

Patient Recruitment in Global Clinical Trials

Highly successful patient recruitment and lower costs in many countries have spurred the surge in globalization of clinical trials. Increasingly, international clinical trials are conducted in developing regions including several countries in Latin America, Central and Eastern Europe (CEE), and Asia. Patient recruitment rates depend on a variety of factors, including each country's total population and the age, gender, genetic diversity, and geographic distribution of the population. Primarily due to their large treatment-naïve patient pools, many emerging regions offer recruitment rates ten times those of the United States and Western Europe (Varawalla 2006). In 2006, the total number of clinical trial subjects in both Western Europe and the United States dropped significantly, accompanied by an increase in the number of clinical trial subjects enrolled in emerging regions (Veryard 2006). The successful initiation of clinical trials in each region, however, largely depends on adequate knowledge of regulatory differences and the ability to overcome language and cultural barriers. With the exponential growth of international clinical research over the past decade, there is an increasing awareness of the importance of these issues.

Enormous language, cultural, political and socioeconomic differences exist among many of the countries that are becoming primary offshoring locations. Every country has a unique set of regulatory bodies responsible for clinical trial approval. Because the Institutional Review Boards (IRBs) and Ethics Committees in each country differ significantly, achieving harmonized ethical review practices in global clinical trials is particularly challenging. Most often local experts and Contract Research Organizations (CROs) with experience in a particular country or region provide guidance for companies interested in conducting clinical trials in a newly emerging region. Sponsors commonly seek the expertise of local professional translators with backgrounds in clinical research because they are well equipped to deal with local regulatory authorities, are familiar with the terminology, and can better address the language and cultural hurdles specific to that region. As many emerging countries gain more experience in clinical research, and ethical standards are better established, regulatory approval processes are becoming more efficient and predictable.

An Approach to Language and Cultural Aspects

According to the Tufts Center for the Study of Drug Development, over 40% of U.S.-regulated clinical trials are currently being conducted in emerging regions of the world (Mahalakshmi and Chowdhary 2008). Thus, there is a growing need to address issues pertinent to global clinical trials. In 2001, the former Inspector General of the U.S. Department of Health and Human Services (DHHS), Janet Rehnquist, released a report entitled "The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects". The report's main objective was to improve protection for participants in international clinical trials. Because a major component of subject protection for most IRBs and Ethics Committees is the language and cultural content of patient informed consent forms (ICFs), one of the most common reasons for delays includes problems with informed consent. Therefore, this is an important consideration for companies planning to conduct international clinical trials. Furthermore, understanding the local culture is critical in dealing appropriately with local regulatory authorities.

Most international sponsors who conduct multinational clinical trials are aware of the importance of language in the recruitment process. Informed consent procedures require that written consent be translated into the patient's native language and any unique cultural aspects be taken into account. Companies that specialize in global patient-recruitment strategies, such as BBK Worldwide, have established the need for culturally adapted methods to facilitate subject enrollment and ensure that ethical standards are maintained.

In addition to native language translation, many countries require multiple language translations, depending on the population demographics. When sponsors do not consider linguistic differences and key cultural factors they can ethically compromise the process of informed consent and decrease patient compliance. These factors, therefore, must be well understood before initiating clinical trials in a specific region.

CEE and Russia.

This region has one of the highest patient-recruitment rates among emerging regions (Platonov 2003). In many CEE countries and Russia, a primary factor in this rapid patient enrollment is the centralized healthcare systems. Because of centralized healthcare patients are separated into specific disease groups and are primarily treated in major hospitals, providing access to large subject numbers.

Among the fifteen CEE countries, currently ten are European Union (EU) member states. The most dominant CEE countries in clinical research include many countries that have recently joined the EU, such as the Czech Republic, Poland, Hungary, Romania, and Bulgaria. All EU member states follow the EU Clinical Trials Directive which was designed to harmonize clinical research practices for subject recruitment and improve patient protection, while aligning clinical research conducted in the EU with international standards. Many CEE countries that joined the EU more recently are at different stages of implementing the Directive.

The requirements for initiating clinical trials in CEE are less well defined than in Western Europe (Motteram and Richardson 2004). For example, there may be undocumented requirements and additional regulations that must be met in parallel with the usual clinical trial approvals. Most CEE countries complete approvals within 60 to 70 days (Getz 2007), and in addition to the national Ethics Committees, there are local committees in many major medical centers. However, no two countries have the same review process or evaluation procedures for IRBs. In Bulgaria, for example, the local Ethics Committee of the respective clinical site approves clinical trials, and approval by the Ministry of Health may take an average of nine weeks. In the Czech Republic, regulatory approval by the Ministry of Health takes up to two months, and both a local Ethics Committee (in major healthcare facilities) and the Central Ethics Committee (established by Ministry of Health) approve clinical trial applications. In Russia, the Ministry of Health issues approval which usually takes up to two months. Clinical trial applications are also reviewed by the National Ethics Committee, which requires another month. (Kordab 2006). Currently, the European Union member states are striving to harmonize their regulatory approval procedures.

After several CEE countries joined the EU, many CEE physicians proficient in English left to pursue better work opportunities in Western Europe. As a result, the number of investigators proficient in English has decreased. Furthermore, according to a 2006 European Commission survey of English proficiency among EU citizens, proficiency in CEE is reportedly lower than in Western Europe. This means that English proficiency is also lower among patients in CEE. According to the EU Directive, all patient-related materials including informed consent must be translated into the patient's own language.

In addition to the language differences of CEE countries, each has a unique culture which must be taken into consideration. CEE and Russia also have common cultural factors that affect clinical research. For example, the patient-physician relationship in the United States is such that patients are more likely to question their physician's recommendations (only one-third of patients enrolled in U.S. clinical trials result from physician referrals (Kremidas 2007)). In contrast, in CEE and Russia, the majority of patients are motivated to participate in clinical trials solely by the influence and encouragement of their treating physicians. There is a strong relationship of trust that exists between the patient and physician in CEE and Russia, in addition to a high regard for doctors in general. According to Natalie Gershman, CEO and medical director of Geny Research, a Russian-based CRO in Moscow, this relationship significantly helps to increase subject enrollment and retention rates, and improves patient compliance (2008 interview with Language Connections). That many patients have not had the chance to benefit from the most recent advances in medical care is another factor which affects patient enrollment in CEE and Russia. Participation in clinical trials therefore provides an opportunity to receive the latest medical treatments for their disease.

Latin America.

Argentina, Mexico, and Brazil, which currently have the most established regulatory environments in the region, conduct the largest number of clinical trials. The majority of patient populations in these countries reside in highly populated urban centers, which greatly facilitates recruitment. In most Latin American countries, the approval times from the Ministries of Health range from 30 to 90 days. Mexico and Brazil continue to have the lengthiest approval times (Gambrill 2006), although both governments are committed to improving the situation. Approvals from the majority of Ethics Committees or IRBs typically range from 30 to 60 days (Glancszpigel 2003). Most Latin American regulatory bodies are working to shorten their approval times. Furthermore, recent government support in many countries has led to regulatory reforms and increased compliance with international clinical research standards.

In most Latin America countries, clinical trial documents must be translated into Spanish, with the exception of Portuguese in Brazil. Most investigators are proficient in both Spanish and English. However, among patient populations English proficiency may be low, and differences in spoken Spanish exist because of influences from the dominant native and immigrant groups in each country or geographic region. The differences between countries in Latin America, as well as local regional differences within each, must be considered separately. For example, Argentine Spanish has certain linguistic

distinctions from other Spanish-speaking countries such as Mexico because of cultural differences (ie. the use of *voseo* in Argentina versus *tu* in Mexico). Pronunciation and local native culture in Mexico City is different from those in Mexico's Yucatan Peninsula. Although these are primarily spoken differences, some linguistic and cultural differences must be considered for their effect on patient recruitment and informed consent procedures.

Other factors that compromise informed consent procedures and affect patient recruitment in the region are poverty and illiteracy. In order to improve patient protection, some countries have increased requirements. For example, in Mexico it is common for subjects to sign a second informed consent form that is written in simpler language and includes the signatures of two witnesses and their relationship to the patient (Fiuza 2006). Taking into account patient differences in literacy, as well as regional variations in spoken Spanish, further ensures that patients' rights are adequately protected.

The emphasis on family in Latin American culture and family decision making on medical treatment must also be considered. Like patients in CEE and Russia, patients in Latin America do not often question their physicians' recommendations. As 80% of subjects in Latin America are offered enrollment by their physician, this greatly influences their decision to enroll in clinical trials (Fiuza 2006). In addition, economic factors play a significant role for many patient populations in Latin America, as many patients have no other treatment options available to them.

India, China, and Southeast Asia.

Among the Asian countries most prominent in clinical research, South Korea and Singapore currently have the most efficient and predictable systems for regulatory approval. For example, the process in South Korea is so streamlined that approval by the Korea Food and Drug Administration (KFDA) can be completed within one month. The IRB approval occurs in parallel, further facilitating the process. In Singapore, the average regulatory approval period is four weeks, followed by an additional four to six weeks for site-level IRB/Ethics Committee approval. Although both China and India have recently become primary offshoring locations because of their extensive recruitment capabilities, their regulatory approval times differ greatly. China currently has the longest approval time in the region (and possibly in any emerging country), up to nine months, because clinical trial applications must pass through six regulatory approval bodies. In India the average time for regulatory approval is 10 to 16 weeks. The approval process with local Ethics Committees at the site level occurs in parallel, facilitating the initiation of clinical trials (Varawalla 2006).

Although English is considered a second language in the majority of Asian countries involved in clinical research, many of the less-educated subject populations have limited proficiency in the language. Despite the prevalence of English in India, for example, English proficiency is low among many clinical trial subjects, and several other languages such as Hindi are dominant among much of the population. In China, low English proficiency among the majority of Chinese subjects is an even greater issue. In addition to Mandarin Chinese, there are several other secondary languages.

The proficiency among investigators is less an issue, as both China and India have an increasing number of well-educated scientists who are proficient in English. However, in China, many investigators often record data in Mandarin, resulting in delays due to translation time. China's rapid recruitment rates due to a large patient pool, centralized healthcare institutions, and highly successful recruitment based on physician-patient communication compensate for the lengthy approval process and translation requirements (Bailey et al. 2007). Although they have been found to be less effective, posters and fliers in waiting rooms at accredited clinical trial sites are also common (Anderson 2007). In India subject recruitment through patient education and advertising is more accepted. Despite concerns regarding India's ethical and clinical research standards, the country's increasing role in clinical data management outsourcing has resulted in a better overall environment for clinical research (Bailey et al. 2007), and some projected data indicates that by 2011 India will be conducting more than 15% of the total global clinical trials (Research and Markets Report 2007).

In accordance with the culture in many Asian countries, it is considered less acceptable for physicians to disclose a patient's complete diagnosis, particularly in the case of terminally ill patients. As a result, physicians often only partially disclose potential risks to study participants. Family hierarchy also plays a major role. The more-senior family members, particularly males, are generally responsible for making decisions about medical issues. In most Asian cultures, the patient-physician relationship is different from that in Western cultures. Recommended participation in clinical trials is more widely accepted than in the United States, which facilitates patient recruitment and retention rates, and improves patient compliance. In India, China, and several other countries in Southeast Asia, economic factors and access to medical care also play a pivotal role in patient recruitment.

Conclusions

As the demand increases for greater patient diversity and more subjects are needed for clinical trials, the ability to optimize recruitment capabilities while avoiding costly and unnecessary delays is critical. In order to successfully conduct global clinical trials, biopharmaceutical companies outsourcing clinical research must take into account linguistic and cultural differences. Companies that specialize in global clinical trial management currently face the challenge of providing expert services around the world. They must provide biopharmaceutical companies with quality translators who are experienced in clinical research, are native speakers immersed in the local culture, and are familiar with the local regulatory

environments. Biopharmaceutical companies that do not have international experience greatly rely on such expertise to help them navigate their way in a region, and those that are already outsourcing clinical research understand the importance of cultural adaptation and linguistic accuracy. Access to these resources will ultimately determine the ability to adequately meet individual requirements for regulatory approval, as well as a company's overall success rate in international clinical trials. Overcoming language and cultural barriers, once secondary in the clinical trials process, has become a mainstream effort.

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