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When We Study Abroad

International clinical research can stumble over contractors and local conditions.

Food and Drug Law | A Practice Focus

By Leah R. Kendall

As pharmaceutical and medical device companies are increasingly recognizing, international clinical studies offer important advantages over studies undertaken in the United States, but they also present numerous complex legal challenges that have to be addressed.

In terms of advantages, studies conducted abroad can be a source of patients not taking other drugs that might affect the study, which can be rare in the United States, and they can provide a large number of patients. Global studies can also help foster sponsors' relationships with different clinical sites, investigators, and thought leaders. Moreover, conducting research abroad allows companies to lay the groundwork for regulatory approvals in markets outside the United States and to expand existing market share.

To ensure that they reap the potential benefits of international studies, however, sponsors should be prepared to address challenges that may arise while structuring and managing international clinical studies. Here, I highlight key challenges and steps to meet them.

Potential Challenges

Sponsors should be prepared to face several health care regulatory challenges with clinical studies conducted partially or entirely outside the United States:

• *Legal agreements:* One potential challenge is the development of an efficient contracting process that protects the sponsor and applies consistently throughout the globe.

If a sponsor has 50 or 100 study sites across multiple countries—some of which have their own specialized requirements—how does the sponsor minimize risk exposure? Further, if the sponsor is a global company, how can it work efficiently with its local affiliates during the contracting process while also ensuring that legal agreements sufficiently protect the entire company?

For clinical site and investigator contracts, each country may have its own legal requirements that affect the clinical study agreement. For example, certain countries have legal requirements for insurance or for indemnification, while other countries have requirements on the types of agreements that a sponsor might need with a clinical site or investigator.

If the sponsor plans to use study data to support a marketing submission in the United States, it needs to know what legal controls are required to ensure that the U.S. Food and Drug Administration will accept the data.

Additionally, sponsors often use contract research organizations to help conduct, monitor, and manage research. This CRO expertise and manpower potentially can be invaluable—especially in global studies where the CRO may have a presence and experience in developing countries that the sponsor does not. That said, companies sometimes struggle with using and managing CROs effectively and ensuring their performance. For example, in an international clinical trial, a sponsor may use multiple CROs or multiple affiliates of a CRO. Sponsors can find it challenging to monitor and measure the various aspects of these CROs' performances, particularly on a global scale.

Sponsors may also encounter a variety of challenges involving interactions with sites. Common issues that sponsors encounter include:

• *Effective monitoring and site access:* Sponsors may be concerned about whether they will have access to well-qualified individuals to monitor the study abroad—through either a CRO or the sponsor's internal resources. Moreover, even if a sponsor has excellent monitors, the sponsor can still encounter basic practical challenges in transportation, adequate site facilities, and language barriers that can impede monitoring, thereby leading to serious compliance problems.

• *Payment issues:* Budgetary issues can involve questions about payments to clinical sites, investigators, and study participants; recruitment incentive payments; and costs surrounding research-related activities, routine care, and injuries to study subjects that may arise during or after the study. These can be extraordinarily complex issues.

Careful and diligent planning is critical to meeting challenges like these—and for being prepared to surmount the unexpected but inevitable problems that will arise during a study. Below are some suggestions for sponsors.

Universal Considerations

Although each sponsor's situation is unique, some universal considerations are useful for sponsors to consider as they plan for international studies.

Sponsors should think carefully about the oversight and management of their trials. Internally, who is going to champion the process? Who is going to be responsible for keeping track of all the moving pieces and ensuring that it all comes together? Substantive knowledge is important here, but equally important is having a detail-oriented and responsive person or team to manage the clinical trials process. Excellent project management skills obviously are needed.

Sponsors should also consider who will handle the contracting process internally—and how they will do it. For example, will internal legal counsel manage it at a high level, or will they draft and negotiate contracts on their own? If outside counsel is involved, what responsibilities will they assume? There are a wide range of possibilities for outside counsel—from negotiating directly with sites, to drafting contract templates, to providing discrete areas of expertise.

The actual substance of the agreements is another issue. Thinking about acceptable provisions within clinical trial agreements before the agreements are negotiated will often save the sponsor time and money in the long run. Among the many provisions to consider are indemnification, payment for study subject injuries, insurance, publication, intellectual property, monitoring, confidentiality, governing law, and venue. Further, assuming that the sponsor's goal is FDA approval, the sponsor should think about FDA data acceptance issues and the legal requirements with which a study site must comply.

A sponsor should also consider the provisions it will require in its contracts with CROs. In this regard, a sponsor is often concerned about how to ensure a CRO performs according to the sponsor's expectations. One way to accomplish this is to contractually require the CRO to meet certain performance metrics. Sometimes these metrics are tied to financial penalties if the CRO fails to meet them.

Drafting a clear, comprehensive, and well-considered statement of work is also critical to obtaining a high level of performance. For example, a statement of work should balance the authority and responsibility given to a CRO with close and careful supervision by the sponsor. A sponsor must always remember that it, not the CRO, is ultimately responsible for the data and marketing submission to the FDA or other governmental entity.

Sponsors should also conduct due diligence when engaging external resources to help them with tasks such as contracting or monitoring. For example, a potential contractor should be able to back up its marketing statements with references and examples of representative expertise. Sponsors also should not underestimate the power of networking—consider asking contacts at other companies for recommendations on resources.

Local Requirements

In addition to due diligence on external contractors, performing due diligence on both potential sites and investigators can also be important for a sponsor's success.

In terms of legal requirements, a critical consideration is whether the clinical sites and investigators comply with good clinical practices, including the International Conference on Harmonization standards and guidelines.

Assuming that the sites and investigators are in compliance with good clinical practices, a sponsor should further consider a country's local requirements and legal infrastructure. One basic question is whether the country has a reputable and solid legal infrastructure where a dispute can be resolved in an expeditious and fair manner. Other legal considerations include insurance requirements, intellectual property rights and patent protection, and jurisdictional issues related to the country's courts and legal system, such as whether the local courts can haul the sponsor before them.

Another important question is whether the standard of medical care in the country is compatible with the study design. For example, might the experimental elements of the study push the envelope on the country's standard of care, such that negligence or malpractice issues are implicated?

Companies should also consider any potential cultural or ethical barriers. For example, in developing countries, the trial participants and even the study sites may believe that the sponsor's purpose is to provide medical care, and, in a placebo-controlled trial, may not fully appreciate that participants may not receive the experimental or medicinal product.

Sponsors will also want to take into account where they or their CROs already have strong relationships with clinical sites and investigators. Prior success is often one of the best predictors of future success.

A final suggestion is that sponsors should consider a plan B for unavoidable setbacks that arise as a study gets under way. What happens, for example, if one or more sites just simply do not move forward with their legal agreements and other required regulatory documents—what is the plan if certain sites just don't come to fruition? Or what if there are major compliance—even data integrity—issues?

Undertaking a clinical study with international sites can be daunting. But by being proactive, diligent, and thoughtful during the initial planning, sponsors can help to ensure their study is a success.

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