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Working with Pharmaceutical Companies on Investigator-Initiated Clinical Trials

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Introduction

Clinical trials sponsored by pharmaceutical, biotech and medical device companies are called "industry sponsored trials." However, the principal investigator can serve as the sponsor for his or her own study. In such trials, the investigator becomes the "sponsor-investigator." Such trials go by many names, including Investigator Initiated Trials (IITs), Investigator Initiated Studies (ISSs), Investigator Sponsored Trials (ISTs), Non-Registration Trials (NRTs), Third Party Studies (TPSs), and Medical School Grants (MSGs).

Sponsoring a clinical trial entails numerous regulatory responsibilities, including those set forth in 21 CFR 312 and 812. There is no "lite" version of sponsor responsibilities for sponsor-investigators.[1]

Although a pharmaceutical or other company may not sponsor a clinical trial from the regulatory perspective, it can provide support to the sponsor-investigator in the form of test articles, grants, services and advice. Although the investigator's objectives may be purely scientific, a pharmaceutical or other company might find the study worthy of support. The study might, for example:

- Explore use of a marketed drug for new indications, in new populations, in new dosage regimes, or in new combinations with other treatments.
- Evaluate biomarkers that could be useful in diagnostic tests or treatment management.
- Refine safety and effectiveness information.
- Foster scientific exchange and collaboration.
- Demonstrate the company's willingness to expose its marketing claims to third-party research.

FDA Regulations

According to the Code of Federal Regulations:

> Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. (21 CFR 212.3)
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> Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. (21 CFR 312.3)
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> Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper

> monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part. (21 CFR 312.50)

Investigator and sponsor responsibilities are described in more detail elsewhere in 21 CFR 312 and other regulations and guidances.

Obtaining Support for an IIT

The process for obtaining IIT support varies by company, but the processes described in this article are fairly standard in the pharmaceutical industry. The trend is to make them faster, more efficient, and more supportive of the company's strategic objectives.

Once the investigator has an idea for an IIT, he or she submits it, along with a curriculum vitae and an estimated budget for the trial, to a pharmaceutical or other company, normally the one that manufactures the test article. The proposal should include a statement of what items the investigator wants from the company. Such items might include:

- Test article, with label and packaging suitable for a blinded clinical trial
- Placebo or active control, with label and packaging suitable for a blinded clinical trial
- Funding for specified activities
- Assistance with writing the protocol and filing the IND
- Site monitoring, data management, safety reporting, and other services

Different companies accept submissions in different ways. There may be a web portal, or medical science liaisons (MSLs) or country directors may accept them. Different companies also process proposals in different ways, but the following process is typical.

The company reviews the preliminary proposal. If the study appears to have scientific merit and falls within its strategy, the investigator appears able to conduct the study, and the company has adequate resources to support the study, it will ask the investigator for a full protocol and detailed budget within 60 to 90 days.

The company's IIT Committee reviews the complete proposal. Committees typically include a broad range of both voting and non-voting members. Voting members include medical and scientific personnel, product and program managers, and regulatory experts. The voting members are supported by non-voting members, including medical science liaisons, regional medical directors, marketing managers, lawyers, patent attorneys, statisticians, epidemiologists, health economists, and drug supply and packaging managers. The committee's deliberations can consider marketing strategy, but should not consider commercial factors like the investigator's prescribing volume. The non-voting members are also available to help the voting members develop the company's IIT strategy.

When a proposal is approved, administrative personnel contact the investigator to make suggestions, resolve open questions, and determine details, such as timelines, support to be provided, budget and other contract terms. Different companies have different levels of interest in such details.

IIT clinical trial agreements (CTAs) are different from CTAs for industry-sponsored trials for three main reasons:

- The company does not have the sponsor's regulatory responsibilities.
- The investigator is asking for help from the company, instead of the other way around.

- The test article is usually a marketed product (as in Phase IV studies).

The main areas of interest in IIT CTAs are the following:

- Investigator and sponsor duties
- Intellectual property (IP) and data ownership rights
- Publications
- Privacy (including HIPAA)
- Confidentiality
- Payments
- Serious adverse event reporting obligations
- Termination rights

In addition, subject injury and indemnification, a major focus in most industry-sponsored trials with experimental treatments, are typically smaller factors in IIT CTAs because the test article is usually a marketed product and the company does not want to accept liability for a study over which it has minimal control. Normally, the company warrants that the test article is manufactured per specifications, the investigator indemnifies the company for subject injury, and the company indemnifies the investigator-sponsor for possible commercialization.

Companies usually rely on the investigator to contract with sub-sites, laboratories and other third-party vendors.

Because of the lead times, the company might start arranging for test article supply, labeling and packaging without waiting for a signed CTA. Regulatory and customs approvals might be required before the test article can be shipped internationally. The company normally takes responsibility for drug supply and transportation. It obtains clearance from the regulatory and customs departments of the country hosting the trial. In addition, it assumes responsibility for quality checks. If the study will be conducted at multiple sites, the company can ship directly, but it normally ships only to the primary site, to minimize liability issues.

If the company will provide site monitoring, data management, safety reporting, or other services, the appropriate departments are contacted and begin making the arrangements.

Reference

1. “Investigator-Initiated Research,” Harvey M. Arbit, Journal of Clinical Research Best Practices, June 2008

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