Avoiding Common Pitfalls in Multinational Clinical Trials

By Dan McDonald

Multinational clinical trials are challenging. The international industry is rapidly maturing, but horror stories are still common:

> "Our study drug is melting in a hot locker in customs, and I can't get hold of anyone."
> "Sure, that country enrolled like gangbusters, but the data was garbage."
> "I have a hard time even understanding the local project manager on our weekly calls."
> "The regulatory agency responded with a single question and no details."
> "My highest enrolling investigator is demanding the latest iPad to keep enrolling."

Despite the challenges, the pressure to conduct clinical research internationally is stronger than ever. However, every country is different, with its own evolving advantages and challenges. In addition to enrollment, cost, time and sometimes even data quality advantages, countries like Poland, China, India and Brazil are rapidly expanding markets that require local trials for marketing approval.

This article will focus on potential pitfalls in four areas, along with ways to address them:

- Regulatory naïveté
- Weak communication
- Deficient feasibility analysis
- Inadequate investigator relations

Pitfall #1. Regulatory Naïveté

Some countries have especially bureaucratic, inefficient, opaque, stringent or plodding processes for reviewing a study application ("IND" in the U.S.). Nevertheless, some applications move through the process much faster than others, for reasons that are under the study sponsor's control.

- **Involve regulatory experts early.** Country-specific regulations and guidelines can be dynamic, obscure and nuanced. Attitudes vary by product category, sample population, study phase, experimental design, etc. If you don't have in-house regulatory expertise for a specific country, find a consultant or third-party service provider who can guide you. Involve them early on in country selection, project planning, protocol development, and regulatory strategy.

- **Finalize your protocol before submission to the regulatory agencies.** If you are still discussing changes to your protocol at the investigator meeting, it is too late. A protocol amendment for just the U.S. is costly and time-consuming, but it's much worse with multinational studies. Many protocol amendments require review and approval by multiple regulatory agencies. In many countries, amending the protocol

essentially means starting the regulatory review process over from scratch. If any one of them objects to the change, keeping the protocol consistent across countries could become a nightmare.

- **Introduce yourself and your study to the agency.** Many countries allow for a pre-IND submission meeting with the agency. This meeting can be invaluable. First, it will help you learn about the agency, its requirements and its processes, and it will help the agency learn about you and your study. Second, it will probably reveal questions or concerns the agency has about the protocol or study design, so you can make the necessary adjustments for your formal application. Third, and perhaps most importantly, personal credibility and relationships matter the world over.

- **Be a known entity.** Regulators are more likely to trust and work constructively with CROs, regulatory specialists, and consultants that have already established their credibility. Competent local experts generally have better access, can better deal with the preferences and quirks of individual regulators, and are better able to find out what is happening behind the scenes. Identify a lead investigator in each country who can attend, if permitted, a meeting with the regulatory agency.

- **Understand data acceptance policies for marketing approvals.** The U.S. FDA accepts data from foreign trials (21 CFR 312.120), but will probably balk at 100% foreign data. On the other hand, some countries don't want to contribute more than 20-30% of a multinational trial's study subjects. In your pre-IND meetings, ask the regulatory agencies about their requirements and preferences. While you're at it, try to determine (and perhaps, negotiate) the number of patients needed from that country to obtain their marketing authorization.

- **Develop a checklist of documents and steps required in the submission process.** Most local CROs and regulatory consultants will have a checklist of IND requirements for their country. You can usually find at least some of them on the agency's website, but it's a lot easier to obtain them from a local expert.

Pitfall #2. Weak Communication

As you move from country to country, regulations, ethics, customs, practices, religions, languages, logistics, etc., all change. Global clinical trials thus require sophisticated local expertise. Even country expertise is often not local enough; just ask someone from South Carolina trying to do business in New York City.

Working with local resources is often the solution to localization pitfalls. Some common resources include the following:

- **Contract research organizations (CROs).** A local CRO or the local branch of a global CRO can provide full-service local expertise. Determine whether a global CRO really has capabilities based in the country of interest and not just a "storefront." A

global CRO or network of regional CROs may have a local partner, which should be evaluated as an independent entity. You may want to employ a hybrid model, in which a global CRO centralizes services like data management, biostatistics and monitoring, while local partners help in areas like regulatory approval and site recruitment. Global CROs can reduce the sponsor's costs in managing a project, while local CROs often charge lower fees, especially in ascending markets.

- **Regulatory consultants.** Some of the best regulatory consultants work independently. Their services might be expensive, but the right local expert is well worth the cost.

- **Site management organizations (SMOs).** While the SMO model has enjoyed limited success in the U.S., it is working well and, in some cases, thriving in other parts of the world. In many countries, strong relationships with clinical investigators, based on day-to-day study conduct support, are essential. The SMO may even employ, train and place their own full-time clinical research coordinators (CRCs) at the study sites, where they are fully dedicated to the sponsor's study or studies. In areas like Brazil, India, parts of Eastern Europe, and elsewhere, investigators might see up to 100 patients per day, so this level of support can make a significant difference. In addition, on-site resources provide transparency and peace of mind, with performance tracking right down to the subject. Transparency also provides accurate information on personnel workload and changes at the site.

- **Clinical research associates (CRAs).** As the clinical research industry grows and matures, the days of flying CRAs across a country or into other countries are coming to an end. Competent, local CRAs are not only more productive and less expensive, but they know the investigators, understand the culture, and can help manage some of the logistics unique to that location. Instead of being CRO employees, these freelance resources are often hired by foreign CROs or sponsors and trained on the protocol and a consistent set of SOPs being used on the study across the globe.

Localization begins with language and communications. While English is the lingua franca for business across the world, it is not 100% universal in clinical research. In some countries, only patient-facing documents like informed consent forms need translation.

In India, regulatory documents are submitted in English, and the language of clinic trials is English. However, 29 languages are spoken by one million or more people, so the informed consent form (ICF) is typically translated into three to five languages.

In other countries, the local language is used. In China, for example, the language of clinical trials is mostly Chinese. Regulatory documents, investigator-facing, and patient-facing documents all require translation. China has 292 languages. The ICF is typically translated into six to eight of them.

Translation companies employ native speakers, often based in their country of origin. But language issues extend beyond the printed documents, especially when communicating with potential and enrolled study subjects. While the ICF might be translated properly, it also has to be explained in the local dialect to potential study subjects and often their family members. Someone from the local area who is well-versed in the protocol and clinical research in general can be very helpful.

Long distances and differences in time zones and cultures require extra emphasis on good communication practices when working with service providers:

- **When possible, interact face to face.** There is no substitute for the eye contact, facial expressions, and body language in face-to-face interactions. However, if the travel cost is prohibitive, videoconferencing through Skype or other low-cost systems is a reasonable alternative.

- **Teleconference times should be convenient for the client.** Most local CROs and other service providers are willing to accommodate the client's work schedule. Choose a regular time for teleconferences with each service provider so they don't have to be on call 24 hours a day.

- **Expect good "soft skills."** Capable service providers should be able to provide a project manager as the point of contact who can meet your expectations for verbal and written language skills, customer service, time management, oral and written communication, and expectation setting. Concepts of time, in particular, vary across cultures. In some countries, such as India, it is unnatural to disclose bad news or unsolved problems, so training in the U.S. business culture is essential.

- **Practice communication discipline.** Assign specific people to handle communications on specific topics. Also, identify someone the service provider can contact in emergencies and for other issues. If service providers will communicate with each other, identify and publish those points of contact, as well.

- **Use a central document management system.** If you do not have access to a clinical trial management system (CTMS), use a technology like SharePoint to share files and work on documents collaboratively.

Pitfall #3. Deficient Feasibility Analysis

It is hard enough for a sponsor to assess study feasibility in its own country. Assessing feasibility in 10 countries is more than 10 times harder, due to unfamiliarity with the countries, challenging local conditions, and a big question: Which countries should be included in the first place, based on likely performance and the need for representative data, often for multiple marketing applications?

- **Wait for the protocol.** Conducting a feasibility analysis with a draft protocol or summary of the study is likely to deliver misleading results. However, reviewing a draft protocol with potential investigators is likely to yield a protocol that is suitable for feasibility analysis.

- **Conduct site visits.** In the U.S., pharmacy prescription data, insurance claim data, prevalence heat maps, and other data sources and technology can help identify sites that are likely to enroll study subjects. Unfortunately, many of these technologies or data sources do not exist in other parts of the world. It is easy to email or fax study feasibility questionnaires, but site visits are the surest way to obtain accurate information about potential enrollment and the suitability and availability of the personnel, equipment and facility. They also demonstrate the sponsor's seriousness about conducting the study in that country. Many countries do not have the stringent patient privacy laws that exist in the U.S., so verification of patient data can take place under a confidentiality agreement with the investigative site. Availability of trained technologists, especially in disciplines such as cardiology and ophthalmology, is crucial to the success of your study.

- **Assess the standard of care.** The standard treatment of conditions, availability of medications, dosage regimes, culture (including religious and dietary considerations), and many other factors vary from country to country, affecting the practicality and ethics of using a placebo or comparator drug, treatment of co-morbid conditions, reporting of adverse events, and other factors. Are you looking for patients who have failed third-line chemotherapy treatment in an area where patients are lucky to even get first-line treatment?

- **Include a mix of investigators.** The medical profession in every country includes key opinion leaders (KOLs), even if they do not publish in leading U.S. journals. Such physicians may not enroll many study subjects, but they give credibility to the study with other physicians and the local regulatory agency. In some cases, you may want to call on one of these KOLs to help defend the study in person to regulators. Experienced investigators with a proven track record are, of course, valuable contributors. In addition, potentially strong investigators are still entering clinical research in many countries, especially in smaller cities where the market is relatively untapped.

- **Localize within the country.** Every country includes cities of various sizes, along with rural areas. Language, religion, ethnicity, infrastructure, disease prevalence, openness to participating in clinical trials, and many other factors vary within a country.

- **Consider the patient catchment area.** In some countries, patients travel for hours to visit their physician. In other countries, especially in Eastern Europe and the old Soviet Union, specialized hospitals serve the entire country. Where does a physician's patient base originate? Do they use public transportation? Is parking available at the site? What highways feed the area?

    - The organization of medical providers varies by country, as does the willingness of physicians to refer their patients for participation in a clinical trial. Referrals are more likely in a country with a national healthcare system that pays physicians' salaries. In some countries, physicians operate in formal or informal networks, where referrals are standard practice.

- **Assess subject recruiting options.** Are there other ways to attract potential subjects to investigative sites? Some countries permit study advertising; others do not. Even if advertising is permitted, it may not fit the country's culture.

- **Evaluate the logistics.** The logistics of operating in some countries can be very complex. Potential challenges include entry points, customs clearance, permits and licenses, fees, transport times, storage conditions, temperature control, and storage facilities for study drug and equipment coming into the country and biosamples going out. For example, Brazil, India and several Eastern European countries require a local representative to pay the customs fees and receive imports in person at the entry point.

    - Infrastructure like reliable electrical power that is taken for granted in the U.S. may not exist at the site or subject homes. Study subjects may have to travel long distances in high or low temperatures.

- **Consider the ethics review process.** Most countries employ local institutional review boards (IRBs) (usually called "ethics committees (ECs)" outside the U.S.); some employ central IRBs/ECs; and others employ a mixture. Some require both central and local reviews. In some countries, IRBs/ECs can grant conditional approval to a study in advance of national regulatory approval. IRB/EC reviews are more consistent and compliant with U.S. standards in some countries than in others.

- **Understand the socioeconomic conditions.** Do potential study subjects pay for their own healthcare, or are they covered by insurance or a national healthcare system? Is clinical trial participation their only way to obtain treatment? Can they afford a bus ticket to visit the research site? Factors such as these can have a significant impact on the availability of subjects and the ethics of their participation.

- **Obtain more than one feasibility analysis.** Given the intense competition for trial management work in most markets today, most service providers no longer charge a fee for conducting an in-depth feasibility analysis. Don't abuse the privilege, but comparing two or three analyses can be very informative and, of course, assist in selecting the best service provider.

Pitfall #4. Inadequate Investigator Relations

Enthusiastic and motivated investigators can deliver strong site performance, while wary or jaded investigators can drag a study down quickly.

The key point about managing investigator relations is that they are based on relationships. In the olden days — 10 years ago — sponsors conducted trials to save money. However, the costs savings often proved illusory. One reason was that long distances led to weak relationships, which generated poor results. To benefit from global studies, some of the savings need to be re-invested in creating strong relationships, especially in countries that emphasize their value.
If you don't get to know your investigators personally, how invested will they be in performing for you? An effective communications plan — regardless of the site's location — might include pre-study phone calls, interaction at an investigator meeting, a monthly study newsletter, quarterly update phone calls directly with each investigator, and annual face-to-face meetings in regional groups, or ideally, in one-on-one settings.

The economics matter too, especially "unfair" differences. An investigator in Chile might not appreciate receiving 20% of the compensation that an investigator in Germany receives for doing exactly the same work, regardless of the lower income standards in Chile. Assume investigators will share compensation information globally. Not every investigator will be dissatisfied, but you risk low morale or fireworks if the range is more than 20-30% across countries. If the investigator and site divide your payments fairly, both are more likely to be motivated.

Payments tied to performance — subject enrollment/retention, data delivery and quality, and protocol compliance — help motivate investigators throughout the entire course of the study. This is easier said than done in some countries, but it should be the starting point. Here again, local representation can help negotiate fair payment rates that do not exploit the investigator or you, the rich foreigner ready to be fleeced.

Conclusion
Conducting global clinical trials can be a formidable challenge. Nevertheless, many are completed successfully every year. The pitfalls discussed above are far from an exhaustive list, but experienced service providers can help even inexperienced study sponsors meet the challenge. To repeat the key message, global trials require local, feet-on-the-ground expertise. Whether working with a single global service provider, a mixture of local service providers, or your own personnel, strong project planning and management are essential, especially given the high stakes and complexity of the task.

Author
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