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Challenges of Foreign Clinical Trials

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Clinical trials present unique risk management challenges — and when they are conducted overseas, the demands on risk managers become more complex.

Managing the Complex Challenges of a Global Insurance Program: Foreign Clinical Trials Case Study

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Operating within the global market offers an unprecedented growth opportunity for U.S.-based companies and multinational corporations. It also creates the potential for non-traditional exposures and governance issues. As a result, risk managers need innovative insurance products and risk management solutions that will address clients' global operations and specialized insurance coverages that protect their company, employees, properties, and production facilities around the globe. The evolving international marketplace offers unique opportunities for companies positioned to operate in this growth-rich, but challenging, environment.

Now, more than ever, it is critical to know how the following dynamics affect international risk management operations and decisions:

- risk management information and resources distributed across continents;
- multiple cultures competing within a global organizational culture and governance structure;
- urban as well as remote overseas operations; and
- escalating rate of change in foreign legal, tax, and insurance regulation schemes.

The critical role of global networks and the introduction of new risk transfer solutions in the marketplace are on the minds of brokers and insurers as they assist risk managers with these issues.

International Clinical Trials: A Case Study[1]

For a variety of reasons, life sciences companies now conduct business all over the world, and their dramatic global growth presents unique insurance and risk management challenges. One of the largest is overseas clinical trials.

More and more U.S.-based life sciences companies are conducting clinical trials overseas to bring new drugs and medical solutions to the market. These trials present unique risks that must be managed. For example, the patient-volunteer may be at risk in several ways, through injury or through developing or aggravating an existing medical condition. In addition, the medical institution or medical providers may be liable if services rendered fall below the required standard of care. The sponsor may also be liable if the experimental medical product causes injury. Insurance is, of course, one way to deal with these risks.

But, as the example of overseas clinical trials indicates, myriad challenges await the risk manager. For instance, to begin a clinical trial, a life sciences company must have local insurance policies (with the required coverages) in many different countries around the world and provide the clinical trial insurance certificate in the local language in a timely manner. In addition, Ethics Committees in these countries may not permit the trial to proceed without an appropriate certificate. If a company is launching a multi-site clinical trial in 25 countries, the required administration and execution can be daunting.

Clinical Trials: The Four Phases

Clinical trials are generally carried out in four phases. Each phase carries unique risks.

- Phase I studies generally consist of 20 to 40 healthy test subjects and they focus on safety.
- Phase II studies typically consist of 40 to 100 test subjects who are part of the sample patient population for the specific product being studied. These studies still examine safety, but they also measure efficacy.
- Phase III studies consist of a statistically significant number of test subjects within the patient population — generally more than 100, but could be thousands — and they measure efficacy as well as safety.
- Phase IV studies are research conducted after the product is marketed to continue to evaluate side effects and long-term risks.

Clinical trial phases carry inherent risks, but their severity depends on the nature of the treatment and the health of the test subjects.

The first three phases can take more than eight years, including preclinical work, and, as a result, the time it takes to bring a new drug to market can exceed ten or even fifteen years.

All clinical trial phases carry inherent risks, but their severity depends on both the nature of the treatment and the health of the test subjects. Risks in Phase I include serious adverse events that have not been seen before (such as allergic reactions, major organ failure, or death), especially in studies that include a novel medicine or a new class of drug. Risks in Phase II differ in that the subjects are now patients with the medical condition that the study drug is designed to treat. Although the same risks present in Phase I studies remain in Phase II, another key risk factor is this: In many studies, the test subjects must stop their existing treatments before they receive the study drug. Placebo-controlled studies present additional risks in that the patients who may benefit from the study drug may be getting a placebo. Risks in Phase III are similar to Phase II studies, and the long timeframe for clinical trials can also present issues, especially in oncology studies dealing with end-stage cancer. The test subjects have shortened life expectancies at this point and may decide to try other treatments that could interact poorly with the study drug. This would also potentially invalidate the study results for that test subject.

Clinical Trials: The Players

Every clinical trial involves a number of different players, but the test subjects are the most vital to the process.

Numerous risk management policies and procedures focus on the volunteers who participate in these studies.

Clinical Trials: Test Subjects

In order to bring a new pharmaceutical, biological, or medical device to market, it must first be tested on people. Experimentation on living human beings brings the risks noted previously, but clinical trials are traditionally accepted as the "gold standard" — the best, and sometimes the only, means for medical researchers to explore new treatments and make new discoveries that may save countless lives.

Numerous risk management policies and procedures focus on the volunteers who participate in these studies for a variety of reasons, including altruism as well as the hope that a new drug will alleviate symptoms or cure their disease, which has so far been without a cure. Phase One volunteers who are healthy get paid for their services. But payment is normally not offered to volunteers who are suffering from the medical condition being studied, although they will generally be compensated for their out-of-pocket expenses.

Clinical Trials: The Sponsor

Under U.S. law, the sponsor or the company or person responsible for initiating the clinical trial has important responsibilities, such as interacting with the Food and Drug Administration (FDA), filing the appropriate paperwork, selecting qualified investigators, and ensuring that the investigation is conducted in accordance with the established protocol. The sponsor must also keep the investigators abreast of any new findings or adverse events and maintain adequate records.[2]

The Food and Drug Administration Amendments Act of 2007 (FDAAA) reauthorizes and amends several drug and medical device provisions and provides the FDA with increased funding and safety oversight duties. It also imposes on the sponsor newly enhanced responsibilities. For example, Title VIII of FDAAA expands the clinical trial registry database (www.clinicaltrials.gov), creates a new clinical trial results database (www.clinicalstudyresults.org), and makes submissions to the two databases mandatory.

Clinical Trials: Contract Research Organization (CRO)

A sponsor may transfer all or some of its obligations to a CRO by written contract, since the sponsor probably does not have, in-house, all of the expertise needed to run a clinical trial. CROs are professional organizations set up to administer all or part of the clinical trial process. Many sponsors rely on CROs to handle such duties as recruiting test subjects, sourcing investigators and sites, negotiating contracts, shipping the study drug, and communicating with the FDA or corresponding foreign agencies. In most cases, it is very difficult to conduct an international or multi-site clinical trial without the help of a CRO, as the expertise needed expands exponentially with the breadth of the study. Many large CROs have offices in countries around the world and provide "boots on the ground" for sponsors that may not have a multinational presence.

Clinical Trials: The Investigator

The investigator (usually a doctor) is responsible for administering the study protocol and is required to secure the legally effective informed consent document from the test subjects.[3] The investigator must also ensure that the sponsor and Institutional Review Board (IRB) are both fully compliant with the established regulations in the specific country or countries where the study is located.[4]

Clinical Trials: The Site

The institution where the study is being conducted is responsible for overseeing the actions of staff during a trial. Hospitals often act as sites, and large research institutions (such as Johns Hopkins, M.D. Anderson, and Duke) may have hundreds of ongoing clinical trials at any given time. Site Management Organizations are sites specifically designed to cater to clinical trials.

Clinical Trials: The Institutional Review Board

The Institutional Review Board's (also known as

Ethics Committees [EC] outside the United States) primary job is to protect the welfare of the test subjects. Many institutions have internal IRBs, and there are independent or commercial IRBs that can be hired, as well. In the United States, IRB approval is required for all studies involving human subjects that are funded or regulated by any federal department or agency.[5] In the European Union, Ethics Committees are required under the Clinical Trials Directive.[6] In most countries around the world, a clinical trial regulated or required by an agency cannot go forward without the approval of an EC.

IRBs and ECs are charged with assuring that appropriate steps are taken to protect the rights and welfare of people participating as subjects in a research study. They review research protocols, informed consent documents, investigator brochures, and other materials to assess the ethics of the study and the safety measures undertaken to protect participants once they are enrolled in the study. A study cannot go forward without IRB or EC signoff, which is obtained when the IRB is satisfied that there is an adequate informed consent form, that selection of subjects presents a fair balance of risk and benefits to the subjects, and that the potential benefits to society outweigh the risks to subjects. For multi-site studies, commercial IRBs are often utilized.

In countries around the world that require locally admitted insurance policies, ECs typically review the certificate of insurance to determine whether the insurance is in place and is appropriate for the study. ECs will review limits, terms and conditions, additional insureds, and other required information.

Clinical Trials: Informed Consent

Ensuring the safety of the test subjects throughout the clinical trial process is important to managing risk successfully. This may be difficult for some studies, as some are inherently dangerous. Others may not be as risky, but all drugs have side effects of some sort. Thus, making sure that the test subjects understand the risks they are taking through participating in the study is key. A required consent form given to test subjects must describe the study, provide information about the study drug or device, discuss the procedures involved, give alternatives to participating in the study, and explain the risks of participating as well as what to do if an injury results. But informed consent is more than getting a test subject to sign the consent form. It is a process of exchanging information that will result in the truly informed consent of all test subjects.

When a clinical trial includes subjects from different cultures and education levels, it can be challenging to make sure that each subject understands — so that his or her "consent" is truly "informed." Some subjects may not be able to read the form or understand the concepts. The content of the form is dictated by certain laws and regulations, but how the information is presented is up to the clinical investigator. After all, it is the clinical investigator's duty to obtain the legally effective informed consent of the test subject.

Making sure that the test subjects understand the risks they are taking through participating in the study is key.

The most effective informed consent processes include reviewing the consent document with the subject and allowing the subject ample time to ask questions. The subject is given the consent form to take home in order to review it thoroughly with family, loved ones, or religious advisors if so desired. The subject can then return with any questions and for another review of the document. Finally, the subject is asked to initial each page and sign and date the consent form in front of a witness and the researcher (each of whom also signs and dates the document).

Although not required by law, most effective informed consent forms include language to the effect that not all risks of participation are known and some likelihood of injury exists despite all the precautions taken. Known possible adverse effects are spelled out. In addition to fully informing the subject about the risks, the process has the added benefit of helping to avoid "failure to warn" lawsuits should adverse effects occur.

Clinical Trials: Regulation

Clinical trials conducted under the auspices of the U.S. FDA must adhere to the Federal Food, Drug and Cosmetic Act (FDCA), the FDA Modernization Act

of 1997 (FDAMA), and the FDAAA. Organizations conducting trials must adhere to these regulations for trials conducted both inside and outside the United States, (provided the sponsor is seeking U.S. FDA approval, in the latter case.) Depending on the country where the clinical trial is taking place, organizations may also be regulated by corresponding foreign regulatory bodies and laws. Many countries require admitted insurance policies with specific terms, conditions, and limits requirements. In addition, local ethics committees have a large role to play when it comes to informed consent language and the type of insurance required. Specific insurance certificates may be needed as well.

Keeping track of insurance requirements around the world is a full-time job.

Clinical Trials: Decisions Regarding Who, Where, and When

There are many smaller decisions that play a part in deciding which country and which organization will conduct a clinical trial. Access to available trial subjects is typically the driving force behind these choices, as well as the quality of the doctors, the testing sites, and the laboratories. The ease of the regulatory environment and the logistics, including costs, are equally important.

The legal department of an organization is typically responsible for negotiating the clinical trial agreement (CTA) with the site and the investigator. The CRO usually recruits test subjects and can be used to deal with local agencies. Many more individuals within the sponsor organization will need to work hard to ensure that the trial can begin on time. The knowledgeable risk manager should request that research and development clinical staff let him or her know, as soon as possible, where and when a trial will take place, since some countries are more difficult to deal with than others. The last thing a risk manager needs is to be blamed for holding up a trial — because the insurance could not be put in place in a timely manner.

Clinical Trials: Insurance Considerations

Keeping track of insurance requirements around the world is a full-time job, and it seems to be the case that just when the regulations in a certain country are fully understood, something will change.

Insurance requirements for clinical trials vary by country. For example, studies in Brazil typically need a local insurance broker, as the premium and fees must be paid locally to the insurer. Other Latin American countries require that the sponsor have a local physical presence in the country, and if not, a local representative will be needed. In Europe, many countries require significant limits, including France, The Netherlands, and Belgium. France also requires a 10-year reporting requirement, and Russia requires a separate per test subject limit. Italy often requires that the sponsor's insurance policy respond to the malpractice of the investigators and sites, while the United Kingdom requires coverage on a "no fault" basis. India, under a banking and finance law, requires payment of the premium before coverage goes into effect. These are only some of the applicable requirements that must be researched, tracked and taken into account.[7] CROs often provide the service of keeping a clinical trial in compliance with international insurance requirements.[8]

Clinical Trials: The Ideal Insurer

Risk managers should work with an insurer that has the unique underwriting expertise necessary to effectively implement complex multination programs such as these. The insurer should also be highly rated and have financial strength and an excellent reputation, as well as have access to a global network. The insurer must be able to provide appropriate products and services to protect insureds across all lines of business, with sufficient underwriting limits as well as needed coverage. The insurer needs to have insight into the emerging exposures stemming from clinical trials in order to help insureds manage those risks proactively.

The ideal insurer will have a long history of serving multinational companies that conduct clinical trials in multiple countries. Additionally, the following attributes of an insurer are desirable in the field of global medical risk insurance and global services:

- breadth of product and geographic reach;
- access to the indigenous resources of a global network;

- ownership of a proprietary database of information that clearly spells out the insurance regulatory requirements for clinical trials in a large number of countries;

- timely, accurate clinical trials, insurance policies, and certificates; and

- ability to deliver as reflected by established standards.

The ideal insurer will operate in a range of countries — from undeveloped and emerging to the fully developed — with a dedicated service organization that specializes in serving multinational clients. The insurer will take a client-focused approach to the delivery of service through its global network dedicated, local multinational managers, claims, and service personnel. The insurer will use hands-on care; internal, domestic, and foreign indigenous expertise; proprietary technology; unique database information; and the application of strict performance standards to execute on behalf of its clients.

Endnotes

1. Since many companies seek to gain United States Food and Drug Administration (FDA) approval, unless otherwise set forth herein, this case study is based upon FDA regulations, standards, and guidelines.
2. 21 CFR 312.
3. 21 CFR 50.20.
4. 21 CFR 56.
5. 45 CFR 46.
6. Directive 2001/20/EC.
7. AXCO Insurance Information Services, 2009, https://www.axco.co.uk.
8. The information contained in this paragraph is based upon the experience of the authors.

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