

# Insuring International Clinical Trials: Navigating the Quirks and Avoiding the Quagmires

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## ABSTRACT

The recent enactment of the European Union (EU) directive on human clinical research illustrates the ever-increasing complexity of multi-site clinical research. The overarching goal of the directive is to raise standards for protecting study volunteers throughout the EU while streamlining regulations to make it easier to conduct multi-center trials in member states. This article discusses the importance of insurance protection against liability in international clinical trials.

## INTRODUCTION

The recent enactment of the European Union (EU) directive on human clinical research illustrates the ever-increasing complexity of multi-site clinical research. The overarching goal of the directive is to raise standards for protecting study volunteers throughout the EU while streamlining regulations to make it easier to conduct multi-center trials in member states. From the perspective of clinical researchers and trial sponsors, anything that eliminates confusion and makes the trial process more efficient should be welcome. But both private industry and academic researchers have noted that even while it creates a uniform framework for conducting high-quality trials, the directive adds new bureaucratic hurdles without eliminating all of the old roadblocks, with some suggesting that it will raise the overall cost of clinical trials by 30 percent.<sup>1</sup>

Critics point to liability insurance for clinical trials as an example of a situation thrown into chaos by the directive, and, in fact, it does create some complications, such as potentially shifting liability from a foreign sponsor to a local, legal representative in the European Union Community.<sup>2</sup> In reality, the insurance and liability issues raised by the directive are emblematic of a far broader problem. When it comes to insurance for clinical trials, requirements vary from one country to another, making the process of securing adequate insurance for a multinational clinical trial frustrating and confusing. Failing to think through insurance issues early in the trial planning process can result in costly delays. Even

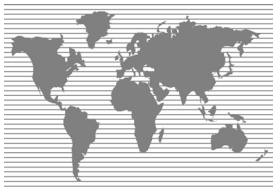
when they have pieced together a patchwork of insurance policies, trial sponsors and research organizations may have gaps in their insurance portfolio that leave them dangerously exposed to significant financial consequences if research subjects are injured as a result of a treatment being tested.

In the same way that a sponsor must take a long-range view to comply with the varying regulatory requirements of each country involved in a trial, they should apply a strategic lens to insurance issues. Not many insurers provide the specialized insurance products and services needed for drugs and devices in the clinical trial stage, and just a subset of those have the capability and willingness to issue insurance in accord with the requirements in the many countries where trials now take place. When considered early on, insurance requirements and availability may bear some influence on how and where a study is conducted. Too often, sponsors of clinical trials don't consider insurance implications until it is time to provide the ethics committee an insurance certificate, and by that time it may be too late. It is important to understand that you will not simply be seeking the addition of a new exposure to an existing policy, but rather acquiring additional policies, each with its own set of limits.

## GROWTH OF GLOBAL TRIALS

Insurance protection against liability in international trials is a growing concern as the trend toward overseas trials accelerates, people become more litigious, and government reforms make insurance an important piece of the

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regulatory process. The number of international clinical trials has increased dramatically with companies looking for ways to shorten the drug development timeline and benefit from potential cost savings. The most appealing locations have a large population of willing, untreated volunteers and able investigators.

By 1999, the FDA tracked the work of 4,458 foreign clinical investigators conducting research under a U.S. Investigational New Drug Application, up from 271 in 1990 and 41 in 1980. The actual number of overseas trials today is difficult to ascertain, but CenterWatch has developed estimates for several countries. Of nearly 40,000 trials worldwide in 2003, CenterWatch estimates that 6,174 were held in the United Kingdom; 2,380 in Australia; 1,300 in Germany; 550 in Japan; 200 in India and 195 in Singapore. The CenterWatch 2004 report includes Phases I through IV studies.

U.S. companies have conducted trials in Europe because of its pool of well-trained investigators, a quicker process for approving study protocols and lower investigative site costs.<sup>3</sup> The possibility also exists that data from a well-controlled European study could pave the way for the FDA to approve drugs and devices in concert with smaller U.S. studies.

As regulatory reform, intellectual property protections and the necessary infrastructure to conduct trials evolves, nations such as India, China and countries in South America and Eastern and Central Europe, are assuming a greater role in clinical research. CenterWatch data show that 20 percent to 30 percent of clinical trials are being conducted in "ascending regions." These regions are also appealing because they offer large, untreated subject populations and low operating costs.<sup>4</sup>

One study has estimated that drug companies can cut the cost of clinical testing by 50 percent to 60 percent by conducting trials in India, but when "hidden costs," such as communication, travel and shipping of drugs, are included, differences in per patient costs may not be so substantial. Nevertheless, sponsors see a more significant benefit in conducting the trial overseas: the ability to bring a drug to market more quickly.<sup>5</sup>

## CHAOS AND CONFUSION

Even when the need for insurance protection is obvious, a trial spanning several countries can seem like an impenetrable knot of obstacles and inefficiencies.

Article 3, section F of the European Directive on Clinical Trials states that "provision has been made for insurance or indemnity to cover the liability of the investigator or sponsor." As of this writing, of the 25 member states of the European Union, 15 require the purchase of insurance to meet this obligation. Of those, 10 countries have compulsory insurance requirements which outline specific terms and conditions of the policy which must be in place, while the remaining 5 do not. The remaining 10 countries are silent on how the financial obligation of the sponsor or investigator must be met.

Even among countries with compulsory insurance laws, the minimum requirements vary widely. Greece, for example, requires a limit of insurance of 200,000 euros per patient, while Germany requires 500,000 euros per patient with maximums ranging from 5 million euros per trial to 15 million euros, depending on the number of participants in a trial. Complicating matters further, sometimes ethics committees involved with the approval of a study have different interpretations of what compulsory insurance laws actually require.

Table 1 lists which European countries fall into each category, but requirements change frequently and additional countries may enact laws requiring clinical trials liability insurance before a trial can proceed.

Table 1		
EU Countries Requiring Compulsory Terms and Conditions		
Austria	Greece	Poland
France	Lithuania	Spain
Finland	Netherlands	Sweden
Germany		
EU Countries Requiring Insurance; No Compulsory Terms and Conditions		
Belgium		Italy
Czech Republic		Slovakia
Hungary		
EU Countries Without Formalized Requirements on How to Meet Financial Obligation		
Cyprus	Latvia	Portugal
Denmark	Luxembourg	Slovenia
Estonia	Malta	United Kingdom
Ireland		
Many countries outside of Europe will fall into similar categories.		

Even in other countries without compulsory insurance laws such as the United States, Canada, Argentina, China and India, liability insurance still may be required for a trial to be approved by an IRB/ethics committee. In Australia, for example, where there is no compulsory insurance law, the Australian Health Ethics Committee expects sponsors to have sufficient insurance to meet potential claims—commonly as much as 10 million Australian dollars.

Once a company decides to purchase insurance, there may be additional restrictions. Some countries require that any policy purchased be written by an insurer licensed to do business under local insurance laws. This is called "admitted" insurance. If a country does not require admitted insurance, clinical trials may be insured under a company's global insurance program.

When a local admitted insurance policy is purchased, a company's master global policy ideally would provide excess insurance over the local admitted insurance policy. Master global policies should also close gaps created by differences

in conditions between the global master policy and the local admitted policy to ensure there is a consistent level of insurance for the insured's operations worldwide.

## LIMIT NEEDS AND AVAILABILITY

Regardless of how much insurance regulatory authorities or ethics committees demand for a trial to proceed, prudent insurance companies restrict the amount they will provide globally on any one investigational drug or device. Just as life sciences companies must manage and mitigate risks, so too must an insurance company. Responsible insurers manage their accumulation of exposure on a single product because of the potential for catastrophic losses across multiple policies if an investigational drug or device causes serious injuries or the deaths of many patients. Without adequate planning, a sponsor could exhaust a large chunk of available insurance in a country whose compulsory insurance law or ethics committees require very high limits, reducing the availability of insurance for a trial on the same product in other countries.

By itself, complying with insurance requirements of different countries and various ethics committees can be frustrating. But sometimes regulators establish insurance requirements that no underwriter would agree to. In other cases, regulations are introduced with the assumption that insurance companies are ready with a product to meet those requirements at that moment. When the demands are out of touch with the realities of the insurance marketplace, a sponsor may have a hard time finding insurance which meets the regulatory and/or ethics committee requirements, effectively stopping a planned trial in its tracks.

The Netherlands and Poland are two examples of countries that eventually reconsidered requirements that were enacted without considering how insurance markets would respond.

In 1999, few insurers were willing to offer human clinical trials liability insurance that satisfied new Dutch requirements because the terms and conditions were too broad, exposing the underwriters to more risk than they were willing to assume. Four years later, in June 2003, the government made positive changes in consultation with the Dutch insurance industry. Still, the changes didn't allow local insurance carriers enough time to interpret the regulations and craft new insurance policies in time for the September 1 effective date.

Poland was also forced to revise the compulsory insurance requirement it issued in April 2004, when insurers were reluctant to provide insurance in accordance with terms they considered vague and ambiguous. Seeing the sudden reduction in insurance capacity for clinical trials, Polish authorities continue to work with local insurers to

revise the regulation to spur the development of viable insurance policies that would protect patients, clinical investigators and trial sponsors.<sup>6</sup>

## EUROPEAN DYNAMICS

In recent years, researchers complained that inefficient bureaucracies and disparate regulations made it difficult to conduct international clinical trials within Europe, denying patients the benefits of state-of-the-art treatments. The European Union directive on good clinical practice in clinical trials was supposed to remedy this by harmonizing regulations. Though the standards may be more uniform, the fact remains that trial sponsors must receive approval from each country in which they plan to conduct a study.

From an insurance perspective a significant aspect of the directive is the provision requiring a legal representative in the European Union if the sponsor of the trial is not located in the EU. The specific language affirming this from Article 19 states:

“... the sponsor or a legal representative of the sponsor must be established in the Community.”

EU countries want to know that they can legally pursue a local representative if they can't get a foreign trial sponsor to fulfill its obligations. More than just a point of contact, the legal representative assumes responsibility for the liability of the sponsor.

Contract research organizations (CROs) with European locations may be asked to serve as the legal representative of their sponsor clients. CROs that decide to act in this capacity must take prudent steps to ensure that they are able to:

- Contractually transfer liability for activities over which they have limited control,
- Meet the obligations of a legal representative, and
- Ensure that sponsors have adequate insurance (both in scope and term). A specific provision which prudent CRO's seek calls for them to be provided with additional insured status under the sponsor's policy.

An alternative approach which raises serious concerns is one in which the CRO purchases the policy and is the first named insured. Even if the CRO is able to pass along the cost of the insurance policy, it can be at a major disadvantage when a claim is filed. A strong defense requires an analysis of large amounts of information which the CRO may not have access to. A CRO could find itself in an untenable position finding that, lacking access to critical information, it can't perform duties required under its own policy, threatening its ability to claim under the policy. A

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CRO may be forced to settle a claim with insufficient information, and attempts to subrogate against the sponsor could be rebuffed. Most seriously, if the CRO agrees to purchase a policy and fails to do so, or fails to secure the proper insurance and maintain it for the full term of the trial, the financial consequences could be severe.

Sponsors might react favorably to the concept of the CRO purchasing the policy for the trial and acting as the first named insured because of the perceived simplicity. However, this approach may expose the sponsor to inadequate and/or lapsed insurance and loss of control of the process, and is therefore not advisable.

## GETTING THE COVERAGE YOU NEED

The European Union directive is just one piece in the complicated insurance puzzle when it comes to international clinical trials. There have been many examples in which trial sponsors assumed that the policy they purchased in one country would apply to an identical trial conducted in another country; however, insurance policies must respond to the ever-changing specific laws and requirements in each country. Without advice from knowledgeable producers and carriers, meeting these requirements can be a source of great confusion.

The key to securing adequate insurance for a clinical trial, when you need it, is early collaboration with an insurer experienced in navigating the maze of insurance requirements for clinical studies around the world.

**Early collaboration.** The process of communicating with an insurer about plans for international trials must begin early, and it must involve not just people at the senior management level, but those deeply involved in planning and running the trials.

Too often, sponsors wait too long to secure the insurance they need. Consider this example, which is far from atypical: Just days before an appointment with the regional ethics committee in France, a trial sponsor realized that it had not secured the scope of insurance required under France's Loi Huriet Law. In addition to requiring policies with relatively high limits of 760,000 euros per patient, France requires that the policy respond to claims for many years after a trial has concluded—a condition that makes the market unattractive to many insurers. Any such policy would require careful underwriting, and with the ethics committee meeting just days away, the sponsor did not leave enough time for the insurance company to underwrite the trial and prepare the necessary insurance documents in time for the ethics committee meeting. Inevitably, the trial would be delayed until at least the next meeting of the ethics committee. This situation could be avoided if a sponsor presents human clinical trial documents and plans

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to the insurance carrier well in advance of meeting with the local ethics committees.

**Communicating changes.** Sponsors that act proactively, consulting with an insurer early in the process, still must be certain to communicate any changes in the trial documentation. The insurance certificate, for example, is written based on specific study information, and ethics committees will reject the insurance certificate if it does not reflect the final version of the study documents.

**Evolving requirements.** Early discussions with ethics committees regarding any request for deviation from standard insurance requirements is highly advisable. Underwriters are routinely providing a market standard policy for clinical trials, so requests for modifications could negatively impact an insurer's ability to respond to the insurance request. If an ethics committee interprets the laws differently or imposes additional insurance requirements, including at times exposures outside the control of the sponsor or investigator, the importance of these early interactions becomes self-evident. Insurance professionals experienced in writing clinical trials insurance in that country can then take the time to have a thoughtful discussion with the ethics committee about the disagreement so as to reach a mutually acceptable resolution

of the issue without delaying the trial and exposing the sponsor to additional and unnecessary liability risks.

**Reinsurance considerations.** There is another important reason for early and frequent consultation with a clinical trials liability insurer: In countries, such as Germany, that require very high limits for large trials,

the primary insurer will likely seek reinsurance through the Probanden to manage its own risk from the trial. The reinsurer will want detailed information about the trial, and the primary insurer cannot issue a policy until it receives approval from the reinsurer. Having said that, reinsurance continues to generally be difficult to acquire for these types of exposures.

**Language issues.** The ethics committees in some countries require the use of local language versions of key clinical trial documents. Insurers also need this information to properly transfer the appropriate translation of key trial information to the insurance certificate.

**Policy duration.** Admitted clinical trial policies are usually issued on an annual, renewable basis. However, where allowed and acceptable to the underwriter, it can be possible to buy a policy for a single trial with a policy term commensurate with the anticipated duration of the trial .

## CHOOSING AN INSURER

Adhering to insurance requirements in an overseas study can be as frustrating as complying with the myriad regulatory


requirements. Both require a long-range strategy and effective relationships with the right business partners. The first step is to choose an insurer that dedicates the time, the energy and the resources to manage the risks involved with global clinical trials. Here are some of the key considerations in choosing an insurer:

- Liability policies customized for human clinical trials.
- Underwriters, claims and loss control professionals that specialize in the life sciences industry and have in-depth knowledge of the risks involved in human clinical trials.
- Loss control experts who can give loss prevention and risk management advice that is specific to the life sciences industry.
- An insurer who can assist in benchmarking your risk management practices against that of peer group companies.
- Understanding of local regulatory and insurance requirements as well as the litigation environment in

jurisdictions around the world.

- A worldwide network of offices to arrange local policies where admitted insurance is required.
- The financial strength and reputation for paying claims fairly and quickly.

## CONCLUSION

The trend toward global clinical trials is certain to continue as sponsors seek larger pools of volunteers for research studies and a speedier approval process. Sponsors that don't take prudent risk-management steps may expose themselves to catastrophic losses. It is unlikely that trial sponsors can keep up with the fast-changing insurance requirements in every country in which they wish to conduct trials. By relying on experts with risk-management expertise in the life sciences and global capabilities, sponsors can protect themselves, protect study participants and focus on getting life-saving products to the marketplace. 

## ENDNOTES

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