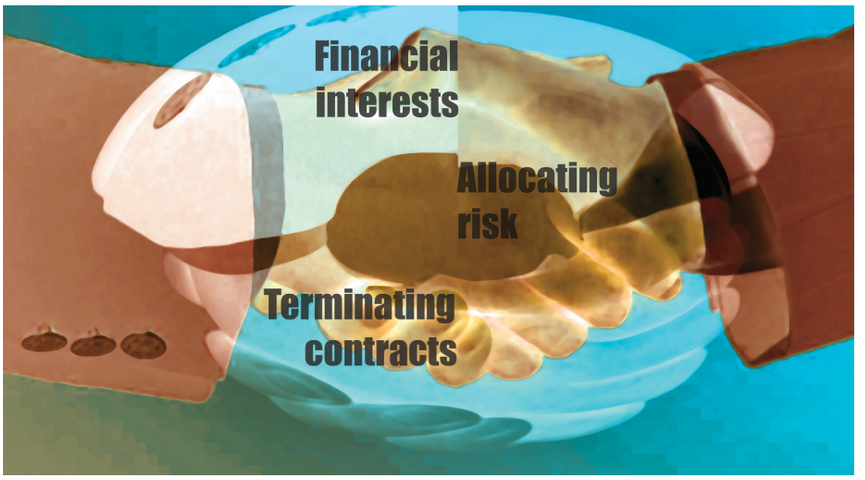
Guarding against conflict

In her second article on negotiating study contracts, **Katherine R Leibowitz** looks at issues around the disclosure of financial interests, allocation of risks and termination of contracts

KEYWORDS: Clinical trial agreement; Milestone payment; Healthcare fraud and abuse laws; Indemnity; Insurance; Limited liability; Audit



Last month's article on business issues raised by the clinical trial agreement focused on confidentiality, intellectual property and publication rights. Financial interests and risk allocation are other important matters for the sponsor to consider.

US FDA regulations grouped under Title 21, Part 54 (21 CFR 54) govern financial disclosure by clinical investigators and are designed to help eliminate the potential for bias that may arise owing to financial conflicts of interest. For example, if the sponsor compensates an investigator with an equity stake in the company, or if the investigator has a proprietary interest in the product, they may be motivated to influence the outcome of the trial data rather than remaining impartial.

While the FDA regulations give the sponsor the option of either certifying the absence of financial interests on the part of the investigators, or disclosing those interests, it is better to be in a position to certify their absence, as this avoids raising a red flag with the FDA. When structuring compensation for a clinical trial, sponsors should try to 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.

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 (PI). These payments are often tied to milestones, such as follow-up visits and/or completion of case report forms. Sponsors should consider basing the last milestone payment on final acceptance by the sponsor of all data pertaining to that subject. This gives the site an incentive to finish its data submissions to the sponsor, which otherwise might drag on at the end of the trial.

The budget exhibit should define conditions where payment may be denied, for example if the subject turns out to have been ineligible to participate in the trial at time of enrolment, or if the PI failed to get adequate informed consent. Some sponsors pay institutional review board (IRB) or EC fees, start-up administrative fees or other one-off charges. Fees can be non-refundable or advances earned against subject follow-up payments. Sponsors may reimburse for study procedures or the cost of the drug. In all cases, the sponsor must take care to avoid falling foul of healthcare fraud and abuse laws, including but not limited to the US federal Anti-Kickback Statute, Stark Laws, and False Claims Act, US state laws and similar laws in Europe. In addition, the payment exhibit should make clear that it sets forth all payments and reimbursements for which the sponsor will be responsible.

Mutual indemnity

The parties to a clinical trial agreement face very real and significant exposure to liability because the trial involves testing humans. Particularly where drugs that pose significant risk are concerned, a trial could lead to injury or death. In today's litigious society, if a research subject is injured or dies in a clinical trial, 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 where it is not at fault.

The fairest approach to mutual indemnity is for each side to be responsible for its own failures. On the sponsor side, if the medicine causes a subject's injury or death, the sponsor would indemnify the institution, the PI and their personnel from the costs of defending a lawsuit they may be dragged into.

Clinical trial agreements provided by institutions include an indemnity from the sponsor, but often do not tailor this indemnity to problems caused by the medicine. Sponsors should make clear that if a research subject is injured or dies, but the institution, the PI or their personnel failed to follow the protocol, applicable laws or regulations, or were negligent or misused the medicine, then the sponsor will not indemnify. Normally, institutions will agree to this condition, as it is a fair allocation of business risk. On the institution's side, if the institution, PI or their personnel are at fault, the institution would indemnify the sponsor for the legal costs of defending a lawsuit where it may be named.

Historically, universities and large medical centres have refused to indemnify the sponsor, though this is rapidly changing. In some cases, state laws prohibit public universities from indemnifying the sponsor. In such instances, the sponsor should still exclude from its indemnity obligations any losses due to the institution's, the PI's or their personnel's failure to follow the protocol, applicable laws or regulations, or their negligence or misuse of the medicine.

Insurance

Insurance provides each party with added assurance that the other will be able to meet its indemnification obligations. The EU Clinical Trials Directive and member state implementing laws require the sponsor to provide clinical trial insurance. In the US there is no counterpart FDA requirement, except a provision that any arrangements should be disclosed to the IRB and prospective subjects. Even so, US institutions have historically 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 offices, as 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. This exclusion of liability protects the sponsor from negative fallout experienced by the institution or PI, and a corresponding claim against the sponsor for lost profits, in the event of publicity relating to serious injury or death during the trial.

The sponsor will also want to cap its liability for direct damages to an amount equal to what the sponsor has paid the institution or PI during the trial. Universities and large medical centres are less receptive to liability caps, but will 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 best practice, three parties should sign the clinical trial agreement: the sponsor, the PI and the institution. However, in some situations a two-party clinical trial agreement (or two two-party agreements) may be necessary.

If an institution employs the PI, the institution may not want the PI to be a formal party to the clinical trial agreement. This should be acceptable to the sponsor under the theory that the institution is, in this case, responsible for the PI. However, because so many provisions of the clinical trial agreement apply to the PI, it is in the sponsor's interest to educate the PI about the agreement. To this end, the institution will normally be amenable to having the PI sign a 'read and acknowledged' signature block at the end of the agreement. If the PI has staff privileges at the institution, but is not an employee, then the sponsor should press for the PI to be a formal party to the clinical trial agreement, as the institution will probably lack sufficient authority to enter into the agreement on behalf of the PI.

Where the PI is not an employee of the institution, but has limited staff privileges at the institution, the institution may prefer not to sign the clinical trial agreement that the PI signs. Because the trial will be conducted on institution premises and will be likely to involve institution personnel and equipment, the sponsor should enter into an agreement with the institution to ensure that the institution bears responsibility for its personnel involved in the trial. If the institution refuses to sign a three-party clinical trial agreement with the sponsor and the PI, then the sponsor should sign one agreement with the PI (with a provision for the institution to receive an information copy) and another with the institution (with a provision for the investigator to receive an information copy). The sponsor should not have much difficulty convincing the institution to sign an agreement, as most institutions will want to be indemnified by the sponsor for any liability to a research subject (or his survivors) owing to injury or death caused by the sponsor's medicine.

The PI usually appoints co-investigators (or sub-investigators) to assist with the conduct of the trial. These co-investigators should not be parties to the clinical trial agreement itself, but should sign an exhibit to the agreement in which, among other things, they agree to abide by the PI's obligations. This will give the sponsor an extra layer of protection, by educating the co-investigators on the requirements of the clinical trial agreement.

Various additional parties may participate in the conduct of the trial, including interns, residents, staff physicians, independent study coordinators, CROs and labs. With the exception of CROs and coordinating centres, these ancillary parties do not typically sign documents that would make them responsible to the sponsor for their mistakes in the trial, or that would assign the intellectual property (IP) they develop during the trial to the sponsor. The sponsor must carefully consider what ancillary individuals may be involved in the trial, and appropriate indemnifications for and assignments of IP should be secured from the institution on their behalf.

If a CRO is to sign the clinical trial agreement on behalf of the sponsor, the sponsor should carefully review the contract before it is signed. Clinical trial agreements provided by CROs often do not adequately protect the sponsor's interests. In addition, the clinical services agreement between the sponsor and the CRO should appropriately address the transfer of responsibilities from the sponsor to the CRO, in compliance with 21 CFR 312.52 and counterpart provisions in other countries' clinical trials legislation.

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; however, the service provider does not have a corresponding right. In the clinical trial context, the course of the trial may be affected by other trial sites, communications with the FDA or other factors, 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. Some sponsors resist this provision on the grounds that, considering the sponsor's significant investment of time and money in the trial, it needs to be able to count on the institution's participation. The institution and PI may legitimately fear that they could be forced to continue a trial when they feel they should terminate it for health and safety reasons. To address this, the parties should consider inserting a provision granting the PI the right to terminate the trial at his/her site if he/she believes that changes to the protocol present an unreasonable risk of substantial harm to the research subjects, or if the emergence of any adverse event is of such concern as to support termination. Other sponsors permit the institution and PI to terminate for any reason, because they do not want someone conducting their trial unwillingly.

Another issue is replacement of the PI. When setting up trials, sponsors will often select high-profile PIs. If the PI overseeing a trial leaves the institution during the study, the sponsor might want to be able to discontinue the trial or move it to the investigator's new institution, or to another PI and their institution. To address these options, the trial agreement should grant the sponsor approval rights over any replacement PI, as well as the right to terminate the agreement should the parties fail to agree on a replacement PI.

Competitive drugs

Some sponsors want to prohibit the PI and the institution from working on trials for a competitive medicine during the sponsor's trial. If

the medicine will be used in a specialised field where only a handful of PIs possess the expertise to conduct a clinical trial, a non-compete clause will be impractical, as there is a high likelihood that the PIs would engage in competitive trials. But to avoid enrolment bias or invalid study results, the sponsor may wish to prohibit the PI from enrolling patients in competitive trials simultaneously. If not, the parties should take care to draft the non-compete in a manner narrow enough to pass muster with the courts in the relevant country.

A PI working on competitive medicines for multiple sponsors can create practical problems in terms of confidentiality and IP, but drug companies typically accept this practice as a reality of doing business in specialised fields. In this situation, the confidentiality provision takes on a more critical role in protecting the sponsor's investment in its medicine, and the sponsor should ensure it is drafted appropriately. With regard to IP, the sponsor should verify that the IP assignment provisions of the clinical trial agreement are inclusive and clear, and should insist on and implement procedures to learn of any IP developed by the institution or PI during the trial, so that the agreed IP provisions in the contract can be applied.

Audits and regulatory inspections

Clinical trial agreements customarily include a right for the sponsor (or the sponsor's designated third-party auditor) to audit the clinical trial site, so that the sponsor can monitor the conduct of the trial and obtain any information necessary to respond to regulatory requirements. If the PI will perform any clinical trial work in an office outside the institution, such as a private doctor's office, then the sponsor's audit right should extend to the both the institution's and the PI's facilities.

It is also standard for the clinical trial agreement to require the institution and/or PI to notify the sponsor of any inspection by the FDA or other regulatory bodies. Sponsors will typically want the right to attend all such inspections related to the trial. If the FDA or another regulatory inspector visits the trial site, the sponsor should receive copies of all correspondence between the regulator and the institution and/or PI. Once again, these requests should not be objectionable to the institution or PI. If the FDA issues Form FDA-483 Notice of Observations or a similar warning letter to an institution or PI, the sponsor should insist on a right of prior approval or review of any responses. A similar provision would apply to replies to reports of inspection by other regulators. Involvement in the response process will help the sponsor protect its investment in its medicine.

It is clear, then, that by applying best practices and carefully structuring the clinical trial agreement, sponsors can take significant steps toward reducing many of the risks associated with sponsoring a trial. GCPj

Acknowledgments

The author would like to thank Linda Horton of Hogan & Hartson's Brussels office for her contribution to this feature. An earlier version of this article appeared in *Medical Device & Diagnostic Industry*, October 2005.

•*Next month: The final instalment of this three-part series of articles will cover the protection of health information and other personal data.*

Katherine R Leibowitz
Hogan & Hartson,
Philadelphia, PA, US
Tel: +1 267 675 4612
Fax: +1 267 675 4601
E-mail: krleibowitz@hhlaw.com

Please fax back to
+ 44 (0)20 7017 6985

SUBSCRIPTION RATES

Europe £530 ☐ / €825 ☐ **USA/Canada** US$1,015 ☐ **Japan** ¥166,000 ☐

☐ YES! Please open my subscription to ***GCPj*** starting ____(month) 2006

☐ YES! Please send me a free, sample copy of ***GCPj***

MY DETAILS

Name _____ Job title _____

Business email _____ Company _____

Address _____

_____ Country _____

Tel _____ Fax _____

Signature _____ Date_____

PAYMENT DETAILS

1**. Cheque:**

☐ I will send a cheque for £/€/US$ _____ payable to **Informa UK Ltd**

☐ I will send a cheque for ¥ _____ payable to Shiryo Kenkyujo drawn on a Japanese bank

2**. Credit Card:** Please charge my ☐ VISA ☐ AMERICAN EXPRESS ☐ MASTERCARD

Card Number: ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ Expiry Date: ☐☐ / ☐☐

Security Code: _____ Name of Card holder _____

3**. Invoice:**

☐ Please invoice me. **PLEASE NOTE**

All EU customers must complete their EU VAT registration number:_____

I accept Informa's terms and conditions of sale, a copy of which is available on request.

Our VAT number is: GB 365 4626 36. If you are exempt, or unregistered, for VAT please tick here ☐

All orders are accepted subject to Informa's standard terms and conditions relating to this title JGC0002B

WHERE TO SEND PAYMENT

WORLDWIDE
Informa Healthcare,
Sheepen Place, Colchester,
Essex, CO3 3LP,
United Kingdom
Tel: +44 (0)20 7017 5540
Fax: +44 (0)20 7017 6985

JAPAN
Mr T Hirata, Shiryo Kenkyujo,
3-5-20-405 Sotokanda,
Chiyoda-ku, Tokyo 101-0021,
Japan
Tel: +81 (0)3 3258 9207
Fax: +81 (0)3 3258 9209

INDIA
Mr A Nair, Informa India,
Mahalaxmi Chambers, 6th Floor,
22 Bhulabhai Desai Road,
Bombay, 400 026, India
Tel: +91 (0) 22 362 1921
Fax: +91 (0) 22 363 1555

www.gcpj.com