.
- Lack of adequate funding is no excuse for non-compliance.
- The FDA is your partner – like it or not.

**References**


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