MD&DI
Medical Device & Diagnostic Industry ®

The Business of Clinical Trials Part 2: Finance and Risk Allocation

Although issues such as financial interests and allocation of risk are fairly standard, parties in a clinical trial should not neglect the details.

Katherine R. Leibowitz

Hogan & Hartson LLP

As with the creation of most business relationships, there are bumps in the road to signing a clinical trial agreement. While Part 1 described some of the more difficult business issues (confidentiality, intellectual property, and publishing) encountered by sponsors, it's important not to forget other aspects of negotiating clinical trial agreements. Commercial issues, such as financial and risk concerns, tend to be less controversial. Nevertheless, they are equally important to the sponsor. This article is written from the perspective of the sponsor, but offers insight on the needs of the institution and the principal investigator. Although interests of the parties will diverge at some point, it's important to negotiate so that all involved will be satisfied.

Financial Interests

Many business considerations in clinical trial agreements grow out of FDA regulatory requirements. Nowhere is this more apparent than with the financial disclosure regulations in 21 CFR 54. These regulations are designed to help eliminate the potential for bias that may arise due to financial conflicts of interest. For example, if a sponsor compensates an investigator with an equity stake in the company

or if an investigator has a proprietary interest in the investigational device, the investigator may be motivated to influence the outcome of the trial data rather than to remain impartial.

The regulations in 21 CFR 54 give the sponsor the option of certifying the absence of certain financial interests of the investigators or disclosing those financial interests. However, it is much more desirable for the sponsor to certify that the investigators have no financial interest. Doing so avoids raising a red flag for FDA.

When structuring the compensation for a clinical trial, sponsors should avoid creating any financial interests that would be disclosable. Sponsors should take care to include in their analysis all other financial arrangements they may have with the investigators, such as compensation for consulting services that investigators may have provided or will provide during the period covered by the financial disclosure regulations. If FDA is concerned about a potential bias from an investigator because of a financial interest, the agency has four options, which are presented in 21 CFR 54.5(c). These options are

- Auditing the clinical data.
- Requesting further analysis to determine whether there is investigator bias.
- Requesting that the sponsor conduct further studies independently.
- Refusing to treat data as the basis of an FDA decision.

While the structure and amount of payments made by commercial sponsors vary, normally the budget includes per-subject payments by the sponsor to the institution or to the principal investigator. These payments are often tied to milestones, such as follow-up visits or completion of case report forms. Sponsors should consider making the last milestone payment based on final acceptance by the sponsor of

all data pertaining to that subject. This gives the site incentive to finish its data submissions to the sponsor, which can often drag on at the end of a trial.

The budget exhibit should set forth conditions where payment will be denied, such as if the subject was ineligible to participate in the trial at time of enrollment or if the principal investigator failed to obtain informed consent. Some sponsors pay institutional review board (IRB) fees, start-up administrative fees, or other one-time fees. Fees can be nonrefundable or advances that are earned against subject follow-up payments. Sponsors may reimburse for study procedures or the cost of the device. In all cases, the sponsor must take care to avoid running afoul of healthcare fraud and abuse laws. Such laws include, but are not limited to, the federal Anti-Kickback Statute, Stark Laws, and False Claims Act. There may be similar state laws as well. In addition, the payment exhibit should make clear that it sets forth all payments and reimbursements that the sponsor will make for the trial.

Allocation of Risk

Indemnification. The parties involved in a clinical trial agreement face very real and significant exposure to liability because the trial involves testing humans. Particularly for devices that pose a significant risk, the trial could lead to injury or death. In today's litigious society, if a research subject in a clinical trial is injured or dies, often all parties will be sued, regardless of who or what caused the injury or death. To protect each party from liability created by the other parties, the clinical trial agreement typically includes a mutual indemnification by the sponsor and the institution. A mutual indemnity protects each party from the cost of defending a lawsuit in cases where it is not at fault.

The fairest approach to the mutual indemnity issue is for each side to be responsible for its own failures. On the sponsor side, if the device causes a subject's injury or death, the sponsor would indemnify the institution, the principal investigator, and their personnel from the costs of defending any resulting lawsuit.

Clinical trial agreements initiated by institutions may seek a wider indemnity from the sponsor, covering more than problems with the device. Sponsors should make clear that if a research subject is injured or dies, they will not indemnify if the institution, the principal investigator, or their personnel failed to follow the protocol, applicable laws or regulations, or were negligent or misused the device. Normally, institutions will agree to this condition, as it is a fair allocation of business risk. On the institution side, if the institution, principal investigator, or their personnel were at fault, the institution would indemnify the sponsor for the legal costs of defending a lawsuit where it may be named.

Often universities and large medical centers will refuse to indemnify the sponsor. In addition, some state laws prohibit public universities from indemnifying a sponsor. In such cases, the sponsor should still exclude from its indemnity obligations any losses caused by the institution's, the principal investigator's, or their personnel's failure to follow the protocol, applicable laws, or regulations, or their negligence or misuse of the device.

Insurance. Insurance provides each party with added assurance that the other will be able to meet its indemnification obligations. Historically, institutions have required the sponsor to maintain insurance, although sponsors are increasingly obtaining reciprocal insurance obligations from the institution. From the sponsor's perspective, corresponding institutional insurance is particularly important for small private hospitals, clinics, or physician's offices, because the sponsor has little assurance that they will be able to meet their indemnity obligations.

Limitation of Liability. It is generally good business practice to exclude each party's liability to the other parties for indirect and consequential damages arising out of the agreement, with the exception of damages attributable to a breach of confidentiality or the indemnification obligations. The term *consequential damages* refers to damages that do not flow directly and immediately from the act of the offending party, but only from the consequences and results of such act. One common type of consequential damage is lost profits.

An exclusion of this liability protects the sponsor from negative fallout experienced by the institution or principal investigator, and a corresponding claim against the sponsor for lost profits, in the event of publicity relating to serious injury or death during the trial. Sponsors want to cap their liability for direct damages to an amount equal to what the sponsor has paid the institution or principal investigator during the trial. Universities and large medical centers are less receptive to liability caps, but often agree to a mutual exclusion of consequential damages, and sometimes to a liability cap, as long as it is clear that these provisions do not apply to the indemnification obligations. Smaller institutions may agree to both provisions more readily.

Parties to the Clinical Trial Agreement

As a best practice, three parties should sign the clinical trial agreement: the sponsor, the principal investigator, and the institution. However, there are some situations where a two-party clinical trial agreement may be necessary.

If an institution employs the principal investigator, the institution may not want the principal investigator to be a formal party to a trial agreement. This should be acceptable to the sponsor under the theory that the institution, as the principal investigator's employer, is responsible for the principal investigator. However, because so many provisions of the clinical trial agreement apply to the principal investigator, it is in the sponsor's interest to educate the principal investigator about the clinical trial agreement. To this end, the institution will normally be amenable to having the principal investigator sign a *read and acknowledged* signature block at the end of the clinical trial agreement. Note that if the principal investigator has staff privileges at the institution, but is not an institution employee, then the sponsor should press for the principal investigator to be a formal party to the clinical trial agreement. This is true even if the institution argues that the principal investigator's signature is unnecessary. The institution will likely lack sufficient authori-

ty to enter into the agreement on behalf of the principal investigator.

In cases when the principal investigator is not an employee of the institution, but has limited staff privileges, the institution may prefer not to use the same agreement signed by the investigator. Because the trial will be conducted on institution premises and will likely involve institution personnel and equipment, the sponsor should enter into a separate agreement with the institution to ensure that the institution bears responsibility for its personnel involved in the trial. In this case, the sponsor should sign one clinical trial agreement with the principal investigator and another clinical trial agreement with the institution. The sponsor should not have much difficulty convincing the institution to sign an agreement. Most institutions want to be indemnified by the sponsor if an injury or death of a research subject is caused by the sponsor's device.

The principal investigator usually appoints coinvestigators (or subinvestigators) to assist with the conduct of the trial. These people do not need to be parties to the trial agreement itself, but should sign an exhibit to the agreement in which, among other things, they agree to abide by the principal investigator's obligations in the clinical trial agreement. Educating the coinvestigators about the agreement requirements and having them sign an exhibit gives the sponsor an additional layer of protection.

Various additional parties may participate in the conduct of the trial, including interns, residents, staff physicians, independent study coordinators, contract research organizations (CROs), and core labs. With the exception of CROs and core labs, these ancillary parties do not typically sign documents that would make them responsible to the sponsor for their missteps in the trial. Nor would they assign to the sponsor the intellectual property (IP) that they develop during the trial. The sponsor needs to carefully consider who is involved in the trial. It also must ensure that the institution indemnifies and assigns IP to the sponsor on behalf of these ancillary parties.

In addition, if a CRO signs the clinical trial agreement on behalf of the sponsor, the sponsor should carefully review the clinical trial agreement before it is signed. Clinical trial agreements provided by CROs may pass through the institution's review process relatively quickly, but these agreements often do not adequately protect the sponsor's interests.

Regardless of the principal investigator's relationship with the institution, investigational device exemption regulations require investigators to sign an investigator agreement. This is a required document that is separate from the clinical trial agreement. The applicable requirements are described in 21 CFR 812.43(c), 812.100, and 812.110. They include, for example, the investigator's commitment to conduct the trial in accordance with the protocol, FDA regulations, and FDA- or IRB-imposed conditions of approval. In addition, the investigator commits to supervising all device testing in humans. Sponsors often commingle the investigator agreement with the clinical trial agreement—and investigators can sometimes confuse the two. However, the investigator agreement should be a stand-alone document because it is subject to inspection by FDA; the clinical trial agreement is not.

Termination

Termination for Convenience. In commercial contracts, it is customary for the company that engages a service provider to have a right to terminate the agreement for convenience; the service provider does not have a corresponding right.

In a clinical trial context, other trial sites, communications with FDA, or other factors may affect the course of the trial, so the sponsor needs the right to terminate for convenience as well as the right to suspend the trial at any time. Some clinical trial agreements proffered by institutions include a mutual right to terminate the agreement for convenience. However, because the sponsor is investing a significant amount of time and money in the trial, the sponsor needs to be able to count on the institution's participation in the trial.

That said, the institution and principal investigator may legitimately fear that they could be forced to continue a trial when it appears advisable to terminate for health and safety reasons, but the sponsor disagrees. To address this, the parties should consider inserting a provision granting the principal investigator the right to terminate the trial if it presents an unreasonable risk of substantial harm to the research subjects or if the emergence of any adverse events is of such concern as to support termination.

Other sponsors allow the institution and principal investigator to terminate for any reason. The theory behind this is that they do not want people conducting a trial unwillingly—it could unfavorably affect the outcome.

Replacement of Principal Investigator. When setting up clinical trials, sponsors often select high-profile principal investigators to oversee the trials. If the principal investigator were to leave the institution, the sponsor might want to discontinue the trial or move it to another institution. To address this possibility, the clinical trial agreement should grant the sponsor approval rights over any replacement principal investigator as well as the right to terminate the agreement should the parties fail to agree upon a replacement principal investigator.

Competitive Devices

Some sponsors wish to prohibit the principal investigator and the institution, during the sponsor's trial, from working on trials for a competitive device. The parties should draft a noncompete clause in a manner narrow enough to pass muster with the courts. There is an exception if the device is used in a specialized field where only a handful of principal investigators possess sufficient expertise to conduct a clinical trial. In such a case, a noncompete clause is impractical because there is a high likelihood that the principal investigators would engage in trials on competitive devices. However, the sponsor can prohibit the investigator from enrolling subjects in competitive trials simultaneously to avoid enrollment bias.

Having a principal investigator work on competitive devices for multiple sponsors can create practical problems

from a confidentiality and IP perspective, but device companies typically accept this as a reality of doing business in specialized device fields. In this situation, the confidentiality provision takes on a more critical role in protecting the sponsor's investment in its device, and the sponsor should confirm that it is drafted appropriately. With regard to IP, the sponsor should verify that the assignment provisions are sufficiently inclusive and clear. The sponsor should implement procedures to track any IP developed by the institution or principal investigator during the course of the trial.

FDA Inspections

Clinical trial agreements customarily include a right for the sponsor to inspect the clinical trial site so that the sponsor can monitor the conduct of the trial and obtain any information necessary to respond to FDA requests. If the principal investigator will perform any clinical trial work in an office outside the institution, such as a private doctor's office, then the inspection right should extend to those facilities as well.

It is also standard to obligate the institution and principal investigator to notify the sponsor of any FDA inspection. Sponsors typically want to attend all FDA inspections related to the trial. If FDA inspects the trial site, the sponsor should request copies of all correspondence between FDA and the institution or principal investigator. Once again, the institution or principal investigator should not object to such requests. If FDA issues a Form FDA-483 Notice of Observations or similar warning letter to the institution or principal investigator, the sponsor should insist on a right of prior approval or review over any responses. Involvement in the response process will help the sponsor protect its investment in its device.

HIPAA

A trial agreement should state that the principal investigator must obtain subject authorizations that meet the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and any applicable state privacy laws. First, the investigator must obtain prior written authorization to use and disclose health information for research in accordance with HIPAA (HIPAA authorization). Second, the investigator must inform the sponsor of any failure to obtain a HIPAA authorization before a research subject's enrollment in the trial. Alternatively, a principal investigator can obtain an appropriate waiver by the IRB or by a properly constituted privacy board.

Many sponsors propose a form of HIPAA authorization, but institutions increasingly insist on using their own forms. Institutions' HIPAA authorizations address the needs of the institution and principal investigator, but often fail to sufficiently address the sponsor's interests. Sponsors want to ensure that they will have access to the trial data at the individual subject level, which would not be possible without a properly drafted HIPAA authorization. Further, sponsors want to ensure that the breadth of the disclosure allows them to use the trial data as desired. Whatever HIPAA authorization form the parties adopt, the sponsor should carefully vet the authorization with HIPAA counsel. In addition, the clinical trial agreement should prohibit the institution and the principal investigator from changing the HIPAA authorization without the sponsor's consent.

Parties may ask why it is necessary to include HIPAA language if the agreement contains a general obligation for the parties to comply with applicable laws. From the sponsor's perspective, it helps to ensure that the data generated through the trial are not encumbered by a HIPAA violation committed by the institution or the principal investigator. Although FDA has not issued a formal statement indicating that it would reject trial data obtained in violation of HIPAA, a sponsor would be in a much better position if it could show that it made good faith efforts to comply. The HIPAA language also helps to ensure that the sponsor or the sponsor's monitors may inspect subject records and other source data maintained by the institution. The trial data are the culmination of a vast investment of time and money by the sponsor in its device. Therefore, protecting the integrity of the trial data and ensuring that no legal barriers interrupt the flow of the data should be paramount.

Due Diligence and Warranties

As with all business ventures, a sponsor should perform due diligence on its clinical trial business partners before entering into the clinical trial agreement. Standard inquiries regarding medical expertise, patient population, trial facilities, and the institution's financial soundness should be considered. In addition, the sponsor should question whether the hospital, its IRB, and the principal investigator have the sophistication and resources to comply with FDA regulations. For example, a physician who is widely regarded as an expert in the field nevertheless may lack comprehensive knowledge of FDA regulations or may have been cited for regulatory violations in the past.

The sponsor can undertake some due diligence by checking the Warning Letters and Responses database on FDA's Web site (see www.fda.gov/foi/ warning.htm). In addition, the sponsor should insert appropriate warranties in the clinical trial agreement that investigators, institutions, and IRBs will disclose that, for example, they have been disqualified by FDA or are under investigation.

Conclusion

To help avoid unnecessary delays in negotiations as well as unwelcome surprises during a clinical trial, the parties to the trial agreement should carefully consider the respective business needs of the various parties. By starting from a clear expression of the parties' rights and obligations during the trial, ultimately each party will come out ahead. ■