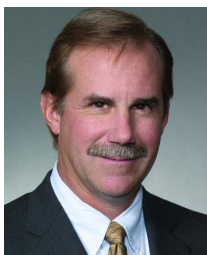




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The Secret to Keeping Phase II Trials on Track? A Targeted Multi-Country Strategy

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Patient enrollment is the single most unpredictable factor in clinical research.

While the average clinical trial seeks to enroll at least one patient per site per month, hitting that target has become increasingly difficult due to the fierce competition that exists in today's drug development environment. This is particularly true for therapeutic areas like analgesia, where an increasing number of compounds advancing through Phase II and III studies, as well as late stage studies for marketed analgesics, are competing for a finite number of investigators and patients.

Add to that the fact that up to 50 percent of screened patients fail to enroll in many analgesia studies, depending on the complexity of the study design, inclusion/exclusion criteria and concomitant medication restrictions. Additionally, many enrolled patients fail to achieve stable analgesia as required during various phases of the study. That all adds up to prolonged, often unpredictable enrollment that can extend the time and cost of your clinical trial for pain, as well as for other indications.

For clinical trial sponsors, delayed timelines and added costs are simply not an option. In recent years, this has become particularly evident in early Phase II trials. Venture-backed biotech companies often depend on that critical proof-of-concept data to close their next tranche of financing. Even multi-national pharmaceutical companies are facing increasing bottom line pressure, and many have strategic portfolio decisions resting on early Phase II outcomes.

Faced with an enrollment bottleneck, some companies will fall back on launching a national media campaign to increase awareness of the trial. This tactic is enormously expensive, and while appropriate for some indications and larger, later phase studies, it seldom is cost effective in early Phase II analgesic trials.

Fortunately, there's an emerging strategy to deal with the increasing competition in North America, where the majority of mid-stage studies are conducted: Implement a targeted multi-country enrollment strategy.

The Benefits of Crossing Borders

Most sponsors don't consider a multi-country strategy in early Phase II because they want to complete their study as quickly and inexpensively as possible. They want to use a limited number of sites and avoid the delays and complexities inherent with identifying sites located in other countries and navigating their regulatory processes. But launching an expensive global program is not the same as selecting a few, carefully chosen countries outside the United States in which to establish a limited number of sites. We have found that these sites often are able to enroll trials twice as fast as U.S. sites, deliver high quality data, and serve as a method of mitigating the risk of not meeting study enrollment timelines.

The main reason that sites outside the United States can often enroll faster is that there are fewer competing trials overseas. A quick search on ClinicalTrials.gov shows 361 osteoarthritis trials in the United States, compared to five in China. And while there are more than 2,000 breast cancer trials listed in the United States, there are fewer than 400 in Germany, France and Russia combined.

But there are other reasons that sites outside the United States tend to enroll quickly, as well. Clinical trials overseas often are conducted through large hospitals, which means a broader population base and a larger site team that can enroll multiple patients simultaneously.

Of course, the United States is and will remain a critical component of most Phase II programs, especially for U.S.-based sponsors. However, the benefits of augmenting U.S. sites with additional sites in two to four other countries extend beyond fast enrollment. Exposing investigators, key opinion leaders and regulators to your product in Phase II can lay the groundwork for a smoother international Phase III program, as well as for registration and marketing in the selected countries.

Sites outside the United States can also serve as a safety net, preventing costly delays caused by unexpected events in the States. Two specific case studies in which a multi-country strategy was prospectively implemented illustrate this point.

In the first example, INC Research conducted a sponsor's Phase II trial in the United States, Germany, India and Russia. Enrollment was proceeding well until the sponsor encountered an unexpected problem importing the product, which was being manufactured overseas, into the United States. Trial sites in the U.S. had to be shut down for four months until the importation issue could be resolved, and only the presence of the sites outside the U.S. allowed enrollment to be completed on time.

In a second example, INC Research ran the sponsor's Phase II study in the United States, Bulgaria, Canada and Romania. In the U.S., dropouts and disqualifications were higher than expected, causing the sites to exhaust their patient populations. While opening additional U.S. sites that late in the game would have proven costly and time consuming, the enrollment from the sites in other countries kept the trial on time and on budget.

Multi-country Phase II trials also can be used strategically to maximize enrollment. A dual-hemisphere strategy obviously makes sense in trials of seasonal flu vaccines, but it can also be effective in trials for acute pain where injuries (such as ankle sprains) can coincide with seasonal sports activities, which are more likely to occur in the summer months when people are outdoors and active.

Experience Overcomes Challenges

As with any strategy, there are challenges to expanding your country exposure in Phase II. Obtaining regulatory clearance in countries outside the U.S. is always time-consuming. To address this, we recommend our customers get U.S. sites up and running as quickly as possible so that the trial can begin, while simultaneously securing regulatory approvals for 10 to 15 additional sites in a few carefully selected countries. This stagger-start method captures both the breaking speed of the U.S. sites and the backstretch boost of the international sites.

There are logistical challenges associated with international trials as well, such as translating protocols and ensuring that the local electronic infrastructure can support patient diaries and online data management. These challenges are easily managed when the CRO has experienced clinical and regulatory teams in place and has operationally proven itself in conducting studies in countries worldwide.

A greater concern among many sponsors is the integrity of data from sites outside the United States. There have been several instances recently in which positive data from ex-U.S. Phase II trials failed to translate in Phase III, creating something of a crisis of confidence in certain foreign countries. A viable solution to this problem is to know your investigators. You cannot walk into a new country blindly. Work with a CRO that has people on the ground in the regions you want to target – make sure they know their investigators personally and that each investigator has a proven track record of conducting similarly designed protocols, executing the required procedures, and delivering clean data.

Cost is also a concern that comes up in discussions of multi-country Phase II trials. But while there are certain extra costs associated with international operations, many sponsors are surprised to find that these costs pay for themselves in terms of more predictable, on-time enrollment. After all, the bottom line is ensuring that actionable data are delivered from the trial on time and within budget, and the cost associated with establishing sites in multiple countries is trivial if it means that bottom line is met.

As a therapeutically focused global contract research organization, INC Research is uniquely qualified to foresee enrollment challenges in clinical trials for pain, cancer, cardiovascular disease, CNS and metabolic disorders, respiratory disease, pediatric conditions and a host of other specialties. Our therapeutic experts then coordinate with our global teams in 40 countries to identify the best international sites for your trial. Add to that our strategic and regulatory consulting expertise, and our Trusted Process – a metrics-driven methodology proven to deliver actionable results – and you've laid the groundwork to make the single most unpredictable part of your clinical trial a little less, well, unpredictable.

To understand how the Analgesia team at INC Research can support your clinical trial needs, please contact Tom Schlagheck at tschlagheck@incresearch.com or visit www.incresearch.com.

About the Author

Dr. Schlagheck's clinical career spans more than 25 years with Procter & Gamble, Endo Pharmaceuticals, and Eastman Kodak Company during which his expertise in analgesic research has supported several sponsors in developing and obtaining regulatory approvals for Investigational New Drug (IND) submissions, Special Protocol Assessments (SPA), and NDAs. He has expertise in global drug development across several therapeutic areas including analgesia, gastrointestinal, respiratory, cardiac, nutrition, and pediatric research. His career responsibilities have included basic clinical research, clinical research management, strategy development, and senior management positions including vice president of clinical operations. Dr. Schlagheck earned a PhD in Physiology from the University of Arizona and completed a Postdoctoral Fellowship at Virginia Tech University. He is the author of numerous scientific articles and Phase I - IV clinical reports and regulatory submissions for the U.S. Food and Drug Administration, and is a frequent lecturer on clinical topics.