



OUTREACH TO GLOBAL MARKETS

Lionbridge's Mark Wade and Premier Research's Chris Nowell explain the rising trend of globalizing clinical trials and the implications of global markets.



Describe your experience with conducting global trials. Why are you conducting them on an international scale?

MW: We have extensive experience with our clients conducting clinical trials in multiple geographies. According to Thomson CenterWatch, 20 percent to 30 percent of clinical trials are being conducted in ascending regions. As more and more companies rush to the global scene, they are naturally looking at the downstream benefits – access to large drug-naïve populations, lower operating costs of running trials and the ability to rapidly recruit suitable participants. Indeed, regulators are demanding ever-larger population pools and longer term monitoring, and more companies running trials are pushing the trial boundaries farther across the globe into the so-called ascending markets of Eastern Europe, Asia and Latin America.

This focus on the end benefits, however, fails to take into account some of the deep challenges of getting to that point. In the rush, companies that are not yet globally proficient are more likely to underestimate the amount of work that goes into the translation process. And, if they are not viewing it as a critical risk, then they are leaving several things to chance that need to be carefully managed.

CN: There is no question that conducting clinical trials on a global basis adds another layer of complexity to any project. However, the potential additional challenge is minimized when the operational team has a thorough understanding of the sponsor's objectives, as well as local laws and regulations. At Premier Research, our geographical footprint and local operational experience in many countries allows us to successfully execute global trials. The team has to be aware of the common practices in the healthcare establishment within each country and the impact this may have on the conduct of the trial overall. We work closely with our clients to translate this experience into practical measures that assure the success of their projects.

Global trials are particularly challenging for psychiatry and cognitive indications. These studies are typically culture-sensitive and the project team has to be mindful of those cultural differences

that can affect enrollment, compliance and even the consistency of the data produced in different countries. With neuroscience research, one of a handful of core therapeutic areas for Premier Research, this is one of our strengths.

What trends are you witnessing? Do you believe the developing world is becoming a greater area of interest to conduct trials than the West?

CN: In general, the developing world is of greater interest, and we see that trend continuing. What has also become clear, however, is that the attractiveness of placing a study outside of Western Europe or the U.S. is not dependent on any single factor. Rather, a myriad of issues can drive the decision. Cost, investigator availability, patient availability, regulatory objectives, commercial planning, the sponsor's previous experience in developing countries and timing are just a few of these. For example, we have seen clients consider central and eastern European countries for early development and only for large late phase trials. This strategy usually aims at decreasing the cost of conducting trials and, more importantly, enhancing enrollment.

Therefore, when approached by a sponsor with an interest in sites outside of the West, we try to understand what's driving that interest and help them understand what the optimal approach would be based upon their objectives. What this means is that it is important to keep in mind that global studies may not be appropriate for some situations. For example, the cost savings are not always realized since the lower labor cost is sometimes offset by other costs inherent to global trials. In addition, with the increasing demand for investigative sites in these markets, and the increasing experience of those investigators, the labor cost is going up even in these markets.

In the end, there are still situations when running the trials on a global basis provides an optimal solution from many points of view, especially for finding the right patients. There will certainly be an increasing need to go global as we tackle less prevalent diseases and diseases that have reasonably effective standard therapies.

How does language play a role in global trials? Describe some of the big issues as well as small issues.

MW: Language is critical to the execution of any trial. Documentation must be in the native language for all participants and investigators. Everything from the phlebotomy kits to the informed patient consent forms must be in the local language and per federal regulation 21CFR46. All documentation must be written in such a way that there is minimal risk of trial participants not understanding what they are participating in. On a simple, more tactical level, the very success of the clinical trial hinges on patient data. The answers given on the patient reported outcome forms (PRO) depend very much on the questions asked. And then, the interpretation of those answers is also critical. The entire protocol, results, future submissions and even patient health are at stake.

CN: Language is certainly an important factor in running global trials. Most investigators and study coordinators can read and write in English even if it is not their native language. This at least alleviates the need to translate the protocol, investigator brochure, etc. in many countries, for the every day use by site staff, although most regulatory authorities and ethics committees still require local language documents to be submitted for review and approval. However, having CRO staff who speak the local languages where the study is being conducted is still critical for effective and accurate communication with the investigators and their staff. This is one of areas where having a diverse and multilingual workforce is a major advantage for the CRO.

Effective communication is clearly essential to convey the spirit of the protocol, assure the accuracy of the data collected, and resolve queries effectively.

Although the site staff may be proficient in English, it is very important to have local language translations of all patient related materials (i.e. informed consents, diaries, self assessment scales, etc.). This of course becomes a more complex task with more countries added to the mix.

What cultural elements have to be considered in order to deploy and complete a global trial successfully?

CN: There are many cultural issues that have to be taken into consideration when running a clinical trial. These issues range from the major clinical practice trends in a given country to the preferred way of communication at individual sites.

The study team has to be aware of many cultural differences, which include but is not limited to:

- Differences in practice trends of practicing physicians in that community
- Standard therapies available for the indication being investigated in the countries involved
- Differences in referral patterns to the sites
- Local differences in a patient's acceptance of "experimental" therapies
- Patient's and family's attitudes toward mental illness and

cognitive declines can differ drastically depending on the community standards

- Investigator's approach in presenting the study to the patient
- Degree of education of the site population and the impact on the patient's ability to comply with study procedures (e.g., using electronic diaries, using voice activated systems, filling out self assessment questionnaires, etc.)
- Different levels of sensitivity toward some questions included in standard questionnaires, especially in regards to mental health or sexual function issues
- Different attitudes toward accepting lack of efficacy of certain therapies

MW: Did you know that India has a population of 1.2 billion people? English is spoken by around 100 million people. Hindi is the dominant language, but it is still spoken by just a quarter of the people. In all of India, there are 11 languages that are spoken by more than 25 million people, and a twelfth language is spoken by just under that number. This makes recruiting a patient population challenging since it matters in what part of the country you recruit patients and you have to be prepared to deliver materials in multiple Indic languages.

This takes on added importance when you consider sourcing qualified translators in the market. Over our 10+-year history, we have vast experience translating all types of deliverables including product documentation, software, mobile devices, Web sites, etc., into the Indic languages and working with translators in the market. Indeed, we have over 1,200 employees in India, so we are very knowledgeable about the dynamics of the market. We can tell you that there is very little correlation between the ability to translate a set of how-to instructions for a toaster oven and translating a PRO for a clinical trial. As a result, we put all of our translators through a rigorous testing and certification program that ensures they are truly capable of conducting the highly specialized translations required by clinical trials.

What steps can be taken to mitigate language risks, as well as global trial risks, as a whole?

MW: A certain amount of risk is assumed with any clinical trial, but a major flaw that leads to a negative outcome has to be considered. Clearly risks exist even when conducting trials in English, but the rapid expansion into diverse cultures and language adds so much complexity that it changes the trial risk profile dramatically. And, as noted earlier, the trend toward global clinical trials shows no sign of abating. So, as we have companies rushing to execute global trials, this issue of translation quality has to be addressed. Indeed, as we strive to simultaneously make each trial site "live," the issue of language is as critical as patient screening or any other trial preparatory component.

CN: The experience of the study team (project management, clinical monitors, medical monitors, etc.) in running global trials is a very important factor. This experience allows the team to anticipate challenges and formulate proactive plans to address them. Having a multicultural, multilingual team on the study is essential to explain the local cultural trends and tendencies to the rest of



the team. This input goes a long way in facilitating communications and managing expectations.

The active oversight of senior management on these projects can also help identify potential issues very early in the process and address them before they affect the conduct of the trial. Also, having the senior management support allows the identification and allocation of additional resources that can be critical to the success of these trials.

If I was to ask you what the fundamental starting point is for you in beginning a clinical trial, what would that be?

CN: The fundamental starting point for any trial or functional service engagement is understanding, as completely as possible, the client's needs and expectations. We are in a professional services business. While we rely extensively on world-class systems and standardized, and in many cases, regulated processes; each engagement and client is unique and should be treated that way.

MW: We counsel our clients and partners to consider the translation challenge as part of the decision to offshore the study in the first place. If economic models and risk profiles are built for the trial and the data inputs do not include a true consideration of the cost, complexity and risk of the translation, there exists a real problem. This isn't an area where tasking your marketing team in that country to execute the translation is a viable option. While they may be bilingual, do they truly understand the nuance of the trial and its goals? Do they have the time to go through the PRO in detail and through each of the review steps? We have a rigorous eight-step methodology for preparing material for a clinical trial. We apply this rigor with our global teams to execute this quickly, with very high quality, and by using trained and certified translations.

Companies that are not making these calculations during the planning phases are getting caught short during the execution and causing unnecessary delays and cost overruns.

What future trends do you see for clinical trials?

MW: We are seeing continued growth in demand for China. The dynamics of the market are similar in many respects to India, making it an attractive market to explore for clinical trials. In 2005, the Chinese pharmaceutical market was valued at \$40 billion (U.S.) and will be the fourth largest pharmaceutical market by 2010. The lengthy submission process coupled with the fact that after 2005, all clinical trials must be carried out by sites that have obtained a Good Clinical Practice (GCP) certificate, represent some of the hurdles that must be overcome. In 2006, there were less than 300 GCP sites in China. Clearly, that will not be nearly enough to support the significant increase that is expected in clinical trial activity.

In terms of language challenges in China, given the multiple languages and the real possibility of patients and trial staff having differing dialects, remedial measures may be needed to reconcile these differences in the trial. Indeed, language errors could very well increase the submission/trial cycle. All documentation to the medicine governing body in China (SFDA) will have to be made in Chinese while European and U.S. agencies will require English submissions. This will undoubtedly increase the costs of translation in a trial. All documentation instructing local CRAs (e.g., phlebotomy kit instructions, etc.) will also have to be translated into Chinese, increasing the length of time needed to ramp up a trial.

When qualified resources are scarce, increases in translated document quantities and the need to achieve quality across multiple languages quickly require language translation partners with a global presence in these emerging and challenging markets.

CN: While it depends upon how far in the future you want to look, it's clear there are what we call "mega-trends" as well as "micro-trends" with respect to the next three to five years. With regards to the overall environment globalization, improving the safety of products, searching for efficiency and reducing timelines will continue to be major drivers in the clinical research industry. To a smaller yet still important extent, enhanced post-approval pharmacovigilance, genomics, bio-markers and adaptive design are just some of the areas that will receive increased attention as a result of those drivers.



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CHRIS NOWELL, Vice President of Clinical Trial Management International at Premier Research, began his pharmaceutical career in 1984 in the research pharmacology laboratories of ICI, and since that time has held various positions of increasing seniority and responsibility in both the pharmaceutical company and CRO environment. He entered the clinical research arena when he joined Bayer as a clinical research associate.