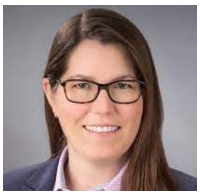
Practical Guidance

Clinical Trial Agreement Considerations for Pharmaceutical Sponsors

A Practical Guidance® Practice Note by Kyle Y. Faget, Foley & Lardner, LLP



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This practice note provides guidance to attorneys who negotiate and draft clinical trial agreements (CTAs) on behalf of pharmaceutical companies. Pharmaceutical companies, commonly referred to as sponsors in the clinical trial context, often underestimate the importance of spending appropriate time and resources on CTAs. This practice note focuses on key CTA provisions that, if overlooked, can be very costly for organizations.

This practice note covers the following topics:

- The Role of CROs in CTA Negotiations
- Preamble
- Confidentiality
- Intellectual Property
- Indemnification
- Subject Injury
- Limitation on Liability
- Publication Rights

For additional information about clinical research agreements, see Clinical Research Support Agreement and Master Clinical Trial Agreement. For information about institutional review boards (IRBs), see Institutional Review Boards. For a tutorial on using Practical Guidance for drafting agreements for clinical research, see Drafting Agreements for Clinical Research in Practical Guidance Life Sciences: How-to Video. For information about FDA regulatory activity affecting clinical trials for pharmaceuticals, see FDA Drug Regulatory Activity Tracker and FDA Warning Letters Tracker.

The Role of CROs in CTA Negotiations

Many Sponsors outsource the negotiation of CTAs to contract research organizations (CROs) because outsourcing negotiation of CTAs is often a less expensive and more efficient way for Sponsors to get CTAs executed than negotiating CTAs on their own.

It is important to remember, however, that CROs work with industry partners that are sponsors of clinical trials, such as pharmaceutical and medical device companies. As part of their work, they interact with institutions that serve as clinical trial sites daily. The upside to this continued communication is that CROs are aware of a clinical trial site's appetite for negotiating certain provisions within a CTA, which leads to the efficiency enjoyed by CROs when negotiating CTAs.

The downside for Sponsors is that CROs are less likely to put pressure on their clinical trial site partners than an in-house or external counsel would for important provisions in a CTA. As a result, Sponsors should reserve negotiation of key provisions in a CTA to their own counsel. For example, if a site requests edits to a subject injury provision, the edit should be elevated to the Sponsor or Sponsor's counsel for review.

Similarly, if a CRO provides its template CTA for use by a Sponsor, a Sponsor should have that template reviewed by Sponsor's counsel. Important CTA provisions and considerations applicable to such provisions are explored in detail below.

For information about CRO agreements and the role of CROs, see Contract Research Organization Agreements.

Preamble

The CTA preamble is often where the principal investigator (PI), the physician clinician who has regulatory responsibilities for overseeing the conduct of a clinical trial, is either included as a party or not. In practice, PIs are often not a party to the CTA and as a result, the CTA should include a provision that clarifies that the site has the authority to bind the PI. This is typically accomplished by making clear in a substantive section of the CTA (in other words, not the preamble) that the PI is an employee of the site. Additionally, when the PI is not a party (does not sign) to the CTA, the CTA should include a "Read and Acknowledged" signature block for the PI because it is important to confirm that the PI is aware of and acknowledges their responsibilities under the CTA. This avoids the possibility that a PI will claim to be unaware of a responsibility arising under the CTA. If the PI is affiliated with and not an employee of the site, the PI must be a party to the agreement because the PI will not be covered under the site's insurance, but rather will have separate liability coverage.

Confidentiality

Sites often request a two-way confidentiality provision. Unless it is absolutely necessary to accept this provision, Sponsors should only agree to a one-way confidentiality provision. The reason for this is quite simple: PIs and sub-investigators are often very open with their ideas, which can really only serve to contaminate a Sponsor's intellectual property. Sponsors have invested significant capital in developing their proprietary products and do not want a site or a PI claiming that they contributed to the resulting intellectual property or to a new proprietary product developed by the Sponsor in the future. Sponsors do not typically want or need site confidential information because the Sponsor has developed its proprietary products on its own without the collaboration of the site or the PI. Drawing this boundary up front via contract helps protect Sponsor from unintended consequences. Well-informed sites may push back on a one-way confidentiality provision claiming that any intellectual property disclosures would need confidential treatment. While a valid concern, a narrow disclosure such as an intellectual property disclosure should not justify wholesale confidentiality protection and drafters can limit the scope of confidentiality that applies to the site to include intellectual properly disclosures only.

The following is an example of confidentiality language for a CTA:

> "Confidential Information" means (a) any and all scientific, technical, business, regulatory, or financial information in whatever form (written, oral, electronic or visual) that is delivered or otherwise disclosed to Site or PI, by or on behalf of Sponsor or its affiliates, including the protocol, the Investigators' drug brochure, information contained in or comprised of materials provided to Site by Sponsor, and the financial terms of this Agreement; (b) all approvals and correspondence with or from an IRB or other entities with oversight responsibilities for the Study, including ethics committees or data safety monitoring committees, all Study correspondence, all Study Drug and accountability forms, and all case report forms (collectively, the "Study Documentation"); and (c) all Study Data; provided, however, that Site and PI may use and/or publish Study Data solely in accordance with the publication provisions of this Agreement.

Intellectual Property

Not surprisingly, Sponsors want to own anything, and everything related to the drug that is the subject of the study (Study Drug). Sponsors should make clear in the CTA that ownership includes the following:

- A method of predicting responsiveness to the Study Drug (and any diagnostic method or product related to it)
- Compositions or formulations comprising Study Drug
- A new method of manufacturing, administration, or dosing scheme for Study Drug -or-
- New uses, enhancements, or improvements of Study Drug

Sponsors should also make clear that anything that uses or relies upon Sponsor's confidential information, such as a new use of Sponsor's investigational product or a new product developed by the site or PI, will be the sole and exclusive property of Sponsor. Together, these will be Sponsor inventions, for example, intellectual property that belongs to the Sponsor.

Sponsors should acknowledge in a CTA that a small number of inventions may arise in the context of a clinical trial that are not Sponsor inventions. These may include an improvement to research workflows within the site or ways to organize study subject information within the site. In a CTA, anything other than a Sponsor invention may be considered an "Other Invention." These inventions are typically owned in accordance with U.S. patent law.

In addition to inventions, Sponsors will want to own the study data. It is customary for Sponsor to permit sites to use study data for internal, noncommercial research purposes and for patient care. Sponsors will want to ensure that a site's use of study data is appropriately limited. For example, study data should be non-sublicensable and in no way benefit any third-party entity.

The following is an example of IP language for a CTA:

> Inventions that relate to (i) the Study Drug, including without limitation, a method of predicting responsiveness to Study Drug (and any diagnostic method or product related thereto), compositions or formulations comprising Study Drug, a new method of manufacturing, administration or dosing scheme for Study Drug, or new uses, enhancements or improvements of Study Drug, or (ii) Sponsor's Confidential Information will be the sole and exclusive property of Sponsor (collectively, the "Study Drug Inventions").
>
> Inventions that are not Study Drug Inventions (the "Other Inventions") will be owned in accordance with inventorship as determined under U.S. patent law.

For information about patents in drug development, see Pre-litigation Preparation and Strategy for Pharmaceutical Product Patents and Exclusivity in the Practical Guidance Intellectual Property & Technology practice area.

Indemnification

Indemnification is one of the most heavily negotiated terms in any agreement and CTAs are no exception.

The acceptable terms of CTA indemnification provisions tend to vary over time. For example, academic institutions used to readily offer indemnification unless constrained by applicable state law. Currently, however, many academic institutions refuse to offer indemnification because sites don't want to incur financial obligations as a result of performing clinical trial services. If this is the case, it is important that Sponsors receive, at the very least, a statement by the site that it will remain responsible for the acts and omissions of site indemnitees.

Note that private, not-for-profit institutions do not have the same justifications as academic institutions for not offering indemnification and should be willing to offer indemnification as part of a just allocation of risk as between the parties. If a party is unwilling to offer indemnification, whether to move forward with contracting is ultimately a business decision.

Sponsors are expected to indemnify sites. Importantly, however, Sponsors should ensure that they are indemnifying only for third-party claims. Sponsors do not want to have to indemnify for first-party claims. A site can always sue for first-party claims.

Also consider the following with respect to indemnification:

- Sponsors will want to limit their liability to claims that occur as the direct result of the Study Drug.
- Sites may wish to limit the scope of indemnification by excluding claims that are the result of the natural progression of the disease or another underlying condition.
- Sponsors may refuse to indemnify for third-party claims if the study subject failed to follow the directions provided by the PI or the Sponsor and the applicable informed consent.
- Sponsors will want to limit indemnification to the extent a claim is the result of the institution or PI's negligence, willful misconduct, breach of the CTA, or an applicable law, regulation, or guidance.

More and more sites are asking to be indemnified for third-party claims of intellectual property infringement related to the Study Drug or protocol. This is not an unreasonable request. Sponsors will have to determine whether to attempt to limit the recovery possible for such claims.

The following is an example of indemnification language for a CTA:

> Sponsor agrees to indemnify, defend and hold harmless Institution, its trustees, directors, officers, employees (including Investigator), Study Personnel and agents (collectively, the "Institution Indemnitees") against any third party claims, including reasonable attorney's fees for defending those claims (each, a "Claim"), to the extent a Claim arises out of or relates to (a) any theory of product liability concerning the Study Drug; or (b) any side-effect or adverse reaction, illness or injury directly resulting from (i) use of the Study Drug in the Study, or (ii) a procedure specified in the Protocol that the Study Subject would not have undergone but for such Study Subject's participation in the Study. The foregoing indemnity will not apply to the extent a Claim arises

out of or relates to (1) an Institution Indemnitee's (A) negligence or willful misconduct or (B) failure to comply with an applicable law or regulation or adhere to the terms of the Protocol or any written instructions from Sponsor or its designee; (2) a claim related to a drug or product other than the Study Drug; or (3) Institution's or Investigator's failure to adhere to the terms of this Agreement.

Institution agrees to indemnify, defend and hold harmless Sponsor and its directors, officers, employees and agents (collectively, the "Sponsor Indemnitees") against any Claim to the extent such Claim arises out of or relates to (a) an Institution Indemnitee's (i) negligence or willful misconduct or (ii) failure to adhere to the terms of the Protocol, or any written instructions from Sponsor or its designee; or (b) Institution's or Investigator's failure to adhere to the terms of this Agreement.

Subject Injury

Almost all sites will require that Sponsors pay for the costs associated with injury to a study participant when the injury occurs as a result of the Study Drug or a nonstandard of care procedure. Sponsors can limit their liability under this "subject injury" provision by drafting the provision to include only injuries that occur as the direct result of the Study Drug.

Sponsors can also make clear that reimbursement from the Sponsor to the site for expenses incurred by the site as a result of subject injuries will include the "usual and customary" rates of the site for the "reasonable and necessary" out-of-pocket medical expenses in excess of a study subject's commercial medical or hospital insurance that are incurred by the site for the diagnosis and treatment of the injury.

Sponsors must be careful to not include Medicare as a potential payor because doing so risks violating the Medicare Secondary Payor (MSP) rule, which requires that Medicare be the secondary payor in specified instances of dual healthcare coverage. Here, the Sponsor is considered an instance of healthcare coverage. Note also that a number of private insurers are drafting policies that mirror the Medicare Secondary Payor rule.

More and more, Sponsors are expected to pay the full amount of a subject injury without respect to payor source. Indeed, some sites as a matter of institutional policy will require that Sponsors pay for a subject's injury without submitting a claim to any available insurance source. Additionally, some sites have gone so far as to require that any injury, regardless of whether the injury is the result of the Study Drug or a nonstandard of care procedure, be covered by the Sponsor.

One critical consideration when drafting subject injury provisions is confirming that the language agreed to in the CTA mirrors that of the informed consent forms provided to study participants. Sponsors have been known to spill a lot of ink during negotiation of subject injury in the CTA but failing to make adjustments to the informed consent. If the informed consent says that a Sponsor will broadly cover injuries sustained in a clinical trial, a study subject has a basis for collecting for such injuries.

The following is an example of subject injury language for a CTA:

Sponsor will:

(a) reimburse Institution, at usual and customary rates, for the reasonable and necessary out-of-pocket medical expenses in excess of a Study Subject's commercial medical or hospital insurance, that are incurred by Institution for the diagnosis and treatment of (i) adverse reactions directly resulting from use of the Study Drug in accordance with the Protocol; and (ii) injuries arising directly from a procedure that the Study Subject would not have undergone but for such Study Subject's participation in the Study; provided, that such adverse reactions or injuries are not attributable to (1) an Institution Indemnitee's negligence, willful misconduct or failure to adhere to an applicable law or regulation, the Protocol, or Sponsor's or its designee's written instructions; or (2) a pre-existing medical condition of the Study Subject or his/her underlying disease; and

(b) reimburse a Study Subject for any injuries sustained as a direct result of Study Subject's participation in the Study in accordance with the terms of the Informed Consent Form.

Limitation on Liability

Whenever possible, Sponsors should limit their liability under the terms of a CTA. Many sites will ask that certain provisions of the CTA be carved out of the limitation, including indemnification and intellectual property infringement claims. Regardless, a Sponsor will want to ensure that it will not be liable for indirect, incidental, special, punitive, or consequential damages arising out of the clinical trial.

The following is an example of limitation on liability language for a CTA:

> Sponsor shall not be responsible to the Site for any lost profits, lost opportunities, or other consequential damages.

Publication Rights

One of the most important provision for sites is the publication provision because an investigator's career depends upon publication of journal articles to establish his or her reputation as an expert in a given field. Consequently, sites will want the freedom to publish site-level data without restriction.

It is not unreasonable, however, for a Sponsor to require, as a condition of publication, that the study was conducted at the site in compliance with the protocol and that the publication or presentation is made in a recognized medical or scientific journal or at a recognized scientific conference, and makes use of all study data and not subsets of study data. It is worth noting that emergency treatment of a study subject will not be deemed noncompliance with the protocol.

It is also not unreasonable for Sponsors to request that Sponsor confidential information be removed from any proposed publication. Sites may refuse to remove such information and only allow a Sponsor time to file for patent protection. A middle ground approach is for a Sponsor to request that a site remove Sponsor confidential information from a publication so long as doing so does not undermine the integrity of the results.

The following is example of publication rights language for a CTA:

> Institution and PI may publish or publicly present the Study Data; provided, that (i) the Study was conducted at Institution in compliance with the Protocol (it being understood that emergency treatment of a Study Subject will not be deemed non-compliance with the Protocol); (ii) such publication or presentation (x) is made in a recognized medical or scientific journal or at a recognized scientific conference; and (y) makes use of all Study Data and not subsets of Study Data.

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Kyle Faget is a Boston-based partner and a health care and life sciences lawyer with Foley & Lardner LLP. Kyle is the Co-Chair of the firm's Health Care and Life Sciences Practice Groups, and she is a core member of the firm's telemedicine industry team. Kyle advises investors, academic medical centers, physician practices, and consultants on a range of business, legal and regulatory issues affecting the telemedicine industry. She helps companies build and refine corporate compliance programs, including advising clients on regulatory and compliance matters involving the Food, Drug and Cosmetic Act (FDCA), the False Claims Act (FCA), the Anti-Kickback Statute (AKS), the AdvaMed Code and the PhRMA Code. She regularly drafts and negotiates agreements required for the development and commercialization of pharmaceutical and medical device products, including licensing agreements, collaboration agreements, clinical trial agreements, and an array services agreements. Prior to joining the firm, Kyle held in-house positions at pre-commercial and commercial stage companies.