

## Ethical Pitfalls for Sponsors in Developing Countries

By Norman M. Goldfarb

Clinical trial sponsors take significant risks when they conduct clinical trials in developing countries where local legal, regulatory and ethical standards are less stringent than in the United States and other developed countries. Developing countries are sensitive to foreign exploitation. The media are very receptive to such stories. A single reporter, government official, researcher or study subject can trigger a major controversy with international exposure. Someone may decide to settle a score with an investigator or see an opportunity for political advantage. If the investigator or research site is pressured with sanctions, it probably will not hesitate to strike a deal with the authorities and place the blame on a foreign study sponsor with deep pockets that "should have known better." The legal system may not operate according to U.S. practices; not all countries publish their laws or enforce them consistently.

The government could take the following actions:

- Terminate the study
- Prohibit use of public facilities for future studies
- Impose civil and criminal penalties
- Delay or refuse regulatory approvals of future clinical studies, drug marketing, equipment importation, etc.
- If the investigator is a public employee, contact U.S. authorities about potential sanctions under the Foreign Corrupt Practices Act

Even without official action, there may be serious international ramifications for the sponsor's public image and ability to conduct business.

As clinical research continues to globalize, the risks increase. The current backdated-stock-options prosecutions in the United States provide a good example of what can happen when the government wakes up to an illegal practice.

Potential risks include, for example:

**Uncompensated use of public facilities.** It is a common practice in some developing countries for physicians to treat private patients in public healthcare institutions without compensating the institution for use of the facilities or staff. In some Latin American countries, this practice is so common that it has a name: "biombo," literally the folding screen that doctors use to give privacy to their private patients in public facilities. Sponsors facilitate this practice when they pay the investigator rather than the institution, especially when the payment does not specify an allocation to the institution. The Borison and Diamond case in the United States started out as a particularly egregious example of biombo.

**Offshore Accounts.** Investigators may request direct payment to an offshore account in a country with strict financial privacy protections. Such arrangements are probably motivated by tax or currency control avoidance, and may be illegal. Although the sponsor is just complying with the investigator's request, the tax authorities are likely to see the sponsor as a willing accomplice.

**Financial disclosure limits.** U.S. regulations (21 CFR § 54.2) set forth rules for disclosure of financial conflicts. For example, investigators must disclose consulting fees in excess of \$25,000 and equity holdings in a public company in excess of \$50,000. If these numbers are reasonable for physicians in the United States, they certainly are too high for physicians in developing countries, where incomes are much lower. By using the U.S. regulatory levels, sponsors may allow conflicts of interest that reduce human subjects protection and clinical trial integrity. If something goes wrong, an embarrassing conflict of interest may come to light. U.S. regulations do not prohibit sponsors from voluntarily using lower disclosure limits that are appropriate for local conditions.

**CRO/SMO combinations.** In the United States, there is usually a bright line drawn between the sponsor and the research site. Thus, contract research organizations (CROs) seldom double as site management organizations (SMOs). In contrast, CRO/SMO combinations are common in developing countries. In theory, the CRO department of these companies can perform delegated responsibilities for the sponsor such as monitoring the SMO department. In practice, combining the two functions under one roof creates conflicts of interest that may result in serious regulatory breaches and damage to study integrity.

**Captive study coordinators.** In some developing countries, some clinical trial sponsors identify study coordinators and require sites to employ these study coordinators. The intention, presumably, is to ensure the competence of the study coordinators. However, with repeated use, these people become known as "Company A's coordinator" or "Company B's coordinator." If the study coordinator's primary loyalty is to the sponsor, the site's independence is compromised. If a study subject is injured, the sponsor's "learned intermediary" defense is weakened, not just in courts of law but also in courts of public opinion.

**Inadequate ethics committee oversight.** Ethics committee (IRB) oversight of clinical trials in developing countries may not meet U.S. standards for human subjects protection. Accepting a lower level of oversight increases the risk of subject injury, with implications for the study sponsor. Review by an ethics committee in the U.S. or other appropriate country, especially one familiar with clinical trials in the developing world, may mitigate this risk.

## **Conclusion**

It is impossible to conduct business, especially internationally, without taking risks. However, some risks can be mitigated by avoiding the temptation to follow the herd and engage in potentially problematic practices. U.S. standards are not necessarily appropriate for other countries, but they provide useful guidance. When the inevitable controversy occurs, defensible ethical standards will pay off. Less prudent companies will suffer the slings and arrows.

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