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Global Issues – Law Firms

Getting The Most From Overseas Clinical Studies

The Editor interviews ***Leah R. Kendall****, Associate in the Health Care and Life Sciences Practice group at Epstein Becker & Green, P.C.*

Editor: Please tell us about your practice at EBG.

Kendall: Within my practice group, I focus primarily on advising clients on the requirements of the U.S. Food & Drug Administration ("FDA") and the Centers for Medicare & Medicaid Services ("CMS"). Within those two broad areas, I focus a substantial part of my practice on the regulatory and reimbursement issues associated with clinical trials. On a daily basis, I help clients navigate the various legal requirements and the practical and ethical challenges pertaining to clinical research. This necessarily includes international clinical trials – an area in which we at EBG have increasingly focused.

Editor: What are some of the primary reasons that U.S.-based companies venture into international clinical trials?

Kendall: There are several driving forces. One of the principal reasons is competition for both patients and qualified investigators – there are so many clinical trials being conducted in the United States for so many different kinds of drugs and medical devices that competition for patients and investigators may drive the research overseas. This is especially true in the case of drug therapies that require a drug-naïve population, because a sponsor may not be able to find an adequate number of drug-naïve patients in the United States. On a related note, as data requirements become more rigorous, sponsors may need to have larger numbers of patient populations.

Leah R. Kendall

Further, in today's global marketplace, companies require more than just FDA regulatory approval, so conducting research outside the U.S. may allow a U.S.-based sponsor to lay the groundwork for marketing approvals in other countries and markets.

Finally, sometimes companies expect to save money by conducting research overseas, although this is not always the case.

Editor: Are all outside the U.S. ("OUS") countries created alike? What do companies need to consider when deciding whether to venture into a particular country?

Kendall: I recommend a few overarching considerations, although every sponsor's situation is unique. One important consideration is whether the OUS clinical sites and investigators are compliant with Good Clinical Practices, also known as GCPs, including International Conference on Harmonization ("ICH") standards and guidelines. Assuming that the relevant sites and investigators are in compliance with GCPs, it is important to consider a country's local requirements and legal infrastructure. This may include, for example, insurance requirements, intellectual property rights and patent protection, and jurisdiction issues related to the country's courts and legal system. For example, one basic question is whether the country has a reputable and solid infrastructure where a dispute can be resolved in an expeditious and fair manner.

Another major consideration is the standard of medical care in the country and whether this standard is compatible with the study design. Companies should also factor in any potential cultural or ethical barriers. For example, in a developing countries, the trial participants and even the study sites may believe that the sponsor is providing medical care and may not fully appreciate the experimental nature of the trial.

Editor: Are the monitors of clinical trials conducted outside the U.S. of the same caliber as those you might find in the U.S.?

Kendall: That is an excellent example of another issue sponsors should consider in evaluating international research – whether the sponsor will have access to well qualified monitors. Even if a sponsor has the best monitors, though, the sponsor can still run into very basic practical challenges in terms of transportation, adequate site facilities, and language barriers and translation that can not only impede monitoring the study, but, relatedly, can also

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threaten data integrity. A company really needs to think about all of these practical issues in the early planning stages.

Editor: In terms of outsourcing, how does a company find resources to help them with labor-intensive tasks like the contracting process, or monitoring?

Kendall: Sponsors should do their due diligence on outsourcing resources, such as contract research organizations ("CROs") by, for example, investigating their relevant expertise and asking for client references. A potential contractor should be able to back up its marketing statements with references and examples of representative expertise. Also, don't underestimate the power of networking – consider asking your friends at other companies for recommendations on resources.

Editor: What skill sets are required for those persons who oversee the contracting process?

Kendall: In my experience, a project management skill set is needed to keep sight of the big picture but also of all the moving pieces – who is doing what, and when it needs to be done. This requires an incredibly detail-oriented and responsive person or team of people.

Editor: What are some of the major challenges that you see companies facing in the area of international clinical trials?

Kendall: As we discussed before, one of the driving forces behind overseas clinical trials is the need to recruit a large patient population pool. But in practice, many companies struggle with recruiting their target patient population due to the localized customs and cultures that affect the recruitment process.

Another major challenge is developing an efficient contracting process that protects the sponsor and is consistent around the globe. For example, if you have 50 or 100 study sites scattered around the world, how do you protect yourself from risk exposure in all of those countries? Further, if you are a global company, how do you work with your local affiliates to leverage your internal resources, while also making sure that your contracts contain the necessary provisions.

I also see sponsors struggle with using and managing CROs effectively. Many sponsors rely on CROs to monitor the research and conduct other functions. In an international clinical trial, sponsors may deal with multiple CROs or multiple affiliates of a CRO. It can be challenging for a sponsor to monitor and measure the various aspects of a CRO's performance.

Editor: To follow up on those points, what are some of the biggest stumbling blocks that companies face when drafting and negotiating contracts relating to international clinical trials, including contracts with CROs?

Kendall: In terms of site and investigator contracts, when a company is conducting research in multiple countries, each country may have its own legal requirements that affect the clinical trial agreement. For example, some countries have legal requirements for insurance or for indemnification, unlike the U.S. Other countries have requirements on the number of agreements you might need. Additionally, if the sponsor plans to use the data to support a submission to the FDA, it needs to know what controls to put in place in order to ensure that the FDA will accept the data.

In terms of contracts with CROs, companies often struggle with how to contractually ensure a CRO's performance. One way companies can do this is contractually to require the CRO to meet certain performance metrics. Sometimes these metrics are tied to financial penalties if the CRO fails to meet them.

Editor: What are the major areas of risk exposure that you see with respect to international clinical trials?

Kendall: Planning is so important. If a company does not plan well by doing things like conducting careful due diligence on its sites, investigators, and CROs and building in realistic expectations for timeframes, the benefits that could flow from clinical studies outside the U.S. can easily be lost. I've also seen problems crop up when sponsors give too much authority and responsibility to a CRO without providing close and careful supervision. If trials are not managed well, then major risk areas can arise, such as data integrity issues. And at the end of the day it is the sponsor's data and marketing submission, not that of the CRO.

Companies should also consider one of the worst case scenarios – in the event of litigation, the governing venue will probably be in a foreign country. Is the company prepared to take on the risk and expense of litigating in the foreign country? For a global company, this might be acceptable, but for smaller companies, this kind of litigation can be a tremendous undertaking.

Editor: I would think that there would be allegations from time to time that research subjects in the Third World countries are being taken advantage of.

Kendall: You're right – currently, there is litigation and controversy surrounding this topic. Sponsors need to think ahead about how the research and related fact patterns might appear to the public or even in front of a jury. Good planning helps to mitigate this kind of exposure as well as to preserve the integrity of the data.

Editor: How should a company plan for OUS clinical trials?

Kendall: Assuming that the company's goal is FDA approval, it should think about FDA data acceptance issues – anything from study size and patient population to the legal requirements with which a site must comply.

They should also think about planning for the oversight and management of their trials. Internally, who is going to champion this process? Who is going to be responsible for keeping track of all the moving pieces and making sure that it all comes together?

On a related note, the contracting process is itself a challenge. Who in the company is going to undertake it? Are there internal legal counsel who are capable of taking on this task? Does the company have the internal capacity and expertise to put in place airtight contracts with CROs, building in quality metrics and payment milestones that incorporate controls so that the CRO meets the sponsor's expectations?

Finally, what about Plan B for both the big and small issues? Recently, for instance, a client had foreign sites that just would not move forward with their legal agreements and other required regulatory documents. What is the sponsor's plan if certain sites just don't come to fruition? Or what if there are major compliance issues?

In short, undertaking a clinical study with international sites can be a daunting task. Sponsors should be aware of the numerous issues that go into the initial planning process, as well as seeing the study all the way through the end of the study and beyond.