

## Negotiating Clinical Trial Agreements

*Katherine Leibowitz and Victoria Sheckler* report on some of the key provisions that should be included in sponsor-initiated clinical trial agreements in the US.

Clinical trials are essential to measuring and obtaining the safety and efficacy data necessary to seek marketing approval of a drug, biologic or medical device by the US Food and Drug Administration (FDA) and similar foreign regulatory agencies. Clinical trials, and the data they generate, are such a critical component in obtaining marketing approval (and in the ultimate success or failure of the drug, biologic or device) that sponsors should carefully craft their agreements governing the trials to ensure that the trials are conducted in a safe, appropriate and legal manner, that the patients are treated appropriately, that the data generated from such trials are sufficiently protected and that their investment in the drug, biologic or device is protected.

This article focuses on some of the key provisions that should be included in sponsor-initiated clinical trial agreements to address the sponsor's goals, and the issues surrounding those provisions from the sponsor's, institution's and investigator's perspectives.

### Principal investigator

The clinical trial agreement should clearly specify the principal investigator's obligations with respect to the clinical trial. These typically include not only following the protocol, but expressly state that the principal investigator is responsible for obtaining the informed consent, *Health Insurance Portability and Accountability Act* authorisations, institutional review board approvals and any other permits or approvals that are required for the principal investigator to perform its obligations<sup>1</sup>. The parties should also consider what rights the sponsor has in the event the principal investigator can no longer act as the principal investigator.

*Agreements covering clinical trials must be carefully crafted...*

*...and should clearly specify the principal investigator's obligations*

### Regulatory compliance

The agreement should require the principal investigator and the institution to warrant and covenant that they will perform their obligations in compliance with all applicable laws, regulations, and industry guidances and standards<sup>2</sup>. It should also include other regulatory representations and obligations of the institution and investigator, including a no-debarment and no-disqualification representation, as well as obligations to report adverse events, to notify the sponsor of any audits and to permit the sponsor to inspect and audit the study records. While these concepts are typically not controversial, institutions may object to the breadth of the obligations.

### Confidentiality

The agreement should address what information will be considered confidential and each party's obligations to maintain that confidentiality. The sponsor generally would like to ensure that any information provided or generated in the course of the clinical trial will be maintained as the sponsor's confidential information. The institution and/or investigator, on the other hand, will not accept restrictions that unduly limit academic freedom or their ability to publish, promote research and the public welfare, and increasingly are interested in having the right to use some of the research results for other purposes. Typically, the most heated discussions surround the identification and treatment of the research results. Sometimes, the parties can reach a compromise by distinguishing between the source data of the research results, and the results provided in the case report forms or other reports, or by addressing the institution's or investigator's concerns regarding academic freedom in the publications provision.

*Institutions and investigators increasingly want more rights to research results*

### Publication

Sponsors and institutions generally recognise the investigator's or institution's need to have certain publication rights, and the sponsor's need to place certain limits on those publication rights to protect the sponsor's intellectual property and competitive advantage. Typically, the agreement will permit the investigator or institution to engage in publications or other public disclosure subject to the sponsor's right of prior review to redact confidential information and/or delay publication or public disclosure to permit the sponsor to seek patent protection.

However, in the event of a multicentre trial, the sponsor will likely require that the results from all of the trials be included in a single publication, and therefore not permit publications by individual sites until after there has been a multicentre publication. In addition, if the investigator is not associated with an institution or other not-for-profit entity, the sponsor may desire to further

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*Care should be taken over publication rights*

restrict the investigator's ability to publish without the sponsor's approval.

Further, if trial procedures will occur at a hospital where the investigator has staff privileges, but follow-up will be at the investigator's private offices, then the sponsor may wish to limit the publication rights to the investigator and to prohibit publication by the hospital. Finally, care should be taken to ensure that the publication right does not permit wholesale publication of the study results, but rather limits publication of trial data in a summary form or some other limited form that protects against a full publication of the raw research results.

## **Intellectual property and study data**

In order to ensure that the sponsor owns any intellectual property that is created as a result of the clinical trial, the sponsors must include an express assignment of such intellectual property from the creator/owner to the sponsor. Institutions may resist such an assignment or object to the scope of the assignment.

From the sponsor's perspective, the sponsor should own all such intellectual property, including any inventions (whether patentable or not), copyrightable works or trade secrets, because the intellectual property would not have been created but for the funding and access to the drug, biologic or device provided by the sponsor. The institution may attempt to limit the assignment to only patentable inventions related to the drug, biologic or device, and not to unpatentable inventions, works of authorship or other inventions related to general research methods or diagnostic techniques. In addition, some institutions have taken the position that they own the study data, but will grant the sponsor broad rights to exploit the study data. Additional complications may arise if government funding is involved. Before making any compromises, the parties should think through carefully what rights each party needs in any intellectual property created during the clinical trial in order to meet their respective goals.

*The parties should carefully consider what intellectual property rights they need to meet their objectives*

## **Indemnification**

In today's litigious society, if a patient is injured or dies in a clinical trial, often all parties will be sued, regardless of who caused the injury or death. To protect each party from liability created by the other parties, a sponsor's clinical trial agreement typically includes a mutual indemnification by the sponsor and the institution that protects each party from the cost of defending a lawsuit where the party is not at fault. Universities and large medical centres may ask that the sponsor provide a broader indemnification. In addition, they may refuse to indemnify the sponsor, though in recent times they appear more willing to provide limited indemnification for damages resulting from their fault. However, even in cases where the institution does not provide indemnification, the sponsor should still exclude from its indemnity obligations any losses due to 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 drug, biologic or device.

## **Subject injury**

Institutions may request that sponsors expressly agree to reimburse subjects for medical expenses incurred in connection with the proper use of the study drug, device or biologic in accordance with the protocol. While sponsors usually will make this express commitment, sponsors may want to clarify that this obligation only applies to reasonably incurred expenses, and not to other injury-related costs or to any medical expenses that are the result of 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 drug, biologic or device. Further, before agreeing to this type of provision, the parties should resolve whether the sites will submit these types of medical expenses to insurance for reimbursement, and assure that appropriate procedures are in place to avoid the "fraud and abuse" concerns that can arise (see discussion below).

In addition, sponsors must be wary of whether their offer to pay for subject injury will turn them into a "primary payor," a position that has been espoused by the Centers for Medicare and Medicaid Services, the federal agency that runs the Medicare and Medicaid health insurance programmes. Finally, any commitment by the sponsor to reimburse subjects for these expenses should be consistent with sponsor commitments in the study budget and injury treatment language in the informed consent.

## **Insurance**

It is customary for agreements to require the sponsor to carry adequate insurance. In addition, several foreign laws require the sponsor to carry such insurance. While historically it has not been typical to ask the institution or investigator to carry insurance, sponsors should consider asking for such insurance, particularly from small private hospitals, clinics or physicians' offices, as the sponsor has little assurance that such institutions or investigators will be able to meet their indemnity obligations without some insurance commitments.

*Sponsors should clarify their commitments on reimbursing medical expenses...*

*...and may want to ask institutions and investigators to carry insurance*

## Payment

In structuring the sponsor's payment obligations for the clinical trial, care should be taken to ensure that the payment structure does not create a financial conflict of interest for the investigator or run afoul of any other regulatory laws or requirements, including any fraud and abuse laws. From a sponsor's perspective, it is preferable to structure these payments so that they do not create any financial conflict of interest (ie no equity stake), to ensure that the payments reflect fair market value for the work performed, and to delay some payments until completion of the final reports required at the end of the trial.

*Payments should be structured to avoid financial conflicts of interest*

## Third-party reimbursement

Because of ever-rising development costs, and initiatives by the federal government to provide payment for certain costs incurred in connection with certain clinical trials, sponsors are increasingly looking to investigators and institutions to make use of whatever third-party health insurance coverage is available to a study subject. Often, third-party insurance will cover the control arm of the study and many of the pre-procedure and follow-up tests and visits, because these are within the standard of care for patients with the study subject's condition. Some insurers, like Medicare, will even cover procedures that make use of an investigational drug or device, although they typically will not pay separately for the drug or device itself. The advent of third-party insurance into the clinical trial world brings with it the attendant "fraud and abuse" risks associated with health insurance billing, including double billing and improper inducements that may be perceived to result from reimbursement guarantees. Since both sponsors and study sites may bear some risk of liability, care must be taken in structuring clinical trial agreements to avoid these pitfalls.

*The use of third-party insurance brings "fraud and abuse" risks*

## Termination rights

The clinical trial agreement should clearly state each party's termination rights and the effect of termination on the study. In order to be able to terminate a study for safety, business or any other reason, the agreement should provide that it may be terminated by the sponsor for convenience. Institutions may insist that either this termination right for convenience be mutual and/or that the institution be reimbursed for costs incurred prior to termination. Sponsors may want to limit the institution's ability to terminate for convenience and/or only agree to pay the institution in accordance with the agreed-upon budget. The parties may also want to consider additional termination rights, such as termination for uncured breach, termination for safety or toxicity reasons, termination if the principal investigator is removed and an adequate replacement cannot be found, or termination for the reasons set forth in the protocol.

*Agreement must be reached on trial termination rights*

In addition to addressing the cost issues noted above, the agreement should obligate the principal investigator to cease enrolling patients upon termination, and cease performing procedures under the protocol to the extent medically permissible and appropriate to do so. Also, the agreement should expressly provide that the sponsor shall not be obligated to continue to supply the study drug, device or biologic after termination.

## Limitations of liability

It is generally good business practice to exclude each party's liability for consequential damages, such as lost profits, with the exception of damages attributable to breach of confidentiality or the indemnification obligations. Sponsors will sometimes also ask for an overall cap on their damages. Institutions are generally not receptive to this, unless it includes an exclusion for the sponsor's indemnification obligations or misconduct.

## Independent contractors

The clinical trial agreement should provide that the parties to the agreement are independent contractors and have no authority to bind one another. While this is generally considered legal boilerplate in a contract, it provides important evidentiary support favourable to the sponsor in the event of a dispute with a patient who claims that either the principal investigator or institution was working as an agent of the sponsor.

*Parties to the agreement should be independent contractors*

## Parties to the agreement

The parties should carefully consider who should be a party to the contract. While clearly the sponsor and institution should be named parties, it is not always settled as to whether the principal investigator or the sponsor's contract research organisation should be parties to the agreement. Generally, it is better practice for the principal investigator to be a party to the agreement to ensure that the sponsor has a contractual remedy against the principal investigator for breach of the trial agreement. However, some parties may feel comfortable not having the principal investigator be a party to the clinical trial agreement if the principal investigator is an employee of the institution and

*The principal investigator may be asked to sign additional forms*

the sponsor is assured that the intellectual property, confidentiality and other applicable provisions will apply to the principal investigator through the employer-employee relationship. In this case, to help ensure that the principal investigator is aware of the agreement obligations, the sponsor may ask the principal investigator to sign a "read and acknowledged" clause in the signature block of the agreement.

Occasionally, parties will have the principal investigator sign a separate acknowledgement form whereby the principal investigator acknowledges and agrees to be bound by the terms of the clinical trial agreement that apply to the principal investigator. The sponsor may request the co-investigators to sign a similar acknowledgement form. If the sponsor is using a contract research organisation, the sponsor should either ensure that it has the right to appoint a representative or agent to perform certain sponsor obligations (or exercise certain sponsor rights) or have the research organisation be a party to the contract. For example, if the contract research organisation will be responsible for making payments to the institution, the sponsor may want the agreement to reflect this. However, the institution may insist that the research organisation be party to the contract so that the institution has a contractual remedy against the research organisation for non-payment.

### Conclusion

*Agreeing rights and obligations at the outset will help to resolve any problems later on*

To help avoid unnecessary delays in negotiations, the parties should carefully consider the respective goals of the parties to the clinical trial agreement. By starting from a clear expression of their rights and obligations in the agreement, the parties should be able to quickly resolve any contractual issues that may arise during the trial.

#### References

1. 45 CFR Parts 160 & 164, [www.access.gpo.gov/nara/cfr/waisidx\\_05/45cfrv1\\_05.html](http://www.access.gpo.gov/nara/cfr/waisidx_05/45cfrv1_05.html)
2. 21 CFR Parts 50 (Protection of Human Subjects), 54 (Financial Disclosure by Clinical Investigators), 56 (Institutional Review Boards), 312 (Investigational New Drug Application) and 812 (Investigational Device Exemptions), [www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfctr/cfrsearch.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfctr/cfrsearch.cfm)

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