Considerations for Efficiently Managing Global Clinical Trials

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According to the Office of Health Economics, "CMRI Data Report," 2011 there has been a 600 percent rise in the cost of drug development from the 1970s to the 2010s. Naturally, pharma companies are looking for ways to increase efficiencies in order to cut development costs while still maintaining the integrity of their clinical trials. One way in which sponsors are doing this is by conducting trials internationally; in fact, a report from Pharma Clinical Trial Services: World Market 2011-2021 predicted that the global clinical trials market will grow more than 50 percent from 2011 to 2015. In this article, we interview Gwen Sunderland, Senior Director, Project Management at SynteractHCR, to discuss important considerations for the conduct of global clinical trials:

Q. What are the advantages of running trials internationally?

A. There are several advantages in running trials internationally and the significant increase in the number of studies conducted internationally is attributable to those advantages. Let's discuss some of the most common:

First of all, the incidence and prevalence of many diseases vary geographically, so that sometimes it is a simple matter of selecting countries where the disease you are studying occurs, or occurs at a much greater rate in comparison to other countries. This can be due to genetic factors, cultural practices, environment, nutrition, etc., or a combination of these factors. So when conducting clinical trials internationally, you can choose to work in countries where the disease you are studying is reportedly more common.

Another advantage is the ability to enroll patients who have not yet participated in clinical trials. In countries where there are many clinical trials conducted but a limited number of patients participating, it can get fairly routine for patients to participate in multiple studies over time. This can make it more difficult to determine the true effect of a single experimental drug; is a change in the patient's condition due to the drug you are testing or is it perhaps long-term effects of a previous drug? It becomes more difficult to understand true treatment effects when the same population is used repeatedly. Another important related factor is that those patients and their doctors, in countries where clinical research is less common, may perceive clinical trials as offering new or otherwise unavailable treatments and they may be more interested in participating.

Third, there can be considerable cost variation between countries in the conduct of clinical trials. In recent years there has been an increasing tendency for sponsor companies to conduct clinical trials in China, India and Eastern Europe. This is in part due to the advantages of working with drug-naive patient populations, as noted above, but also because it is much less expensive to conduct clinical research in these countries. In some cases, the per-patient costs of working in these countries are 30-60 percent less than conducting the same study in the U.S. or Western Europe.

I should point out that in some cases, disease incidence and country costs for research are quite similar, but start-up time, including regulatory approval, varies significantly. In those cases, all other things being equal, sponsor companies may elect to work in countries where trials can be initiated more quickly.

Global studies also allow the participation of countries in which the drug will later be marketed. Regulatory approval may require the participation of that particular patient population within that country or region. Global studies provide physicians in those countries early experience working with the investigational product in their patients, setting the groundwork for regulatory approval in that country.

Finally, in studies involving seasonal diseases, global study conduct spanning varying or alternate climate zones, can allow year-round testing and shorten the time needed to conduct the study.

In summary, the advantages of global studies range from the ability to work where the disease being studied occurs most frequently, the chance to work with drug-naïve patient populations, the ability to have some control over study costs, start-up time, and study duration, to the opportunity to begin work in countries where the drug will later be available and build the knowledge base in those countries.

Q. What are the considerations when planning a global trial, and what are challenges that sponsors might encounter?

A. While there are many advantages in conducting global trials, there are also a number of issues and challenges. The CRO should ensure that a sponsor company is aware of both the benefits and disadvantages; indeed it is the primary responsibility of the CRO to support the client in maximizing the benefits and mitigating study risks, including those specific to global studies.

Perhaps the biggest challenge is the incredible diversity of rules and regulations that govern global trials. Despite many and ongoing attempts to standardize process, each individual country will have its own rules and regulations for study conduct. And in addition, there are separate and often almost equally complex standards regarding the site contracts under which the studies are conducted, including the insurance and legal documentation needed within each country. Complicating matters, these standards are not static but change over time, so it is a continuously changing body of rules. These rules and standards affect the study start-up timelines, which thus differ according to country, and may vary according to the protocol requirements and study population. For example, including pediatric patients will almost always increase the start-up approval time and regulatory complexity, and the use of placebo (as opposed to other available treatments) is often questioned. It is a labyrinth of rules and regulations, and the CRO must provide guidance and support to sponsor clients, so that the process of running a global clinical trial can be navigated in the most efficient and timely manner possible.

After disease incidence and prevalence, another important global study consideration is country standard of care. In this category, we include both the customary medical care provided to patients with the disease being studied (not always an easy thing to assess) and also standard of care during the study, or protocol adherence. When working within a single country or geographic region, there tends to be a natural homogeneity of care, but when multiple countries are involved this can't be assumed. It is important to the accurate analysis and interpretation of study results that the standard of care is taken into account adequately. And, to play devil's advocate for a moment, it is also true that drug approval authorities sometimes like to see that a new drug works well even in different scenarios of background treatment because such variety will inevitably occur later in practice, once the new drug is on the market. So sponsor companies need to consider these different viewpoints when planning their studies and selecting countries.

Patient recruitment on global studies may need to be tailored to each country or region. For example, some common types of recruitment practices used in the U.S. may be seen as intrusive by people in other countries. In short, there will be less "one size fits all" and more customization required on global trials.
It is important to understand the specific concerns of the sponsor when planning any trial, including global trials. But the single most important thing, the one commonality, is to always focus on the goal: a well-run trial with patient rights protected, protocol adherence, and quality data.

Q. What role do feasibility studies play?

A. During feasibility we review our internal indication experience for fit to the proposed study, as well as research the current status of the disease incidence and prevalence, competitive trials, past trial enrollment information, country assessment, clinical/medical review of the protocol, study plan or synopsis (including potential logistical or operational challenges), and where warranted, identify sites and conduct site surveys for further site feedback on the proposed study and enrollment targets.

Feasibility studies allow us to provide the sponsor company with thoughtful feedback on their planned studies, from a perspective of having run thousands of trials. Often a sponsor company will have an incredible knowledge base regarding the particular indication they are researching, but we have the perspective of hundreds of active studies ongoing every day, involving hundreds of employees, regulatory agencies in North and South America, Eastern and Western Europe, the Middle East, and thousands of research sites all over the world.

Finally, since we work in a variety of indications, we have seen and developed all kinds of methods, study designs, and solutions to problems or obstacles with clinical trials. This allows us to brainstorm with the client and offer solutions that may not have occurred to them.

Q. Do language differences create problems?

A. Yes, all information provided to patients must be translated from English (or the originating language) into the patient's native language, or a language in which the patient is fluent. In addition, there is country variation in English fluency among physicians and research staff. This must be identified during site assessment and selection, and study materials translated as required. It is also a consideration during investigator meetings, to ensure that all research staff are appropriately trained and express a clear understanding of the protocol and study requirements. All of these issues are readily addressed, but they add to the cost and complexity of the study.

Q. How are differences in standards of care, cultural or ethical considerations addressed or standardized?

A. These are important considerations. As mentioned, the standard of care for the disease under study is a very important consideration; this is assessed as part of country and site selection. And, as also noted, protocol adherence during the study is critical to the success of the study. This is achieved through the selection of appropriate sites, thorough site training prior to study start and retraining as needed, and confirmed by monitoring oversight during the life of the study.

All study staff must conform to the same ethical standards; ensuring appropriate patients are selected, fully informed, properly consented, and treated per protocol and with full protection of their rights. Study staff must also conform to the standards of their research institutions, regulatory and country regulations, and according to industry standards of Good Clinical Practice.

There will be cultural differences between countries involved in global studies, as I have discussed in regards to patient recruitment, as one example. Some of these do present logistical challenges (such as countries in which August is a holiday month) but as long as the above criteria for standard of care and ethical considerations are met, these are not showstoppers. The primary point is to be aware of cultural differences and to take them into consideration when developing the study plan and timeline.

Q. What are the top 3 or 4 ways to increase efficiencies?

A. One important factor in global trials is to solicit feedback from thought leaders and operational staff in each country/region prior to protocol finalization. Because a considerable amount of translation is required, any protocol changes incur significant work, so it is important that any protocol issues are identified prior to finalization. In the same vein, when doing site selection, choosing sites with English language fluency when available can help to reduce study costs.

The importance of early study planning in running a study efficiently cannot be stressed enough. Global studies are more complex to plan and to manage, and sufficient time for planning must be allocated and time allotted for regulatory feedback and questions. Study timelines and CRO/client expectations need to incorporate regulatory questions and time to respond to these questions.

A final way to increase study efficiency is to ensure that opportunities for site training are maximized. During investigator meeting pre-planning, the sponsor and CRO should identify the critical components of study success, and then ensure these are made clear during the meeting. Too often, meetings are seen as an opportunity to cover every little detail, exceeding the ability of attendees to absorb the information. A wiser strategy is to reduce the information provided, pare it down to essentials, and ensure that this message is clearly delivered. The initiation visit should include a presentation that reiterates these points: this ensures that all sites are trained to the same standards.

Q. If there are regulatory differences between the FDA and international regulatory agencies, how are these resolved or addressed?

A. Yes, there can be differences in how submissions are made and the extent of information required, as well as differences in what the competent authority in each country may expect from a sponsor's development program to obtain affirmative action/marketing approval for the product. Our approach to this reality is to be knowledgeable of the current requirements and expectations of the competent authorities in the regions where the client is planning to file a submission. This is a task that necessitates an ongoing updating of our regulatory awareness across the many regions we operate in, including up to date awareness of new guidance and policies, and supporting our clients in understanding how these affect the conduct of the trials.

It is clear that implementing clinical trials on an international scale is a challenging, complex undertaking. Nevertheless, with careful planning and thought given to the key considerations discussed in this article, conducting trials in multiple countries has the potential to increase efficiencies and potentially reduce the time and cost associated with drug development.

As an international, full-service CRO, SynteractHCR utilizes our intelligent clinical development approach, ICD+, to anticipate requirements and develop the best study plan for the trial, allowing sponsors to get to decision points faster while maintaining a uniform approach to consistent standards and high quality. We recognize potential challenges that arise across various countries, and our clinical experts can help clients overcome them and maximize efficiencies. With a presence in 16 countries around the globe, SynteractHCR will staff trials with local experts and project managers who are trained to deliver high quality results on time and within budget.

About SynteractHCR
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SynteractHCR is a full-service contract research organization with a successful two-decade track record supporting biotechnology, medical device and pharmaceutical companies in all phases of clinical development. With its "Shared Work – Shared Vision" philosophy SynteractHCR provides customized Phase I through IV services collaboratively and cost effectively to ensure on-time delivery of quality data so clients get to decision points faster.

About the Author

Gwen Sunderland is a Senior Director, Project Management at SynteractHCR, and has 20 years of broad-ranging experience in clinical development, strategic and operational planning, and the conduct of international clinical trials. She has been at SynteractHCR for 8 years.