

Legal conflict on a global scale:

Clinical trial agreements in the international context

Clinical trials are increasingly a global business – yet the multiplicity of national and regional regulations can prove to be a major barrier.

Norman M Goldfarb reports on moves to simplify the situation.

Most industries globalise to reduce costs: Cost is not, however, the primary driver for the globalisation of clinical research: Low site fees currently are offset by high communication and logistics costs. The primary attraction is generally subject availability. As a side benefit, data quality is better in many developing countries than in developed countries. The multiplicity of legal and regulatory regimes offsets these advantages, and can be serious problems in multinational trials. Clinical trial agreements are a small area of the legal and regulatory impact that will grow in importance as globalisation of the industry continues.

In the United States, it takes clinical trial sponsors an average of 35 days to negotiate clinical trial agreements (CTAs) with community-based sites and site management organisations, and 96 days with academic centers.¹ Investigative sites have ranked 'Legal Review' and 'Contracts & Budgets' higher than 'Subject Recruitment' as a source of delay for clinical trials.² New drugs can generate revenue of over USD1 million per day, so the cost of these delays adds up quickly. In addition, most new drugs enjoy patent exclusivity for only a few years at best, so time is of the essence.

In the United States, some of the delays occur when the sponsor is in one state and the site is in another. The difficulties are magnified when the sponsor or site is outside the United States. It is magnified further when sites are in multiple countries. It is magnified further when sites and sponsors on multiple trials are in multiple countries. It is magnified still further when sites and sponsors are in multiple states

and provinces within multiple countries. With the steady globalisation of clinical research, these difficulties will become ever more burdensome.

Investigators are subject to rules on multiple levels: Nations have laws, as do many states and provinces. International bodies define rules for clinical research. Multinational (e.g., European Union and Mercosur) regulations may apply. Cultural norms may not be legally codified, but restrictive nevertheless.

Legal conflicts are normally resolved by priority of law. For example, national laws override state laws. However, one nation's laws do not automatically override those of another. It may not always be straightforward to untangle (or remember) overlapping conditional requirements, authorisations and prohibitions. Some laws may apply to one party in an agreement, but not to the other party; they may be in different jurisdictions or be different types of entities. The parties to the agreement may be unaware of the conflicts of law, entirely unaware of a law, or may interpret the laws differently.

Here are a few examples of regional legal requirements³:

Some US states interpret their sovereign immunity to prohibit mandatory binding arbitration; others accept it if it follows the rules of that state.

Many countries require that the official version of the contract be in their language. For example, France requires that contracts with state-owned entities or entities "participating in the provision of services of public interest" must be in French.⁵ Some countries require that their law must govern for an agreement to be enforceable.

The statute of limitations for contract disputes is three years in Maryland, four in Pennsylvania, five in Kansas, six in Oregon, eight in Montana, ten in Rhode Island, and 15 in Ohio. In Utah, it is one year for state institutions. It is three years in Austria, four in Finland, five in the Netherlands, six in Ireland, ten in Sweden, 15 in Spain, and 20 in Denmark. In France, it ranges from three months to 30 years, depending on the basis of the claim; in Germany, from six months to 30 years.⁵

In the US, Florida requires minimum aggregate medical malpractice insurance coverage of USD300,000. California caps non-economic medical malpractice liability to USD250,000. In the EU, the investigator and sponsor must have insurance or indemnification for subject injury liability. For example, Germany's insurance requirement includes a minimum of EUR600,000 for death or permanent inability to work.⁵ In South Africa, malpractice insurance does not cover staff members. Members of the Australian Pharmaceutical Manufacturers Association must provide compensation to injured subjects. In Australia and Singapore, a local company must provide the sponsor's indemnification. In many countries, suitable malpractice insurance is unavailable.

In Spain, sponsors must publish trial results in scientific journals, identifying the ethics committee that approved the study.⁵ In Brazil, ethics committees must receive a copy of publications, or a written explanation.

In the US, investigators must retain records and reports for two years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until two years after shipment and delivery of the drug for investigational use is discontinued, and the Food and Drug Administration has been notified. In the EU, the same rules apply, but the two-year period begins when



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research on the study drug is discontinued for *any* indication. Argentina requires retention for 15 years. Canada requires retention for 25 years. Mercosur requires retention of case report forms for five years after a trial's final report.

In the US, open-records states such as Alabama and Texas require public disclosure of clinical trial agreements with state institutions.

In Chile, study coordinators must have a five-year university degree in the biological sciences valid in Chile.

In US litigation, each party normally pays its own attorneys' fees. In the UK, the loser pays both parties' attorneys' fees.

What's to be done

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International has published a guide to state laws in the US, but it does not fully address CTA issues.⁴ The author has begun the process with a paper that describes a subset of regional laws and regulations.³ The paper is available at www.firstclinical.com/resources/articles.html

In a related initiative, the author founded and chairs MAGI, the Model Agreement Group Initiative. Members from over 200 sponsors, sites, Contract Research Organisations (CROs), Site Management Organisations (SMOs) and law firms have begun drafting a flexible, 'multiple-choice' model CTA. The model CTA will not eliminate negotiations, but will streamline them with clear, 'certified' text. Commentary on the multiple-choice alternatives will explain the pros and cons of each alternative. MAGI will publish its model CTA in 2005.

Most of MAGI's current members are based in the United States, so drafting is now focused on contracts between US

parties. However, MAGI's multiple-choice structure easily accommodates alternative texts for different legal jurisdictions. MAGI's model CTA can also accommodate multiple languages, with 'certified' translations of the text. MAGI therefore welcomes international members. Active members commit a total of two to eight hours. Everything is done remotely; there are no meetings. There are no membership dues. By participating, members are not obligating their organisations to use the resulting model CTA. MAGI has no hidden financial objectives.

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