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## Insuring Global Clinical Trials

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**A**s clinical trial sponsors look to foreign countries to shorten drug development timelines, lower operating costs, and expand the pool of study participants, one growing concern is the use of insurance to compensate patients who might be injured in international clinical trials.

Governmental reforms are making insurance an important piece of the regulatory process in many countries. In some countries, however, these requirements—whether mandated by statute or ethics committees—are having the unintended consequence of limiting the availability of insurance, thus compromising the ability of sponsors to conduct trials.

Of the 60,775 worldwide clinical trials listed by the US National Institutes of Health in late August 2008, 26,311, or 43 percent, were outside the United States. Within three years, according to the Tufts Center for the Study of Drug Development, the top pharmaceutical companies expect to conduct 65 percent of clinical trials in foreign countries—increasingly including developing countries in Eastern Europe, Latin America, and Asia. CenterWatch has estimated that 20 to 30 percent of all clinical trials are being conducted in what it characterizes as “ascending regions.” Synergy Research Group, a contract research organization (CRO) based in Russia, reported that 174 new clinical trials were approved in Russia in the second quarter of 2008, a 53 percent increase over the same period in 2007. Of those, 107 were multinational trials.

Regulators are trying to balance participant safety with the desire to

avoid putting bureaucratic obstructions in the path of life-saving innovations. Still, regulatory variations from country to country and differing legal frameworks on such issues as advertising, recruiting, reimbursements, data privacy, and human subject protections are making it a challenge to draft clinical trial agreements and informed consent documents.

Attempts to harmonize regulations are a step in the right direction, but so far they have achieved only limited success. According to CenterWatch, a growing number of countries in Asia, Latin America, and Eastern Europe, as well as South Africa, have adopted the Good Clinical Practice standards promulgated by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as a guideline or law. Adoption of these guidelines, along with growing coordination among the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Australia's Therapeutic Goods Administration, and other governmental agencies may improve patient safety and ultimately lead to more consistent regulations. But there are still plenty of obstacles, and failure to think through insurance issues early in the trial planning process can result in costly delays.

Insurance underwriters consider many factors when deciding whether to insure a trial, how much insurance to provide, and at what cost. Insurers may be willing to underwrite a clinical trial, even in an emerging market, given a well-designed protocol, use of qualified CROs and investigators, thorough yet

easily understood consent forms, and a corporate culture that demonstrates a concern for patient safety. All these issues are within the control of a trial sponsor. An insurer will also consider external factors, such as the availability of qualified investigators, medical facilities and the desired patient group; the litigation climate; a legal framework that allows a sponsor to adequately defend against a claim; and insurance requirements imposed by statute, regulation, or ethics committees.

### European Requirements

The situation in Europe presents the most obvious example of how good intentions can go awry. On May 1, 2004, the European Union's Clinical Trials Directive was implemented with the aim of simplifying and harmonizing regulation of clinical trials across the European Union. While the directive in many ways will benefit the internal market in medicinal products while protecting study participants and public health, it certainly did not simplify governments' positions regarding insurance.

The directive includes a basic requirement that no clinical trial may be held without providing insurance or indemnity to cover the liability of the investigator and the sponsor. The directive leaves it to the member states to set their own standards for how to meet the financial responsibility requirement. It's a simple provision, but it has created a complex web of insurance demands that make it impossible for a single insurance policy to meet the requirements of every country in a multi-center trial. One challenge is that most countries in

Europe—the United Kingdom being a major exception—require “admitted insurance,” which means the insurance must be written by an insurance company approved by insurance regulators in that country.

The United Kingdom does not specifically mandate insurance, but in practice, insurance for injuries regardless of fault is always required.

In some countries, the challenge is even greater. Insurance requirements—either by statute or the demands of an ethics committee—may impose a liability so great that many insurers are unwilling to bear it. For example, France requires insurance of 1 million euros per participant and 6 million euros per clinical trial, and policies must insure liability for 10 years after the trial ends. Under Belgian law, a sponsor is liable for damage, even without fault, and the law voids any provisions in the insurance contract aimed at limiting liability. The law also establishes significant hurdles to defend against a claim. Italy requires insurance to be written by a locally licensed insurer, but the statute does not set a required limit of insurance for clinical trials. In this void, ethics committees have required limits that were not supportable in the local insurance marketplace.

Sweden presents an unusual circumstance. The country has no statutory requirement for insurance, but the Swedish Drug Association makes insurance available to sponsors through a group facility. The facility provides limits of insurance on a group basis, so companies share limits in a pooling arrangement rather than having a dedicated limit for their specific trial. In this scenario, pay-

ment of future claims will depend on the adequacy of limits available from the facility at the time of a claim. In other words, claims against a sponsor of one clinical trial could drain a substantial amount of the pool’s capacity, leaving other sponsors with little protection.

Even in countries where the statute requires specific limits, individual ethics committees may demand higher limits than the law requires. If a trial sponsor is required to buy more insurance than is warranted, that will unnecessarily drive up the cost of insurance for the trial—assuming, of course, that insurers would be willing to write such high limits. Excessive demands by ethics committees for insurance requirements, strict liability, and limited defenses could impact both the availability and affordability of insurance in a particular market, impacting the decision about whether the trial should even take place there.

### **Asia and Latin America**

Asia and Latin America present other insurance challenges for sponsors of clinical trials, even though these cultures tend not to be very litigious.

China’s 833 studies recently surpassed fast-growing India, which had 739. In both countries, authorities view clinical trials and drug development and manufacturing as drivers of economic growth, but regulators are struggling to keep up with the pace of clinical trials in an effort to protect participant safety. China requires clinical trial insurance from an admitted insurer, but it has pragmatically accepted non-admitted insurance. The reason? Until very recently local insurance markets have not offered insurance.

In Latin America, clinical trials insurance is not mandatory, but some ethics committees, most notably in Argentina, as well as the Argentinean regulatory authority, will sporadically request evidence of insurance as part of their clinical trial document reviews. Increases in the demand for insurance from ethics committees and regulators may spur the growth of clinical trials insurance in local markets that have not shown much interest in insuring this growing risk.

### **Global Insurance**

In a climate where international trials are growing unabated, trial sponsors should consider insurance requirements as one factor in the determination of where to conduct a trial. Requiring unnecessarily high insurance limits can increase the cost of a trial, and in places where liability is unlimited, insurance may be unavailable. In countries where local insurance is required, sponsors should seek a global insurer that has locally licensed subsidiaries or affiliates. A global insurer with local expertise in the markets where a pharmaceutical company operates can help ensure that its policy meets local requirements and that the company avoids insurance gaps that can leave it exposed.

In the long term, pharmaceutical executives have a stake in joining with insurers in lobbying for reasonable laws and regulations that protect patient safety without compromising their ability to conduct clinical trials in their country.

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