

CLINICAL TRIALS IN CENTRAL & EASTERN EUROPE: The Challenge of Dealing with Multiple Languages & Cultures

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As costs for drug development in the United States (U.S.) increase, pharmaceutical and biotech companies are increasingly considering clinical studies abroad. This is in large part due to the fact that many countries can conduct clinical trials at a lower cost than the U.S. because of their ability to recruit large numbers of eligible subjects. One of these newly emerging regions for conducting international clinical trials is Central and Eastern Europe (CEE). CEE consists of nineteen countries including Poland, Romania, Bulgaria, Hungary, the Czech Republic, and countries of the former Soviet Union such as Russia and Ukraine. Recently, ten CEE countries joined the European Union (EU), and clinical research in these countries is currently being conducted in accordance with international regulatory standards. Russia and Ukraine have also adopted international regulatory guidelines. In addition to regulatory differences, many additional factors play a role in the success of clinical research at international sites, including differences in medical practices, language, and culture. Although some of these issues are well understood, the importance of language is often underestimated. This is especially the case throughout countries of the EU, where there are more than twenty official languages.

The European Union (EU)

The EU is a political, economic community made up of twenty seven member states, each representing a unique set of cultural traits and native language(s). Since its formation in 1993, and the establishment of the European Commission which unified legislative procedures, there has been a concerted effort to facilitate the growth of pharmaceutical and biotech industries. More specifically, the establishment of ICH-GCP guidelines for international clinical research standardized regulatory procedures among countries of the EU, Japan, and the U.S. In 2004, the EU implemented the European Clinical Trial Directive to further assure consistency, quality, and safety in the drug approval process. Although regulatory differences still exist in the interpretation and application of the European Clinical Trial Directive throughout the EU, within the next few years these differences are expected to diminish. The CEE countries which more recently joined the EU are still in the process of implementing the European Clinical Trial Directive. Western Europe is already well-established in clinical research, with countries such as the United Kingdom, Germany, France, the

Netherlands, Italy, and Spain responsible for the majority of clinical research in this region. Because of their compliance to ICH-GCP standards, the quality of clinical research in these countries is relatively high. However, the cost of conducting clinical trials and insufficient subject enrollment rates are forcing companies to consider outsourcing to other parts of Europe. In fact, 43% of Western European sites, and 45% of United States sites, report delays due to enrollment and recruitment problems (1). As more CEE countries join the EU (Estonia, Czech Republic, Hungary, Latvia, Lithuania, Poland, Slovakia, Slovenia all joined the EU in 2004, and Romania and Bulgaria are new members as of 2007), companies are (2) increasingly taking advantage of their ability to conduct high-quality clinical research at a significantly lower cost than in the U.S. and Western Europe. Russia and Ukraine have also emerged as new clinical trial locations due to the many advantages of conducting research in these countries.

Advantages of Central and Eastern Europe (CEE)

Clinical research in CEE has been steadily growing, with the number of new trials in this region more than doubling particularly over the past five years (1). Countries such as Poland, Hungary, the Czech Republic, Ukraine, and Russia are already playing an important role in clinical research and are becoming major locations for outsourcing of clinical trials. This is due to the presence of large, untreated patient populations located near urban centers, highly specialized treatment centers set up by the previous medical system, the existence of a centralized healthcare system, and the availability of well educated investigators in these countries. Importantly, it is also related to the solid reputation of clinical research in this region, considered to be equivalent to U.S. and Western European standards. Many countries in CEE offer excellent technological infrastructure which facilitates new data collection methods such as electronic data capture. Typically, Phase II and III clinical trials are the most common in CEE countries because of the large numbers of patient pools associated with these types of clinical trials. Another advantage to conducting clinical trials in CEE is the prevalence of specific patient populations which are no longer present in the West. These patients are treated in large, specialized medical centers, which reduces the need for numerous, multi-center sites. The primary disease areas for study include oncology, cardiology, rheumatology hypertension, arthritis, and neurology. Finally, long term clinical studies are attractive in this region because of the population's geographic stability which allows for patient follow-up. The reasons for outsourcing clinical research to CEE countries are numerous. The challenge of native language communication in these countries, as with outsourcing in any non-native English speaking country (including most Western European countries), must be taken into careful consideration. Although the English proficiency of many clinical investigators may be relatively high in some CEE countries, this should not be taken for granted. Furthermore, throughout Europe regulatory documents must be translated into local languages for submission to local regulatory authorities. Finally, many patients may not be fluent in English, and therefore relevant study materials are normally translated into the patient's native language. This means that informed consent forms,

patient diaries, and other relevant patient information materials are consistently provided to the patient in their native language. Ultimately, it is the accuracy of these translations will determine the quality and success of clinical research in these regions.

Language Barriers in Clinical Research

Czech Republic: Among countries in CEE, the Czech Republic is currently one of the most dominant clinical trial markets. With a population of approximately 10.2 million, reportedly good compliance to ICH-GCP guidelines, and the presence of highly qualified (3) clinical investigators, the Czech Republic offers a good environment to perform clinical trials. As with the former political system, the larger hospitals and academic medical centers are funded by the state. Clinical research is principally carried out in university hospitals within major cities such as Prague. However, language is still a major issue as English proficiency in the Czech Republic is not consistently high, even in these urban areas (2). Furthermore, regulatory documentation must be submitted in the Czech language for local regulatory authorities.

Poland: According to CenterWatch, in 2006 the number of clinical trials in Poland reached 8.7 per million people (4). A population size of 38 million, recruitment rates reportedly twice those in Western Europe, the availability of investigational sites at teaching hospitals, and the presence of well-educated investigators are some of the major factors which make Poland attractive for clinical research. Most clinical sites are located within academic centers of major cities, produce quality research, and comply with current ICH-GCP standards. However, since Poland's entrance into the EU, many well educated physicians who are fluent in English have recently immigrated to other Western European countries which can provide them with better salaries. Thus, the availability of investigators who are English proficient has decreased (3). Furthermore, all regulatory documentation must be translated into Polish for EC approval.

Ukraine: Ukraine has a population of about 50 million, extensive healthcare facilities, physicians are that are highly trained, and excellent subject recruitment rates. Clinical trials in the Ukraine are conducted in accordance with ICH-GCP requirements, despite the fact that it is not a member of the EU. However, language barriers are still being overcome. The fact that there are two official languages in the Ukraine, Russian and Ukrainian, further complicates the translation of study documents. Furthermore, English proficiency even among clinical investigators is not adequate to eliminate the need for interpreters and translation in clinical trials (4).

Russia: Russia is another country in this region which has experienced a significant amount of growth in clinical trials. Currently, Russia ranks third among the top emerging countries for clinical research according to recent statistics. In order to comply with international standards of clinical research, a Russian language version of ICH-GCP guidelines has been established in Russian clinical

trials since 1999. With a population of 144 million people, (over 14 million in both Moscow and St Petersburg alone), Russia's role in clinical research is due largely to successful recruitment. In fact, patient recruitment in Russia is reportedly ten times faster than in the U.S (5). This is reflected in the number of approved clinical trials in Russia which nearly doubled between 2000 and 2006, while the number of participants in global clinical studies tripled between 2002 and 2006 (6). Russia's main growth in clinical research is reportedly due to an increase in international, multi-center sites in the region. However, language is still an issue here, as the most commonly spoken language in hospitals where most clinical research is conducted is Russian. Furthermore, all regulatory documentation must be translated into Russian, with translations back into English and other languages for EU and FDA regulatory approval. In addition to language, cultural differences which affect clinical research should be taken into account. For example, the labeling of medical supplies may (4) be considered advertising in certain countries of CEE including Russia. The barriers to conducting clinical research in this region must be well understood. According to a survey regarding English proficiency among members of the EU, only thirty eight percent of EU citizens reported that they possess adequate communication skills in English (European Commission Survey; Feb, 2006). This is despite the fact that English is taught as a second language in many European schools. Furthermore, the percent of people who speak English as a second language varies throughout the region, with countries in CEE reporting significantly lower percentages than Western European countries. Thus, in all of these countries, language barriers remain a key issue. Importantly, most EU countries require that all necessary regulatory documents for clinical trials be translated into their own respective native language. This holds true for all CEE countries including Russia and the Ukraine, where multinational trials must be conducted in several languages. The accurate translation of regulatory documents by native speakers who are knowledgeable about both regulatory issues in the EU as well as FDA requirements can provide the best solution to overcoming any language barriers. In addition to the importance of quality translation for regulatory documents, the successful completion of international clinical trials relies heavily on clear communication between study participants and investigators. Furthermore, investigators must clearly understand the clinical study protocols which they are expected to follow, while the process of patient informed consent and accuracy of patient information can also be greatly compromised by language barriers. For this reason, summaries of clinical study protocols and patient-oriented information are translated into respective native languages throughout CEE. In Russia, the entire study protocol is translated into Russian for local regulatory authorities. However, the quality and accuracy of these translations is of primary importance as poor translations can result in approval delays, produce inaccurate results, ethically compromise the process of informed consent, and adversely affect the outcome of a clinical study.

The issue of language is as important as that of culture when dealing with a region that is composed of many cultures. Despite the geographic proximity of CEE countries, there are important cultural differences between these countries,

such as the patient/physician relationship, which may affect clinical research and should be taken into consideration (7). The impact these cultural factors may have on clinical research must be addressed when outsourcing clinical trials to CEE. With the number of clinical research organizations (CROs) in these regions quickly growing to meet current needs, there is an even greater incentive to overcome language and cultural barriers.

Conclusions

CEE and Russia are quickly becoming important areas for clinical research as the demand for higher subject enrollment within a shorter time frame continues to grow. Since 2000, the number of clinical trials in CEE increased by twelve percent per year as compared with eight percent worldwide, and in Russia the growth rate reached an even higher eighteen percent (8). The advantage of conducting quality research at a lower cost in this region is definitely a major factor. "There is no alternative to streamlining research (5) and development departments", said GlaxoSmithKline chief executive Jean-Pierre Garner when asked about the company's current trends in CEE countries such as Poland, "We are trying to move thirty percent of our clinical trials to low-cost countries"(9). Outsourcing to emerging markets such as CEE will continue to increase as U.S. biotech and pharmaceutical companies look abroad for solutions to their development costs and recruitment problems. In order to ensure the high quality of international clinical trials, an understanding of the cultural differences which affect clinical research along with the implementation of accurate native language translation is crucial. Successful clinical trial management in this region of many languages and cultures requires high expertise in translation and localization strategies.

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