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The anatomy of a clinical trial agreement

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Clinical trials and contracting

Those involved in clinical trial agreements (CTAs) are intimately aware that the agreements are lengthy, complex to negotiate, and riddled with compliance pitfalls. If new to this area, it may be easy to overlook a key section or consideration in contracting—especially when time is of the essence in developing new products. Pressure comes from different parties to get an agreement executed so that testing may continue and development timelines are met.

This article explores the hallmark agreement in the research associated with any investigational product: the CTA. CTAs memorialize the agreement among the companies that develop the investigational product, the site at which the investigational product will be tested, and the physician overseeing the testing at that site. The following outlines the basics of any clinical trial, including the various stages of testing, an overview of the CTA, and a deeper dive into the core sections of any CTA. In this deep dive, compliance professionals may note risk areas of which to be aware. Parties are more likely to enter a compliant CTA when understanding the required elements and potential pitfalls.

Clinical trial basics

Companies develop new drugs, biologics, devices, and other medical interventions (investigational product) that must be tested through clinical trials to ensure safety and efficacy. Clinical trials involve human subjects and require collecting, storing, and sharing of subject data. They are conducted at many locations, including facilities in the United States and abroad. This process is regulated by the U.S. Food and Drug Administration (FDA), Centers for Medicare & Medicaid Services (CMS), Office of Civil Rights (OCR), and foreign counterparts.

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The development process for an investigational product follows multiple stages: (1) discovery and development, (2) preclinical research, (3) clinical research, (4) FDA review, and (5) FDA postmarket safety monitoring. The clinical research phase is the main component of the process that involves testing the investigational product in human subjects and is when contracting occurs. This research phase has various steps that must successfully demonstrate safety and efficacy before the FDA is willing to review the proposed investigational product for approval. This phase is generally referred to as the clinical trial or clinical study phase.

Companies that develop new drugs, biologics, devices, and other medical interventions sponsor the clinical trial and are therefore referred to as the "sponsor" in all contracting documents. The sponsor's responsibilities include selecting the principal investigators (PIs), providing those PIs with a roadmap to conduct the clinical trial (typically called the "protocol"), ensuring proper monitoring of the study, confirming all necessary reviews and approvals are obtained for the study, and making sure all reviewing entities and regulatory agencies are informed of the information before, during, and after the study. The protocol is developed, and the study is conducted, in accordance with the FDA regulations relating to good clinical practice and clinical trials.[1] These regulations outline requirements pertaining to informed consent forms, electronic records, institutional review boards (IRBs), and much more.

The sponsor typically hires a clinical research organization (CRO) to assist in administering and managing the clinical trial. The CRO often has site-specific and country-specific knowledge to efficiently manage the contracting process, which is integral to a successful clinical trial. With this knowledge, CROs often recommend site selection, provide patient recruitment support, assist with biostatistics and clinical monitoring, and offer clinical data management.

The sponsor and CRO choose facilities where the clinical trial will be conducted, referred to as "sites." The site is often an academic facility, referred to as an "institution." Each site employs or contracts with a PI. The PI is the physician who will oversee the clinical trial at the institution. The protocol is approved by the site's IRB. The IRB is made up of physicians, researchers, and members of the community. Its role is to ensure the study is ethical and that the rights and welfare of participants are protected. Abroad, many countries use an ethics committee (EC), which serves a similar function as the IRB.

CTA overview

The CTA governs the relationship between the sponsor, the PI, and the site, setting forth the purpose of the agreement between the parties. It may describe the CRO's relationship with the sponsor and the CRO's role in managing and administering the clinical trial. In some situations, the CRO may be the party to the CTA on behalf of the sponsor. In those cases, the sponsor typically executes a separate letter of indemnity with the site outlining the sponsor's indemnification obligations for any liability associated with the clinical trial and the CTA's provisions. Similarly, there are situations where the PI may not be a party to the CTA but may be required to acknowledge their obligations in overseeing the trial.

The CTA sets forth the parties' obligations and responsibilities for performing the clinical trial. This includes information regarding the investigational product and the protocol that governs how the trial is performed, plus how the protocol may be amended and acceptable deviations from the protocol. Common terms include payment and reimbursement terms, intellectual property (IP) rights and ownership of data collected during the trial, insurance and indemnification requirements, how injuries to subjects enrolled in the trial will be handled, record keeping, termination provisions, dispute resolution provisions, and confidentiality requirements. Additionally, CTAs typically include representations or warranties that are advisable for regulatory compliance. For instance, anticorruption, antibribery, and debarment and exclusions provisions are necessary to comply with applicable US laws (or their foreign counterparts). Such representations and warranties are important for the site, PI, and the

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sponsor. Moreover, from the sponsor's perspective, if a clinical trial is being conducted abroad and the sponsor wants to use the data for submission to the FDA, additional language may be necessary to ensure compliance with the FDA regulations.[2]

CTA: A deep dive

Institutions, PIs, and sponsors engaging in clinical research are subject to complicated legal regulations and practical considerations. Navigating the myriad factors that play into the decisions of institutions, PIs, and sponsors involved in clinical research requires experienced advisors and counselors. Below is a brief discussion of select CTA provisions and considerations for parties involved in clinical research.

Description of the study

The CTA—or one of its accompanying documents like the protocol—should clearly outline the purpose of the clinical trial and describe the purpose of the various agreements. This is an essential contracting principle for any healthcare agreement; however, it is especially vital for payments from healthcare organizations to healthcare professionals and institutions.

The Physician Payment Sunshine Act, referred to as the "Sunshine Act," requires transparency around certain financial relationships between manufacturers of drugs, medical devices and biologics, and teaching hospitals and physicians.[3] Applicable manufacturers must submit annual reports to CMS, and the information provided may be published on the Open Payments website for public review.[4] Notably, information submitted concerning product research or development or clinical investigations shall be published in a delayed fashion after the FDA approval date or four calendar years after such payment was made, whichever is earlier.[5]

Sponsors may incur civil money penalties for noncompliance, and those may quickly accumulate as they are applied to each payment not reported. The Sunshine Act has a capped fine of $150,000 per applicable manufacturer concerning each annual submission of information for any failure to report.[6] A *knowing* failure to report incurs higher penalties, with a cap of $1 million per applicable manufacturer for each annual submission of information.[7]

Ownership and use of data

The purpose of clinical research is to collect data on the safety and efficacy of an existing or potential investigational product, whether it be a chemical compound, biologic, or device. Ownership of, and the right to use, the final data from a clinical trial is a valuable commodity. If the trial is a multicenter interventional study where the sponsor is the owner of the investigational product, the sponsor will nearly always contract for ownership rights in the data collected during the trial. However, institutions and PIs often require that the contract provide them with certain rights to use the data.

Many institutions and PIs—particularly at academic centers—require the right to publish the data and results of a clinical trial, either independently or as part of a multicenter publication. This right to publish is often heavily negotiated with the sponsor seeking to maximize its control over the data and the institution and PI seeking an unlimited right to publish.

In general, the sponsor will agree to allow the institution and PI the right to publish if a multicenter publication is not completed within 12 to 24 months from the end of the trial. The sponsor typically will require that the article or presentation be submitted to it for review in advance of publication. Nonetheless, the sponsor generally does not have a right to alter the article or presentation unless it contains confidential information or would

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disclose unprotected IP of the sponsor. The data and results themselves are not confidential information, so an objection regarding confidential information by the sponsor would need to be based on the disclosure of some process or strategy of the sponsor within the publication that the sponsor considers proprietary. Similarly, most agreements provide for a delay in publication (between 30–90 days) to allow the sponsor to seek IP protection; though, the existence of the IP in the article or presentation should not ultimately prevent publication. Sponsors typically assert a license to reproduce, distribute, and use any publication by institution and PI.

Furthermore, while the sponsor may own the study data, in most instances, the sponsor will grant the institution and PI a right to use the data. This right is usually described as the right to use the study data "for noncommercial internal research, educational purposes, and patient care." Institutions and PIs should be cautious of the right to use the study data for "patient care" for two reasons. First and foremost, the usefulness of data collected in the context of clinical research must be assessed, bearing in mind, among other things, the phase of the study, the study results, the size of the study, inclusion and exclusion criteria for study subjects, and the trial protocol. The existence of study data from clinical research does not make its use "standard of care," and the Institution and the PI should make a standard of care assessment before using the study data for patient care. Second, if use of the data is limited to noncommercial purposes, the institution needs to consider whether "patient care" is a commercial or noncommercial purpose.

The study's informed consent form should disclose the use of data and privacy protections to study participants. This should be done in a manner that complies with the FDA's regulation for protecting of human subjects.[8] Sponsors should also keep in mind privacy laws when drafting the informed consent form, which will ultimately be reviewed and approved by an IRB or EC as subsequently described.

Indemnity and insurance

Indemnity and insurance are two heavily negotiated sections of most CTAs. Institutions and PIs have a significant interest in protecting against third-party liability that may arise from using the investigational product per the sponsor's protocol. If a study subject is injured in a trial because of the investigational product or a procedure required by the protocol, the institution and the PI want to have language in the CTA making the sponsor responsible for: (1) treating the injuries or illness; and (2) paying any damages that may be claimed by or on behalf of the injured study subject. If the sponsor is a party to the CTA, the CTA should contain language wherein the sponsor agrees to indemnify the institution and PI against these damages and expenses. Where the CRO is contracting directly with the institution and the sponsor is not a party to the CTA, the institution should seek a separate letter of indemnification from the sponsor wherein the sponsor agrees to indemnify the institution and PI against these damages and expenses.

Indemnity agreements are only useful if the sponsor has sufficient assets to cover any indemnity obligations. Sponsors come in all sizes, from small start-ups to multinational pharmaceutical conglomerates, so institutions should assess the risks associated with the investigational product and the sponsor's assets to ensure that it is adequately protected against third-party claims. Sponsors routinely carry commercial general liability insurance and an insurance product called "clinical trial insurance" that insures the sponsor against claims arising out of a clinical trial and provides some security behind the sponsor's indemnity obligations to the institution. It is not unreasonable for a sponsor to be asked to have limits in excess of $5 million and provide a certificate of insurance evidencing its coverages and limits.

The sponsor is also interested in ensuring that the institution and PI agree to be responsible for their acts or omission that may cause injuries during a clinical trial. While the sponsor is responsible for claims arising out of the testing of the investigational product following the sponsor's protocol, the institution and the PI are liable for injuries or damages incurred because of their negligence, such as a failure to follow the protocol. Often this

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comes in the form of contractual indemnity and insurance provisions. In the US, most institutions and/or PIs will agree to maintain certain levels of insurance, although these may vary depending on state laws related to medical professional liability. In the rest of the world (ROW), laws, customs, and practices regarding insurance coverage fluctuate greatly from country to country. In the ROW, the size, credibility, and reputation of the institution and PI are significant factors for many sponsors in assessing the risk of proceeding with an institution because of the varying availability of insurance.

Budget terms

Negotiating the budget payable to the institution and the PI is crucial to any CTA. Because clinical trials are living events subject to change, it is advisable to include all budget parameters in one exhibit to the CTA. This allows the budget to be easily updated, as necessary, without needing to execute an entirely new CTA. If utilizing this approach, the CTA should not contemplate remuneration to any party in any other portion of the CTA. This could create confusion and room for misinterpretation.

Privacy – HIPAA and GDPR

The privacy landscape in the US, Europe, and much of the world is quickly evolving. Clinical trials involve the collection of personal health information (PHI) as defined under HIPAA and its accompanying regulations[9] within the US and "personal data" as defined by the General Data Protection Regulation (GDPR)[10] within the EU. Accordingly, one or both privacy laws may govern data collection and use and storage from a clinical trial. Additionally, many US states have their own versions of HIPAA or are implementing privacy laws similar to HIPAA or GDPR, so these should be considered when assessing compliance.

In the US, HIPAA applies to "covered entities" such as health insurers and healthcare providers and their "business associates." Accordingly, HIPAA compliance is required of most institutions and PIs. However, sponsors are not typically classified as a "covered entity" or "business associate." As such, sponsors generally take great care not to assume compliance with HIPAA through contractual terms. Nonetheless, sponsors will normally agree to maintain PHI confidentially and only use, process, and store such information as allowed by the applicable informed consent form.

In the EU, GDPR applies to all parties to a clinical trial—not just the institution and PI. The roles of the parties to clinical research need to be assessed to determine the responsibility of each party under GDPR as either a data controller or a data processor. Factors to consider in making such a determination include the following: is that party determining the purposes and means of processing personal data (controller) or is that party simply processing personal data at the direction of another party (processor)? While the definitions are fairly simple, interpreting each party's role in clinical research involves a more complex analysis.

GDPR imposes obligations upon a data controller making this party responsible for how it processes data and the operations of data processors who are processing data on its behalf. The broader regulatory responsibility of a data controller leads to tension between the sponsor and the institution regarding their respective roles in clinical research under GDPR. In many instances, the different parties wear different hats for different data cohorts. For insurance, an institution may be a data processor for clinical trial data but a data controller for the study subject's medical records and health data. All parties should consider these obligations and be aware of their respective positions prior to executing a CTA.

IRB and EC approval

Institutions require approval from their IRB to participate as a site in a clinical trial. The IRB functions as an

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oversight body, reviewing and approving the sponsor's protocol, and operates under the applicable IRB FDA regulations.[11] The foreign equivalent of an IRB is often referred to as an EC.

Institutions may add language to a CTA that the institution's IRB or EC requires for all CTAs. Sponsors must consider how familiar they are with regulations governing IRBs and whether such language is acceptable. Often this is a business decision for the sponsor, as the IRB or EC-required CTA provisions are generally non-negotiable for the institutions.

Record keeping and inspection

An agreement's record keeping section is always important, but for CTAs, it holds a unique purpose. It evidences the agreement between the sponsor and institution regarding how long trial data will be stored after the trial is complete. Different parties may have additional record-retention requirements mandated by regulation. This section of the CTA also provides for the sponsor's right to audit the institution and verify data and the institution's responsibility to cooperate with inspections from regulatory agencies, like the FDA.

Conclusion

Experienced parties are aware that many terms are required to execute a complete and compliant CTA. Sponsors and CROs often create template CTAs and offer those to institutions and PIs to begin the negotiation process. Template CTAs that clearly cover the areas in this article, in addition to other standard agreement terms, are likely to move through the contracting process more efficiently, and in a compliant manner.

Takeaways

- Clinical trial agreements (CTAs) are conducted in accordance with the U.S. Food and Drug Administration regulations relating to good clinical practice and clinical trials.
- CTAs should outline the purpose of the agreement since sponsors may need to report to the Centers of Medicare & Medicaid Services payments made to teaching hospitals and physicians.
- CTA should clearly outline ownership and use of data, including publication rights and intellectual property protections.
- Indemnity and insurance provisions are often the most negotiated terms of any CTA.
- Parties to a CTA must understand their respective roles and responsibilities for maintaining data confidentiality under HIPAA, General Data Protection Regulation, and any other applicable privacy laws.

1 U.S. Food & Drug Administration, "Regulations: Good Clinical Practice and Clinical Trials," January 21, 2021, https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials.
2 21 C.F.R. § 312.120.
3 Section 6002 of the Patient Protection and Affordable Care Act (Public Law No. 111-148); 42 U.S.C. § 1320a-7h, Transparency reports and reporting of physician ownership or investment interests.
4 U.S. Centers for Medicare & Medicaid Services, "Search Open Payments," last updated June 2022, https://openpaymentsdata.cms.gov/.
5 42 U.S.C. § 1320a-7h(c)(1)(E).
6 42 U.S.C. § 1320a-7h(b)(1).
7 42 U.S.C. § 1320a-7h(b)(2).

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821 C.F.R. § 50.
945 C.F.R. §§ 160, 162, and 164.
10 Regulation (EU) 2016/679.
1121 C.F.R. § 56.

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