Regulatory Outlook

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The Business of Clinical Trials, Part 1: Negotiating Confidentiality, IP, and Publications

Understanding the nuances of clinical trial agreements and the motivations of people involved can ensure that everyone gets what they need.

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Clinical trials play a critical role in the ability or failure of a medical device to make it to market. A trial enables the sponsor, typically the device manufacturer, to gather and evaluate safety and efficacy data that will form the heart of the premarket approval (PMA) application to FDA. Trials are essential to premarket approval of all Class III devices. Device manufacturers also increasingly use clinical trials to gather data for 510(k) premarket notification submissions to FDA. Trial sponsors generally devote substantial resources to regulatory compliance. Compliance includes following the investigational device exemption regulations in 21 CFR 812, and the requirements for informed consent in 21 CFR 50, financial disclosure in 21 CFR 54, and institutional review boards in 21 CFR 56.

However, sponsors that give such attention to compliance often gloss over the business relationships embodied in the clinical trial agreement. The clinical trial agreement involves several parties, including the sponsors, the institution, and the principal investigator. It establishes these parties' rights and obligations with regard to the clinical trial. Although clinical trials are conducted under the FDA regulatory framework, they have become big business, and a sponsor should approach negotiation of the clinical trial agreement as a business necessity.

As with the creation of most business relationships, there will be bumps in the road to signing a clinical trial agreement. This article describes the most difficult business issues encountered by sponsors when negotiating clinical trial agreements. These issues include maintaining confidentiality, arguing successfully for intellectual property rights, and assessing publication opportunities. It also offers tips to minimize the time and energy spent negotiating. Part 2 will address commercial issues such as financial considerations and allocation of risk. This article is written from the perspective of the sponsor, but offers insight into the needs of the institution and the principal investigator. Although the interests of all parties diverge at some point, it's important to negotiate so that all involved are satisfied.

Confidentiality

General Motivations. In the best scenario for a sponsor, the clinical trial agreement would state that all information relating to the trial and the device is confidential. The sponsor may argue for such blanket confidential treatment because it can help ensure that trial results stay out of the hands of the sponsor's competitors. Without some protection, competitors could otherwise unfairly benefit from the sponsor's investment in its device. Confidentiality could also help the sponsor with any damage control that might be needed regarding the trial.

Universities and large private medical centers, however, do not agree to confidentiality obligations that place unacceptable limitations on their academic freedom or that interfere with

their mandate to promote research and public welfare. These centers want to freely share and publish what they discover. Therefore, it is important to iron out the definition of *confidential information* carefully.

When institutions propose the clinical trial agreements, they generally make everything the sponsor provides confidential. They are allowed to make public everything the institution and principal investigator develop during the course of the trial. Under this scenario, the device and the protocol would be confidential. Patient medical records, case report forms, and other reports required by the protocol would not.

From the sponsor's perspective, such a proposal does not adequately protect its commercial interests. The institution and principal investigator could share all information collected or created during the trial with any third party, including a competitor or the general public. This scenario also fails to protect the sponsor's interests in any intellectual property that may come out of the trial.

Nevertheless, the sponsor should avoid insisting that everything relating to the trial or the device be confidential. Even if such a definition makes it through the institution's review process, it is unlikely that the parties clearly agree on what is confidential and what can be published.

A standard publications clause lets the sponsor determine whether it wants confidential information to be removed from any proposed publication. If the clinical trial agreement contains an all-encompassing definition of *confidential information*, the institution and the principal investigator could end up with nothing to publish. Many sponsors do not intend to have such draconian oversight over publication rights. Other sponsors do want complete control over what information can be published about the trial, although they rarely obtain this control. Either way, by failing to clearly agree upon what information is confidential, all parties are setting themselves up for disappointment, a strained working relationship, and possibly a legal dispute.

Compromise. To ease negotiations, the sponsor may want to break down the definitions of *confidential information* as follows:

- *Terms and conditions of the clinical trial agreement.* The institution and principal investigator typically agree to treat the clinical trial agreement as confidential.
- *Information disclosed by or on behalf of the sponsor to the institution and investigator.* This includes the device, technical information relating to the device, the protocol, and intellectual property of the sponsor that existed before the trial began. The sponsor may also include data from animal studies or any other preexisting proprietary information for which it wishes to claim trade secret status (see below). Institutions and principal investigators typically agree to this stipulation.
- *Miscellaneous information relating to the regulatory side of the trial, such as the regulatory status of the device, communications with FDA, and correspondence with IRBs and data safety monitoring boards.* This may also include trial enrollment progress in terms of the number of research subjects who are enrolled in the trial at any given time. Although these are somewhat novel items, the language enables the parties to move away from all-or-nothing definitions of *confidential information* typically proffered by each side. Institutions and principal investigators usually agree to this because they have no need to disclose such information.
- *Research results.* This is the most controversial. Here the sponsor's desire to keep a tight lid on the trial is directly at odds with the institution's mandate to publish, because the standard publications provision allows the sponsor to require removal of sponsor confidential information from any proposed publication of the institution or principal investigator.

Although clinical trials are conducted under the FDA regulatory framework, they have become big business.

With regard to research results, there are legal and practical distinctions between source records such as x-rays or patient charts, and reports produced for the protocol—like case report forms. The institution and principal investigator have a legitimate need to use data contained in source records in scholarly publications and research. Without this source data, they would have nothing to publish. The sponsor has an equally compelling need to prevent a full-scale disclosure of trial data to competitors or the general public.

Underlying source data, such as x-rays, CT scans, and patient medical records, should not be included in the definition of *confidential information*. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) and state law govern confidentiality of those items. Items such as case report forms and other reports required by the protocol that do not include protected health information are not covered by HIPAA. The sponsor has commercial motivations to keep research results that are not protected by HIPAA confidential, while the institution and principal investigator have concerns about encroachment on their publication rights.

When pressed, most institutions and investigators agree that they have no intention of publishing actual case report forms or other reports provided during trial. Rather, they are more concerned with their ability to engage in scholarly publication based on the data collected during the trial. One compromise is to include these items in the definition of *confidential information*, and to clarify in the publications clause that the sponsor cannot require the institution and principal investigator to remove them from their proposed publications. This way, the information is generally afforded confidential treatment, but can be disclosed by the institution and principal investigator as agreed to in the publications provision.

Sponsors should also consider whether they want investigators to present early trial results at medical meetings and whether these presentations need the sponsor's prior approval. If the trial site is a small office or a clinic, or if the institution will serve as the trial's core lab for the trial, the sponsor may demand a more-expansive definition of *confidential information*, along with more-restrictive publication rights.

Marking. As a general rule, the more specific the sponsor can be about the information it wants kept confidential, the less likely the institution or principal investigator is to disclose information that it was unaware was confidential. Some institutions require the sponsor to mark as confidential or proprietary all information that the sponsor wants kept confidential. Marking requirements, however, may be too risky for the sponsor, because valuable confidential information may inadvertently not be marked. If the institution will not compromise, then the sponsor should insist on language stating that, regardless of the marking requirement, certain enumerated types of information will be considered confidential. This information includes the protocol, technical information, and correspondence with FDA.

Intellectual Property Ownership

As a matter of law, the creator of intellectual property (IP), or the creator's employer, owns the IP it creates unless it transfers ownership to a third party in writing. Therefore, institutions or principal investigators retain ownership of any IP they develop during a trial unless they expressly assign ownership to the sponsor. For example, if the investigators were to develop an additional configuration for the sponsor's device or to enhance the sponsor's surgical instrument during the course of the trial, the sponsor would not own these developments or enhancements.

While it has become relatively customary for sponsors to own the IP arising from their trials, many institutions' clinical trial agreements either fail to include an IP assignment provision or include only a very limited assignment. Institutions are used to sponsored research agreements where ownership of IP remains with the institution and principal investigator. Moreover, many universities have policies that require them to retain ownership of IP they create.

Patents and Inventions. A patent is an exclusive right to prevent others from making, using, selling, offering for sale, or importing the goods or services that are covered by the patent claim. Federal law governs patents. Patents are costly to obtain, and by the time the clinical trial commences, the sponsor has likely invested hundreds of thousands of dollars in developing and testing its device. Many consider patent protection to be the most powerful form of IP protection available to sponsors. For example, if the sponsor were to patent its device, the sponsor could prevent competitors from making and selling similar devices that infringe upon the patent for the life of the patent. Note that this article uses the term *invention* as a catchall to refer to inventions, discoveries, improvements, know-how, processes, ideas, compositions of matter, and other terms that are typically the subject of patent licenses. The terminology in clinical trial agreements often includes a subset of the foregoing, but the term *invention* is always used.

Institutions normally insist on the right to publish research results.

Many institutions' clinical trial agreements do not assign inventions by the institution and principal investigator to the sponsor. Some may include a limited assignment of inventions that are derived entirely from the protocol or the sponsor's proprietary materials. Some agreements allow for the creation of joint inventions and offer one party the right of first refusal to process these joint inventions. Other institutions postpone the issue, stating that the parties will determine patent ownership after a patentable invention is created. It is common for institutions to try to limit the scope of assignment to patentable inventions, thereby excluding inventions that are not patentable.

From the sponsor's viewpoint, without its funding, materials, and information, the institution and the principal investigator would not have access to the device or be able to conduct the research. Therefore, the sponsor has a legitimate claim to ownership of the inventions arising from the clinical trial. The sponsor's clinical trial agreement will include both patentable and nonpatentable inventions because it is impossible to determine whether something is patentable until patent protection is sought.

A sweeping assignment of all inventions arising from the trial is ultimately more than the sponsor needs to achieve its business purposes. The sponsor has a legitimate claim to ownership of all improvements to and new uses for the device that are created during the trial. These are an extension of the sponsor's investment in its device. As a compromise, the parties can generally agree upon two principles. First, the institution and principal investigator should agree to assign all inventions to the sponsor. This should be observed whether or not patentable, if inventions arise from conduct of the clinical trial or otherwise relate to the sponsor's confidential information. Second, the sponsor should agree that the institution and principal investigator retain ownership of all inventions from the trial that relate solely to research methods or documentation techniques. This compromise reflects a fair allocation of invention ownership. Although these negotiations can be difficult, sponsors should firmly resist any attempt by the institution or principal investigator to retain any broader scope of invention ownership.

Copyrights. The owner of a copyright has the exclusive right to copy, modify, distribute, perform, and display the work of authorship. As with patents, without a written assignment to the sponsor, the copyright will reside with the author, or in some cases, the author's employer. In the clinical trial context, reports written during the trial, such as case report forms, may be eligible for copyright protection. By contrast, the raw data contained in these reports would not be eli-

gible for copyright protection.

Institutions' clinical trial agreements rarely include an assignment of copyrights to the sponsor. However, a sponsor should not have restrictions on its ability to use, copy, or distribute the written materials prepared by the institution or principal investigator pursuant to the protocol. The sponsor should therefore insist on having all copyrightable works assigned under the clinical trial agreement. This copyright assignment should not extend to publications of the institution or principal investigator. In addition, the institution and principal investigator often reserve the right to use copyrighted materials and inventions for education and research purposes.

Trade Secrets. A trade secret is a creature of state law, and its definition varies from state to state. In general, a *trade secret* is information that the owner makes reasonable efforts to keep confidential, is not generally known, and affords the owner a competitive advantage. State trade secret laws protect the owner from unauthorized use and disclosure of its trade secrets. Clinical trial agreements usually do not include a separate provision for trade secrets, but the confidentiality provision can afford protection to certain sponsor-provided information.

To protect its investment in the device and the trial, the sponsor may wish to treat all inventions and research results as trade secrets by including them in the definition of *confidential information*. However, while institutions and principal investigators generally agree to assign ownership of inventions and research results, they almost universally refuse to grant trade secret protection. Doing so would interfere with their publication rights. It would also give the sponsor too much power to remove inventions from any proposed publication.

As a compromise, institutions and principal investigators will most likely give the sponsor the ability to require a publication delay so that the sponsor can seek patent protection. Institutions and principal investigators normally insist on the right to publish research results, thereby precluding trade secret protection, even though they may otherwise accept limited confidentiality, such as by agreeing not to share research results with competitors. Occasionally, small institutions or private hospitals may grant trade secret protection for inventions and research results arising from the trial, but the sponsor should take care to confirm that the parties are clear on the effect this has on the publication rights.

Trademarks. A trademark is an exclusive right to use a word, name, or symbol to indicate the origin, quality, and ownership of a product. It is also used to distinguish a product from the products of a third party. As with trade secrets, clinical trial agreements typically do not have a separate provision for trademarks. In fact, institutions often prohibit the sponsor from using the names of the institution and principal investigator, or any trademarks of the institution, in connection with sponsor publications about the trial or the device. Similarly, sponsors' clinical trial agreements often prohibit the institution and principal investigator from using the sponsor's name and trademarks for any purposes. Despite this prohibition, the institution and principal investigator will typically assume they can use the sponsor's name in their publications. Therefore, the parties should make sure they agree on how to apply this prohibition to the publications clause. (Some agreements enable one party to disclose the other party's name and trademarks only with permission.) Sponsors may want to disclose the name of the institution or principal investigator at trade shows or in scientific journals.

Institutions normally insist on the right to publish research results.

Binding Assignments. An assignment is the act of transferring all or part of one's property or rights to another. When obtaining assignments of IP rights from other parties, the sponsor should understand that an assignment by the institution does not necessarily include IP created by the principal investigator. For this reason, it is critical that the sponsor obtain written assignments of IP rights from both the institution and the principal investigator.

Parties other than the institution and the principal investigator may be involved in the creation of IP during the trial. As a matter of law, coinvestigators, staff physicians, residents, interns, independent study coordinators, and contract research organizations or their employers own the IP they develop during the trial unless they execute written assignments. The sponsor should ensure that the IP assignments also bind these ancillary personnel. Where appropriate, the sponsor should independently obtain written assignments from other ancillary parties.

Preexisting IP. Clinical trial agreements regularly include a provision stating that each party will retain ownership of the IP that it brings to the trial. This is noncontroversial, yet worth reciting in the clinical trial agreement in order to make clear that the IP ownership transfers in the clinical trial agreement do not affect a party's preexisting IP.

Publications

From the institution's and the investigator's perspectives, the publications provision may be the most critical right they will obtain from the sponsor. If the parties have reached open and informed agreement on the definition of *confidential information* and on the allocation of IP ownership, addressing publication rights is relatively simple with the exception of one thorny issue: so-called data dumps, which will be discussed later.

Standard Language. The publications clause in the clinical trial agreement has become relatively standardized. Typically, the sponsor grants the institution and the principal investigator the right to engage in publications, presentations, and other public disclosures regarding their activities subject to prior sponsor review. A definition of *publications* in the agreement should extend to oral presentations and other public disclosures.

Prior sponsor review normally begins at least 30 days before the sub-

mission of any proposed publication and consists of two rights, as follows:

- The sponsor can require the institution and investigator to redact sponsor confidential information from the proposed publication.
- The sponsor can require that the institution and principal investigator delay publication for an additional period, typically 60 to 90 days, so that the sponsor can seek patent protection.

If the trial is a multicenter study, the sponsor needs to coordinate the results from all trial sites into a single publication. Typically, the clinical trial agreement requires each institution and principal investigator to defer any independent publication until after release of the multicenter publication. To protect institutions and principal investigators from unreasonable delay, it is standard for sponsors to permit site-specific independent publication if the multicenter publication has not been released within one year after completion of the trial at all sites.

Sponsors should note that if the trial site is a small doctor's office or a clinic, or if the institution will serve as a core lab for the trial, the sponsor may demand control over publications.

Data Dumps. Despite the standardization of publication clauses, there is still a risk that a literal reading of the publications clause would allow disclosure of a large bulk of trial information, or *data dump*, to the sponsor's competitors or the general public. To address this, some sponsors permit the publication of trial data only in summary form. This approach generally does not satisfy the publishing goals of the institutions or principal investigators. A better solution is to prepare for this possibility at the beginning of a relationship. The sponsor should establish that it does not intend to leave the investigator with nothing to publish, and likewise the sponsor should be assured that the investigator does not intend to engage in a data dump. The agreement could provide that the institution and principal investigator will not disclose trial results to any third parties in greater detail than has been disclosed in scientific journals and other noncommercial publications.

Publicity. Sponsors should not underestimate the prestige factor for institutions that agree to serve as trial sites. Often an institution finds it is a significant benefit to offer patients access to a new device. However, an institution's desire for publicity must be balanced against regulatory requirements.

The sponsor should include a provision that prohibits the institution, principal investigator, and their personnel from engaging in interviews or other media contacts, including television and Internet, about the trial or the device without the sponsor's consent. The sponsor should insist on this provision to avoid violating regulations relating to the promotion of devices under investigation, because any comments could be attributed to the sponsor.

Conclusion

By addressing the very real issues involved in negotiating a clinical trial agreement, the sponsor can ensure that all parties are aware of and satisfied with the resulting agreement. Although concerns such as confidentiality and IP can be contentious, they cannot be ignored or set aside for later. When negotiations are begun early in the agreement process, and if they are sufficiently explored, they will ultimately create a better clinical trial environment. ■