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Sponsor Agreements with Research Sites and CROs

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Pharmaceutical, biotech and medical device companies ("sponsors") use clinical trial agreements (CTAs) to contract with research sites to conduct clinical trials. They use service agreements (SAs) to contract with contract research organizations (CROs). The two types of contracts have many similarities but also differences that shed light on the sponsor's differing relationships with CROs and research sites. A major difference is that, while sponsors usually buy services such as protocol writing and site monitoring (activities) from CROs, they buy data (results) from sites.

A second set of differences relates to market power: The CRO market is much less fragmented than the research site market. Most CROs are more business-savvy than most research sites. CRO contracts are typically much larger than site contracts, so there is more incentive for CROs to negotiate. There are far fewer CRO contracts than site contracts, so sponsors can allocate more time to negotiating individual CRO contracts.

Table 1 outlines important differences that may be found in the agreements. Different organizations use different variations of these terms or may not include all of them.

Table 1. Clinical Trial Agreements vs. Service Agreements

	CRO Service Agreements	Clinical Trial Agreements
Study personnel	Sponsor must approve CRO's assignment of key personnel and reassignment off the study. Sponsor may require CRO to replace personnel on the study.	Sponsor selects site based on principal investigator and other study personnel. It may terminate agreement if principal investigator leaves the study without an acceptable replacement.
Standard operating procedures (SOPs)	Sponsor may review CRO's SOPs under confidentiality. Sponsor may require that CRO uses sponsor's SOPs.	Sponsor requires that site follow study protocol. It does not require review of site's SOPs or use of sponsor's SOPs.
Delegation of authority	Sponsor delegates certain authorities to CRO.	Sponsor does not delegate authority to site, but site has its own authorities.
Intellectual property & publication rights	Sponsor owns all study data and intellectual property. CRO has no publication rights.	Site has various rights to (and perhaps ownership of) data, intellectual property, and publication.
Liability insurance	CRO must carry professional liability insurance.	Site must carry medical malpractice insurance.
Invoicing and payment schedule	CRO invoices sponsor with net 30 terms. Sponsor may pay pass-through costs in advance. Milestone and time-	In most cases, site does not invoice sponsor. Instead, site monitor determines fees due to site. Sponsor pays

	based payments are common.	according to various schedules, usually much slower than net 30. Activity- and data-based payments are common. "Holdbacks" of 10% or more are common.
Scope of services & change orders	Sponsor pays for additions to contracted activities.	Contract is silent on payment for changes in contracted activities.
Project delay or cancellation	Sponsor covers CROs reasonable costs caused by delay or cancellation.	Contract is silent on payment for delay or cancellation.

Discussion

Study personnel. Key personnel at the CRO may include the project manager, lead CRA, statistician, medical monitor, programmer, report writer, quality assurance manager, and account manager. In addition, the sponsor may have the right to approve site monitors as a group or individually. CROs often want to move personnel among projects. The same is not true for sites and study personnel. Many sites do not have quality assurance managers or account (customer relationship) managers. Sponsors select sites in large part based on the competence and qualifications of the principal investigator, and secondarily on the competence and qualifications of study personnel. Note, however, that sponsors seldom, if ever, ask investigators for professional references.

Standard operating procedures (SOPs). Because sponsors are delegating their responsibilities to CROs, they often want to review the CRO's SOPs. In some cases, especially with large sponsors and small CROs, the sponsor may want the CRO to use the sponsor's SOPs, which may be more stringent than good clinical practice (GCP) standards. Sponsors may verbally ask sites to review SOPs but seldom or never include this requirement in CTAs. There are several possible reasons for this difference: While sponsors usually buy services (activities) from CROs, they buy data (results) from sites. Sponsors may want to keep an arms-length relationship with sites ("learned intermediary doctrine"). Many sites do not have SOPs or do not follow the ones that they do have.

Delegation of authority. Sponsors delegate many responsibilities to CROs that require regulatory compliance. 21 CFR § 312.52 permits such delegation, provided it is documented in writing. While the CRO assumes responsibilities from the sponsor, the site has its own responsibilities.

Intellectual property & publication rights. CROs generally do not write scientific articles about the studies they manage for sponsors, so giving up publication rights is not an issue. CROs operate on a "work for hire" basis, meaning that the sponsor owns their work product, including intellectual property. In contrast, many research sites, especially academic medical centers, absolutely require publication rights and may want ownership rights in data, inventions and biological samples.

Liability insurance. Research sites provide medical treatments to study subjects, so medical malpractice insurance that covers clinical research is essential. CROs do not provide medical treatments, so they do not need medical malpractice insurance. However, they need professional liability (errors and omissions) insurance in case they cause harm to the sponsor by, for example, writing a bad protocol or losing the study database. (These things actually happen.) Research sites may carry non-medical professional liability insurance, but claims against such policies are extremely rare.

Invoicing and payment schedule. CROs, like most service businesses, generally invoice their clients monthly for professional services on "net 30" terms (payment within 30 days). (Of course, sponsors may not pay on time.) If the CRO is disbursing funds to research sites and other vendors, the sponsor often pays these costs in advance so the CRO is not "out-of-pocket." Sites generally rely on the sponsor's study monitors to determine what work is completed and payable. (One exception is pass-through costs such as recruitment advertising fees, which may be paid on invoice or in advance.) Many sponsors pay sites more than 120 days after the work has been completed, and more than 60 days after it has been inspected by a site monitor. Milestone payments for CROs may serve a similar function to payment holdbacks for sites. Given the significant percentage of sites that enroll zero subjects, many sponsors are reluctant to pay for activities, such as study initiation, which do not directly generate evaluable data.

Scope of services & change orders. With a well-written protocol and study manual, changes to a site's scope of work ("change orders") are uncommon. If the sponsor amends the protocol, sites can usually obtain payment for extra work, such as new procedures and re-consenting subjects. However, if the protocol is unclear, the sponsor adds non-protocol requirements (e.g., meetings or reports), or unexpected activities occur (e.g., serious adverse events), additional payment is often difficult to obtain. In contrast, additional work is frequently required for CROs, e.g., when site or subject enrollment runs behind schedule. CROs may generate 25% or more of their revenue from change orders. Sponsors often refuse to pay sites for unanticipated work, e.g., work that is related to serious adverse events and lost-to-follow-up subjects, as "just a cost of doing business." The line between anticipated overhead costs and unanticipated extra charges is much clearer for CROs than for sites.

Project delay or cancellation. Sponsors often compensate CROs if the sponsor delays or cancels the study, because the CRO loses the opportunity to bill its personnel and amortize its up-front costs. In most cases, sponsors do not offer the same compensation to sites, but sites may be able to negotiate for it during the original negotiation or after the fact.

Conclusion

There are valid differences between CROs and research sites, and therefore between clinical trial agreements and service agreements. However, some of the differences are difficult to justify except by historical custom and market power. The global expansion of clinical research makes it difficult for most research sites and CROs to negotiate better contract terms with sponsors, but the comparison may inform discussions of meaningful, long-term partnerships.

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