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All Global Clinical Studies Are Local

By Vladimir Bogin

Global clinical studies are very complex. Even minor oversights during the planning stage can result in significant problems. The following issues often do not receive the attention they deserve:

Culture and Socioeconomics

Know the local customs, the healthcare system, the standard of care, and attitudes toward Western medicine.

For example, in psychiatric trials, what is considered an "illness" varies dramatically across cultures and may have very different connotations. For instance, in India, it is shameful to have a relative with a psychiatric illness. This attitude makes recruiting study subjects more challenging, since they might be hidden away at home rather than admitted to a hospital. It also discourages subjects from reporting symptoms, so subjective scales and measures have to be carefully designed to avoid under-reporting.

Patients in the former Soviet republics often downplay the severity of their illness(es) and minimize subjective scores. Here again, there are implications for enrollment and adverse event reporting, so objective assessments are important.

In many countries, participation in a clinical study might be the patients' only chance of receiving adequate medical care. This situation can raise ethical issues for enrollment. It can also create scientific issues related to adverse event reporting, since study subjects might over-report symptoms to obtain treatment or under-report symptoms to stay in the study.

Because of these and other factors, adverse event rates can vary substantially across countries and thus affect a study's validity. Choose countries that are likely to yield a composite adverse event rate similar to the U.S. rate, and be prepared to explain the data from the outlier countries to the FDA.

Local Presence

Local service providers with the necessary expertise and relationships are essential, especially for regulatory approvals and materials logistics. In many countries, the published laws and regulations tell only part of the story, so knowing how things *really* work and *personally* knowing the people who control the process are essential. Having feet on the ground in Ukraine does not equate to feet on the ground in Belarus; they may be neighbors, but they are different countries, with different rules, customs and attitudes.

When working through a global or regional CRO, it is important to know about any local subcontractors and understand their capabilities. Wherever possible, speak directly with the subcontractors on the telephone or in person and also request and verify their references. While it can be difficult to assess a subcontractor on the other side of the planet, discussions with a number of them should suggest who is relatively likely to underperform. Visits are expensive and time-consuming, but they yield more information and impress people with your commitment to the study.

Local Project Managers and CRAs

Local project managers and site monitors will be your eyes and ears, so they must understand your expectations for site monitoring, eligibility criteria, source documentation, etc.

Clear decision-making algorithms are very helpful, especially in the many countries that, unlike the U.S., do not prize individual initiative. Some decisions, e.g., in unscheduled interactions with regulatory agencies, require quick action and local expertise, so make sure you and your local teams understand their authority to make such decisions.

Local Investigators

Investigators and other local personnel often need visas to attend the investigator meeting, so allow adequate lead time.

It should come as no surprise, but often does, that every nation has its own laws and regulations. Some clinical trial agreement terms might conflict with local laws, be unenforceable, or just not understood by investigators more familiar with the local laws and regulations. For example, privacy laws in the European Union are stricter than in the U.S. but essentially non-existent in some other regions, such as parts of Southeast Asia and the Middle East.

Budgets and Payments

Global trials often yield cost surprises, sometimes doubling the contracted amount, so make careful and detailed assessments of all costs in advance, where they originate, and what exactly they are for. Overages can bust your budget, but, if left unpaid, are likely to dispirit the service provider. Understand the tradeoffs, e.g., in site selection vs. travel costs. Investigator fees are often higher than one might expect based on the average income level in a developing country. Be careful with local service providers that might not appreciate the significance of the U.S. Foreign Corrupt Practices Act. The cost of entering each country is substantial, so it is often more economical to focus on a smaller number of high recruiting countries, provided they are consistent with your filing strategy.

Physicians in many developing countries are poorly compensated, even by local standards, so they are highly motivated to supplement their income with clinical study fees. However, any delay in payment can be perceived as a sponsor cash-flow problem and be very demotivating.

In some cultures, investigators consider discussing financial issues with the sponsor's team as awkward and distasteful. Therefore, have someone with good site relationships (but not the site monitors) periodically contact each investigator to ask about any issues, including those related to compensation and the payment process.

Communications

It is common for foreign-language speakers to understand written English very well but find spoken English more challenging. Ask follow-up questions to make sure they understand the topic that has just been discussed. You might find their accents hard to understand, as well, so feel free to ask them to speak more slowly and repeat their sentences, as necessary. Detailed written meeting minutes can also reveal misunderstandings and missing information.

Protocols and investigator's brochures are technical documents that might be beyond the reading skills of some investigators, site monitors, and other local personnel. Correct

translations are, of course, essential. In some countries, like India, there are many languages, so someone who is fluent in several of them still might not be fluent in the one(s) you chose for translation purposes. Here again, asking follow-up questions is useful.

Conclusion

As multinational clinical studies have become common, the interactions between sponsors, CROs, investigators and regulatory authorities have become more complex and sophisticated, and less forgiving of studies that do not operate at the higher standards. Global, regional and national CROs all have their pros and cons, but the success of a study ultimately depends on understanding of the eccentricities of each country and working closely with capable local teams.

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