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Ancillary Service Provider Agreements in Clinical Research

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Just as clinical research protocols have been growing more complex,[1,2] so have the structures and relationships of the organizations that conduct them. Study sponsors often engage numerous contract research organizations (CROs) and other service providers in a study. While the concept of the "principal investigator" survives in the world of regulatory compliance,[3] that person almost always operates, not as an individual, but as the owner or employee of a clinic, hospital, health system, or other clinical research site, which draw on the resources of other organizations (referred to in the regulations as "institutions" or "facilities").[4]

The contractual centerpiece of a clinical study is the clinical trial agreement (CTA) between the study sponsor (or CRO) and the clinical research site. The multitude of other relationships should also be governed by contracts that set forth their terms and conditions. Most study sponsor use contracts to formalize their business relationships with service providers, but it is still common on the site side to find professional colleagues working under handshakes and other informal arrangements.

Ancillary Service Providers

Ancillary service providers (ASPs) support clinical studies by contributing clinical or other services to the principal investigator and study team that they cannot perform themselves. Common types of ASPs include cardiology, laboratory, ophthalmology, radiology and interventional radiology/surgery centers. Other types of ASPs also support clinical studies. For example, a neurologist might monitor and diagnose disorders of the nervous system during the course of a clinical study. (See Figures 1 and 2.)

At academic medical centers (AMCs), clinical departments often support the conduct of each other's clinical studies, with mechanisms in place to ensure that procedures are performed to professional standards and payments are issued to the correct departmental account. Less frequently, an AMC might need to secure services externally. In the community setting, services are more commonly provided by separate legal entities (e.g., medical corporations, hospitals or non-profits that have different tax identification numbers).

Sites can contract with ASPs on a study-by-study basis, but ongoing relationships with reliable ASPs enables quick study start-up and smooth study conduct.

A professional service agreement (PSA) provides the framework for a site/ASP relationship.[5] A PSA is a written agreement between two parties (e.g., companies, institutions or organizations) in which one party (the ASP) provides professional medical services to another party (the research site). PSAs are also sometimes called clinical service agreements (CSAs).

Sites can delegate business development, contracting, billing and collections, and other research support services to site networks, site management organizations (SMOs), and various consultants. These relationships are not governed by PSAs because they do not involve the provision of clinical services.

Academic Medical Centers

AMCs often consist of multiple medical corporations and other legal entities operating under a common name or similar names. Just because a medical or support service is located on the campus of an AMC does not mean it is a legal part of the AMC (i.e., that it shares the same tax ID number). Related entities that operate under separate tax IDs should establish PSAs (or their equivalent) among themselves to address how fair market pricing is determined, how testing is ordered and performed, how confidentiality is maintained, etc. Documenting expectations before work begins on a study can avoid problems during the study. Even when two departments are part of the same legal entity, they should still document their business arrangements. For example, a radiologist supporting a research program would routinely be expected to perform RECIST measurements. RECIST measurements are not typically performed in the clinical setting.

Community Practices

PSAs should document the relationship between the community practice conducting the clinical study and other entities providing clinical services. In these cases, the PSA forces the parties to consider and structure their relationship. What services will be provided? The answer can be found in the PSA. What will the site pay the ASP for work performed? The answer can be found in the PSA. Who is responsible if an ASP injures a patient? The answer can be found in the PSA. How are services ordered? The answer and requisition form(s) can be found in the PSA. Does either party indemnify the other party if a study participant experiences a serious adverse event? The answer can be found in the PSA.

Figure 1. Example of an ASP Arrangement

A community-based medical oncologist agrees to conduct a clinical study of a new investigational product designed to disrupt the blood supply of growing tumors. The study sponsor and FDA require patients participating in the study to have an echocardiogram performed at screening to establish baseline cardiac health. Echocardiograms are then conducted periodically during the course of the study to ensure cardiac function is not adversely affected (or ensure complications are identified quickly so investigational therapy can be stopped and treatment provided). Because the principal investigator is a medical oncologist (not a cardiologist) and does not provide echocardiogram services as a part of her practice of medicine, the principal investigator must generate an order for a cardiologist to perform the test, the patient must travel to the cardiologist's office for the echocardiogram, the cardiologist must provide test results to the principal investigator in a timely fashion, the study team must place the echocardiogram results into the study record, the study team must collect payment from the study sponsor for the service, and the principal investigator must pay the cardiologist for the service provided.

Key Points for PSAs

A PSA provides structure to the relationship between a site and an ASP, and a record of how the parties intended to work together. PSAs should be consistent with the CTA, confidential disclosure agreement (CDA), and any other pertinent contracts. Most PSAs should address the following areas:

- **Services to be Provided.** Describe the services to be provided in enough detail so the parties are clear on the nature of the services, their quality, and their timeliness. Specify when the ASP may provide clinical services to patients, in addition to those requested for research purposes.

- **Pricing.** A fee schedule, often in an appendix, should list the fees for all research services, so the site can negotiate the study budget.[6,7]
- **Payment Terms.** Study sponsors generally do not pay for study visits on the date services are provided. Often, sponsors "hold back" part of the money owed to sites until the site's work is complete, data is recorded in the EDC system, and the database is locked. Such holdbacks might not apply to "pass through" fees. PSAs should detail when the ASP can expect payment for services provided and, if the site plans to withhold any fees from the ASP, describe the terms.
- **Compliance with Laws.** Draft the PSA so it complies with the Stark Law, Anti-Kickback Statute, False Claims Act, HIPAA and any applicable state laws related to referrals, reimbursements, physician employment, patient privacy, and other applicable laws and regulations.[8-12]

Figure 2. Examples of ASPs

Cardiology service providers might perform electrocardiagrams (ECGs), provide ECG "over-read" services (i.e., provide professional interpretation of ECG tracings collected on sponsor's equipment), or perform echocardiograms (ECHOs). Cardiology services are often provided to collect data and medically monitor study volunteers receiving investigational products that could adversely affect the function of the heart.

Laboratory service providers often fill gaps in the ability of sites to provide laboratory services in support of clinical studies. Community-based practices, hospitals and AMCs might all be able to provide laboratory services (e.g., near testing). When requirements of clinical studies go beyond those services routinely provided by the site, samples must sent to an ancillary laboratory provider for testing (e.g., a hospital-based pathology department or commercial laboratory). Laboratory data might be collected to advance our understanding of how an investigational product is metabolized or to monitor patient safety.

Ophthalmology service providers might be asked to perform visual field exams or inspections of a patient's retinas to check for changes that occur during the course of a clinical study. Services are often provided to monitor for visual changes and to ensure the safety of study volunteers receiving investigational products that could adversely affect vision.

Radiology service providers might perform computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), or multigated acquisition (MUGA) scanning in support of clinical studies. In cancer studies, it is common to find radiology-based study endpoints (e.g., progression, partial response, complete response). As a result, clinical investigators frequently communicate with radiology service providers to discuss key findings, ensure key disease features are tracked correctly, and request clarifications to ambiguous reports. Radiology services also help to ensure patient safety by monitoring the impact of investigational products on patients.

Interventional Radiologists and Surgeons utilize minimally-invasive, image-guided procedures to diagnose and treat diseases in nearly every organ system. Radiologists and surgeons might provide services associated with the collection of fresh tissue and other samples under image (CT or ultrasound) guidance. These samples are increasingly important in the era of precision medicine. Freshly collected specimens might be fresh-frozen or formalin-fixed for later analysis by a study sponsor or its designee.

- **Confidentiality.** In addition to site and ASP confidential information, the ASP might need access to the study sponsor's confidential information. The PSA should, therefore, bind the ASP to confidentiality provisions that are at least as restrictive as those contained in the CTA, and the CTA should permit the site to share the sponsor's information with the ASP.
- **Access to Source Data.** PSAs should address access to source data. The study sponsor might need the original or a copy of certain types of data, such as electrocardiogram (ECG) tracings or CT scans. Or, the ASP might only need to provide data or a report to the site for inclusion in its study records. The sponsor might also need access to the ASP's data and records for monitoring or auditing purposes.
- **Sharing Information with the ASP.** If the ASP needs to understand the context of its specialized services, it might need a copy of the protocol, investigator's brochure, safety reports, and other study documents.
- **Intellectual Property Assignment**. The PSA should be consistent with the CTA on intellectual property rights, e.g., the PSA should specify the ownership of any inventions made by the ASP using the sponsor's intellectual property.
- **Responsibility for Research-Related Injury.** Any ASP that interacts with study participants should agree to provide its services in accordance with professional standards and accept responsibility for any injury it causes to a participant (but not for an injury caused by the investigational article). The PSA should describe the process and documentation for dealing with an injury thought to be related to study.
- **Periodic Review of the Relationship.** Things change, so the parties should review the PSA periodically, e.g., annually.

Central ASPs

Study sponsors regularly contract with laboratories and other service providers to provide central services in support of a clinical study. Contracting with a central service can offer streamlined contracting, a single point of contact, consistent quality, and volume discounts. Service providers compete vigorously for these contracts.

In contrast, each site in a study typically contracts with its own ASPs. In some cases, a better approach would be for multiple sites to contract with the single best cardiology ASP in a city, or for multiple sites nationwide to contract with the single best central lab ASP, without involving the study sponsor.

This consolidation of services could give sites the same benefits that study sponsors gain from their central service providers. It could also make research more accessible to patients by providing study participants the ability to access services when they are traveling.

Example Agreements

An example Professional Service Agreement (PSA) and an example Business Associate Agreement are available at

https://www.sitecouncil.org/attachments/1802a_PSA_Template.docx and
https://www.sitecouncil.org/attachments/1802a_Business_Associate_Agreement_Template.docx
Neither these documents nor this article should be considered legal advice.

Conclusion

Clinical study sites often require ancillary services from other legal entities. Clinical trial agreements (CTAs) do not cover the rights and obligations of the parties in these relationships. Sites should, therefore, utilize PSAs to document their legal and operational arrangements with their ASPs. These PSAs should detail how services are provided to speed study startup, collect high-quality data, and help ensure the protection of human subjects who participate in clinical trials.

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