

GLOBAL

Patient Recruitment

Patient recruitment has and will continue to evolve in a global marketplace, with all countries competing equally and being measured on performance for the quality of patients screened and recruited within the shortest amount of time.

“The U.S. market was the most developed in terms of patient recruitment and its expertise in patient-directed communications advanced strategic development,” says Liz Moench, president and CEO of MediciGlobal. **“But in certain countries, a U.S. model cannot be applied because of several factors, including regulations and cultural norms that preclude direct-to-patient communications.”**

Vijai Kumar, M.D., president and chief medical officer of Excel Life Sciences, says sponsors need to be aware of both regulatory and cultural differences related to patient recruitment.

“Effective patient recruitment in India is often dramatically different from patient recruitment in more mature clinical research markets, often requiring strong local expertise, day-to-day study support of the right sites, and other more traditional grassroots approaches, as opposed to the PR, design, and technology-based strategies often being used today in the United States and Western Europe,” he says. “Depending on the study, strategies such as patient education and awareness materials might be far less effective than strategies like building a physician-referral network, ensuring that patients have access and transportation to the study site, constant follow up with enrolled patients, and in some cases even having members of the study team, for example the study coordinator, personally picking up and transporting the patient to some study visits. The rapid surge in the telecom network has vastly helped to reach out to all enrolled subjects and this ensures a near 100% compliance.”

Bruce Garrett, M.D., president and CEO of Global Research Services, says China will be the No. 1 country for drug development in the next two to three years.

“This prediction is based on the number of compounds in preclinical development that will be ready for clinical research as well as the need for faster enrollment in large, multi-national trials,” he says. “China-based research centers have access to large numbers of subjects



DR. LEONE ATKINSON • *PTC Therapeutics*

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with common diseases, many of whom have never been treated with Western medications. There also will be continued expansion in India, and the number of trials in the next two to three years in South America will double. The growth in India is due to the large numbers of subjects who have

common diseases such as diabetes and cardiovascular conditions. South America is an untapped market of research subjects who are rapidly aging.”

Aize Smink, executive VP, project management, at Chiltern, agrees that proper assessment of the regulatory hurdles in each country is important because of specific requirements many regulatory bodies have in each country.

“This is specifically true for early phase, placebo-controlled trials as well as for pediatric trials,” he says. “More and more attention is given to safety issues in the protocol population with many questions from authorities and IRB/ECs directed toward this. When building a recruitment plan, use of realistic regulatory and ethics timelines for each country will result in a more accurate projection of recruitment. Where possible, the site should assess real data about where the target patients are for the trial before the study starts, this information can be used to estimate a per-site patient number for the recruitment plan. Contingency planning at the get-go ensures swift implementation when required to enable continued drive toward early patient recruitment.”

Derek Winstanly, MBChB, executive VP, strategic business partnerships, at Quintiles Transnational, also cautions developers about exploiting patients.

**AIZE SMINK** • *Chiltern*

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“Companies and investigators must always be mindful of the principles of ethical and responsible conduct of research: respect for persons, beneficence, and justice,” he says. “This requires far more than obtaining protocol and informed consent approval from an ethics committee. Consideration must be given to what will happen to patients after the study ends. Will approval for the experimental therapy be sought in the country in which trials are being conducted? Is there sufficient healthcare infrastructure in place? And are there qualified investigators in place so that data derived from the trial will be valid and reliable?”

**DR. BRUCE GARRETT** • *Global Research Services*

The downfall of every trial and every CRO/sponsor relationship is poor trial recruitment. When both parties participate fully in the process, the best results are obtained.

“In many countries that are becoming dominant in clinical research, the strong relationship between patients and their physicians greatly facilitates patient enrollment and retention,” Ms. Virk says. “However, there are several factors that must be considered by the sponsor to ensure that ethical standards are maintained globally.

“In many emerging regions, illiteracy is a major obstacle because it creates significant barriers to informed consent,” she continues. “Some countries are addressing this problem by using different means of communication or additional informed consent forms. Furthermore, because of poverty many patients do not have access to medical treatment, which greatly influences their decision to participate in clinical trials. The challenge, then, is to ensure that patient rights are fully protected.”

Raymond Panas, Ph.D., director of international clinical development, Sucampo Pharmaceuticals, stresses that one of the keys to any successful recruitment effort is to reach those patients who can qualify for a study.

“A mobile campaign while successful in Japan could fail in Mexico,” he says. “A television spot in the United States might not have the same impact in India. It is important to understand the market and the form of delivery that is likely to be most successful in a specific region. Cultural variations and cultural understanding of clinical research needs to be considered when recruiting patients in these emerging markets.”

CULTURAL IMPLICATIONS

Enormous language, cultural, political, and socioeconomic differences exist in many of the countries that are becoming primary outsourcing locations for clinical research, says Karen Politis Virk, director of biotech and pharmaceutical research at Language Connections. “These create significant barriers to patient recruitment, especially in obtaining informed consent. In addition, regulatory approval processes and timelines in each country vary considerably. Addressing the differences in each country, therefore, are some of the greatest challenges companies face in recruiting for global clinical trials.”

Global clinical trials are increasingly affected by the regional linguistic and cultural differences associated with a particular potential subject population, Ms. Virk says.

“International clinical research involves unique issues because of the linguistic and cultural diversity of clinical trial participants,” she says. “In some cases, countries with limited clinical research experience may not have established translation equivalents for standard clinical trial terminology in their language(s). Frequently there are multiple language translation requirements, such that multiple versions of the same documents must be provided by the sponsor. In some countries there are regional dialects or several dominant languages that must be taken into account, especially in the translation of informed consent forms.”

Sandra DiGiambattista, project director, clinical operations, periapproval services, at Covance, says language barriers play a role in effectively developing global recruitment tools for use in the trials.

“The same tool would have to have customized language depending on the country,” she says. “Medical standards of care differ among countries making the use of one protocol with the same inclusion-exclusion criteria difficult to adhere to globally. Patients who would be eligible in one country may be automatically given a restricted concomitant medication as standard of care in another country and would not be eligible for the trial.”

Ms. DiGiambattista says doctor-patient relationships also differ according to culture, creating challenges for recruiting patients.

BEST PRACTICES FOR GLOBAL PATIENT RECRUITMENT

- Select countries and sites with experience in conducting clinical trials under GCP guidelines and a track record of successful patient recruitment.
- Have a high-quality clinical monitoring plan to ensure data quality and integrity.
- Include effective on-going communications between the sponsor, the CRO, and the trial site to anticipate and proactively resolve potential logistic and quality issues.
- Make a recruitment plan with realistic and achievable milestones and a contingency plan with well-defined triggers.

Source: Tomás S. Bocanegra, Senior VP, Clinical Development, Daiichi Sankyo Inc.

For more information, visit daiichisankyo-us.com.

ADVOCACY ASSISTANCE

Patient advocacy organizations are critical partners in the recruitment of patients for clinical trials in any country, says Leone Atkinson, M.D., senior director of clinical development at PTC Therapeutics.

“As the operations of advocacy networks outside the United States may vary, it is essential to share clinical-trial information in ways that account for a group’s capabilities and cultural sensitivities, including its method of communication with patients and native language,” she says. “To facilitate patient recruitment for our pivotal Phase IIb clinical trial of ataluren in patients with nonsense mutation Duchenne and Becker muscular dystrophy, PTC tailored clinical trial and disease edu-

cation materials for advocates in 11 countries, including translation into eight languages.”

Dr. Atkinson says a challenge is to ensure that both the clinician and patient communities are well-informed about the study and its enrollment requirements, as soon as possible.

“Participation in a clinical trial is always associated with some burden for patients and their families, so efforts to minimize these burdens may assist in improving enrollment,” she says. “Such efforts include, assisting with travel requirements, arranging for some procedures to be performed at the patients’ home or more local to them, and providing them with tools to help organize and complete study requirements.” ♦

An Approach to Language in GLOBAL Trials



Most international sponsors who conduct multinational clinical trials are aware of the importance of native language communication in clinical research.

Informed consent procedure requires that written consent be translated into the patient’s native language, and any unique cultural aspects be taken into account. In addition, many countries have multiple language translation requirements, depending on the population demographics.

When linguistic differences and key cultural factors are not considered, they can ethically compromise the process of informed consent, decrease patient compliance, and negatively affect patient enrollment. These factors, therefore, must be well-understood before initiating clinical trials in a specific region.

CENTRAL AND EASTERN EUROPE AND RUSSIA

The most dominant Central and Eastern Europe countries in clinical research include many countries that have recently joined the European Union, such as the Czech Republic, Poland, Hungary, Romania, and Bulgaria. Approval for clinical trials in Central and Eastern Europe is divergent and still in flux. No two countries have the same review structure or evaluation procedures for IRBs. In Bulgaria, for example, the local Ethics Committee of the respective clinical site must approve clinical trials, and approval times by the Ministry of Health may average up to nine weeks. In Russia, the Ministry of Health must first issue approval, which usually takes up to two months.

In addition, clinical-trial applications must be reviewed by the

National Ethics Committee, which may take an additional month (Cordab 2006). Currently, the European Union member states are striving to harmonize their regulatory approval procedures.

Following the addition of several Central and Eastern Europe countries to the EU, many physicians proficient in English left in pursuit of better work opportunities in Western Europe. Thus, the rate of English proficiency among investigators has decreased. In addition, English proficiency among subjects in CEE is lower than in Western Europe (European Commission Survey; February 2006).

Each country requires that all documents be translated into its native language(s). Some countries may have multiple language translation requirements, such as Ukraine where both Ukrainian and Russian translations are necessary. Each of these countries has a unique culture that should be considered separately. However, CEE and Russia have some common cultural factors that affect clinical research, especially the patient/physician relationship. In contrast to the United States where patients are more likely to question their physician’s recommendations, the majority of patients in this region are more amenable to following their physician’s suggestions, including the recommendation to participate in clinical trials.

LATIN AMERICA

Argentina, Mexico, and Brazil currently have the most established