

Understanding Asia: linguistic & cultural considerations Outsourcing Clinical Trials to Asia

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The cost of conducting clinical research in North America and Western Europe is steadily escalating — due in large part to difficulties associated with subject recruitment and exorbitant development costs — forcing pharmaceutical and biotech companies to look for solutions in emerging markets. Reportedly up to forty percent of product development costs are incurred during the clinical trial process. It is therefore understandable that companies are increasingly outsourcing clinical research to countries where costs are significantly reduced. Many emerging regions produce quality research and can boast higher patient recruitment rates and reduced drug development costs, compared to North America and Western Europe. Among emerging regions, Asia is quickly becoming a dominant outsourcing location. Phase III clinical trials, in particular, are moving to emerging markets in Asia due to the growing demand for multiple trials, and larger, more genetically diverse subject pools (1).

The Asian Advantage Several Asian countries, especially India and China, have become prominent outsourcing locations for clinical research. The number of clinical trials outsourced to Asia has increased tremendously over the past few years - between 2005 and 2006 alone, clinical trials conducted in Asian-Pacific countries increased by 50% (2). In addition to significantly lower clinical research costs, the region offers the advantage of a genetically diverse population of over 4 billion, many of whom have never been treated for their condition. Thus, subject recruitment is easily facilitated, and the enrollment requirements are more readily met. Furthermore, due to changes in lifestyle, many Asian populations are experiencing a higher incidence of diseases once prevalent in more developed Western countries. India, for example, has an increasingly large population of diabetes patients. As a result, clinical studies include a wide range of therapeutic areas.

There are several factors responsible for successful patient recruitment in Asia. While the large, urban patient populations in these countries play a major role, the patient-physician relationship is another important factor. Asian cultures tend to treat their relationships largely based on professional position, gender, and age. Physicians are highly respected, and patients often readily accept their physician's recommendation to participate in clinical trials as a course of treatment. This factor greatly facilitates patient enrolment, as well as patient retention and compliance. Limited healthcare access, especially for cutting edge treatments, is often another influencing factor in patient enrolment. Once again, however, sponsors must be aware of ethical concerns regarding informed consent (see *Socio-economic Factors* section below).

In addition to a large patient population, there is an abundance of highly skilled investigators in the region, many of whom have been educated in the West. Most international clinical trial sites are located in major urban centers, where IT and infrastructure are more established, and there is access to large patient populations. Other factors which facilitate foreign-sponsored clinical research in Asia include high English proficiency and improved regulatory systems. Several Asian countries dominant in clinical research speak English as a second language, and in some countries, such as India, Singapore, Hong Kong, and the Philippines, English is one of the official languages. In these countries, especially among the educated classes, English proficiency is high. As the biopharmaceutical industry becomes more established in these emerging countries, efforts to streamline the regulatory processes and improve transparency have further facilitated growth in the clinical trial sector. Finally, the adoption of ICH-GCP guidelines in many Asian countries has encouraged foreign sponsors to increase outsourcing of clinical trials in the region. However, outsourcing clinical trials to Asia introduces new complications that must be addressed, including vast differences in regulatory procedure, language, culture, medical practices, and socio-economic development. Therefore, despite the advantages of outsourcing to Asia, several challenges remain.

Regulatory Issues Addressing regulatory differences has always been a primary concern for foreign sponsors conducting clinical research in Asia. However, the establishment of a growing number of Contract Research Organizations (CROs) in many Asian countries, such as South Korea and Hong Kong, has helped to ease some of the difficulties associated with conducting multinational trials in the region. Furthermore, several Asian countries have successfully streamlined their regulatory approval processes, including South Korea, Taiwan, Singapore, and Hong Kong, and currently have comparable timelines (averaging between one to three months) with Western Europe and North America. These countries have shortened their timelines by allowing parallel submission of clinical trial applications to both IRBs and regulatory agencies at the same time. To date, Singapore and South Korea have the most streamlined and efficient regulatory systems among Asian countries dominant in clinical research. In India, under the more recently established Schedule Y system, approval for Type A or clinical trials that have been previously approved in developed countries including the United States, Europe, and Japan, it usually takes about three months. For Type B, or all clinical trials not in the previous category, it may take considerably longer. Despite attempts to streamline regulations to align the country with international standards, China continues to have one of the longest approval times – in some cases approval make take up to nine months as a result of individual submissions to several separate regulatory bodies (see Table 1).

Although in some cases, the lack of sufficiently trained clinical research staff and IRB personnel has been a problem, many Asian countries are increasingly participating in a growing number of training programs. Despite increased transparency, issues of corruption and bureaucracy continue to pose a problem, especially in India and China. However, the regulatory environment is expected to improve significantly with the opening of U.S. FDA offices in both of these countries. In addition, India's newly established centralized government agency is expected to better monitor clinical trial activity. On the other hand, South Korea, Singapore, Hong Kong, and Taiwan have made rapid improvements as a result of strict new regulations, government financial incentives, and efforts from the local pharmaceutical and biotech industries. Japan and Hong Kong are both officially ICH-GCP members (Japan being one of the original

members along with countries of the European Union and the United States), while other countries in Asia have adopted their own version of GCP guidelines, such as South Korea and Malaysia. South Korea, which implemented its own revised version in 2002, has one of the most recently established regulatory systems in the region for foreign-sponsored clinical trials. However, the country's regulatory system has progressed rapidly to meet growing demands, and has served as a model for others.

Language, Translation, & Localization The importance of addressing language and cultural barriers is commonly underestimated in international clinical trials. Although English is considered a second language in the majority of Asian countries involved in clinical research, this is not so for many of the less educated patient populations. Thus, even in those Asian countries where English is widespread, many language barriers still exist. Translation requirements for regulatory documents vary (in some Asian countries protocols may be submitted in English); however, all patient-related information must be translated into the language of the patient population. In addition, important cultural differences exist in each of these countries, and in some cases there are significant differences among ethnic populations within the same country. These cultural factors must be taken into account in the translation of patient information, as well as for their effects on medical practices relative to Western countries outsourcing in the region.

As with all international clinical trials, regulatory documents, especially patient information, must be translated into the native language of the target patient population. In some countries, regulatory documents must be translated solely into the country's official language. In Korea, for example, there is only one language requirement, since the official language, the Korean dialect spoken in Seoul, is well understood by the majority of the population. Cantonese, the official Chinese language of Hong Kong, is spoken by the majority of the ethnic Chinese population (95%), although one-third of the population also speaks the other official language, English (British). Although Japan has a single translation requirement, the written form of the Japanese language uses a Kanji script which is composed of 20,000 unique characters. This has posed new challenges due to the fact that it is difficult to convert to electronic data capture.

In China, where Mandarin Chinese (850 million speakers) alone is the official language, and the only written form of the language, there are several other dominant languages spoken throughout the country, including Shanghainese (90 million speakers), Min or Taiwanese (70 million speakers), and Cantonese (70 million speakers). Despite English proficiency among Chinese scientists that have been educated in the West, the majority of the Chinese population is not fluent in English or other languages. In addition, depending on the level of literacy, proficiency in the written Mandarin language varies. Moreover, there are two character types of written Mandarin, and depending on the population, translators must know which one to use. In mainland China, the original or Traditional Mandarin characters were changed in an attempt to simplify the writing system, and Simplified Mandarin characters are now used. In Taiwan and Hong Kong, Traditional characters remain the most common form of writing. The situation is further complicated by pre-existing linguistic differences between the respective users of Simplified and Traditional characters. For example, in mainland China, a bicycle is a "zi xing che" (self-propelled vehicle) while in Taiwan it is a "jiao ta che" (foot-pedaled vehicle). As a result, when someone from mainland China writes "bicycle", he writes with Simplified characters and uses a different Chinese word than his Taiwanese counterpart. Furthermore, although the two written character sets correlate with each other, only well-

educated populations are fluent in both. (Translations were graciously provided by a Chinese to English translator).

In some Asian countries, multiple language translations are required. In India, for example, where there are several official languages (including English), there are numerous regional languages and dialects that must be considered. To complicate matters further, each state is allowed to define its own number of official languages, although the central Indian government has currently recognized twenty-one. In addition to Hindi, which is spoken by one-fourth of the population, there are at least ten other Indian languages with more than 25 million speakers each. In the Philippines, where English and Filipino are the official languages, there are over eight additional dialects that are dominant among significant portions of the population. Although international clinical sites are primarily located in major urban centers, because of urbanization trends, there are significant numbers of speakers of minority languages or regional dialects in major cities. Thus, a closer look at the complex linguistic challenges among Asian countries dominant in clinical research leads to a better understanding the importance of translation (see Table 1).

Quality, accurate translation is a key element in the success of global clinical trials, and involves more than just simple translation from a source language into a target language. The translated text must also be culturally adapted in order to avoid being misconstrued. It must take into account the cultural context of the patient population for which it is intended. Back translations are also performed in order to ensure that the translation has been done accurately. Inconsistent and inaccurate translations can potentially introduce serious problems, including delays in the initiation or completion of a clinical study. In addition, poor translation can affect data interpretation, ethically compromise the process of informed consent, interfere with the reporting of adverse events, and compromise the safety of trial participants. Finally, cultural context is also an important factor in dealing with regulatory authorities and IRBs in a particular country. These issues can be overcome to a large extent with proper clinical trial management. Successful translations must therefore be performed by professionals who are native speakers, are familiar with the culture, and have a professional background in clinical research. Language service providers with experience in a specific country are best equipped to help overcome any linguistic or cultural barriers.

Culture and Medical Practices In addition to culturally adapting regulatory documents, the effect that cultural attitudes have on medical practices must also be taken into account. Asian culture propagates a holistic view of the mind, body, and spirit in maintaining wellness, in contrast to Western societies which primarily base health on the physical being. As a result of these cultural perceptions, there are important differences in medical practices. For example, physicians in Asian cultures tend to shield their patients from information which they believe will interfere with the positive outcome of a treatment. Studies with Asian American patients have shown that it is common for terminally ill patients, such as cancer patients, to be unaware of their full disease status (3& 4). For this reason, physicians may not reveal all of the potential risks associated with a particular clinical trial. It is more common in Asian cultures for physicians to disclose full information to the patient's family, and for family members to make medical decisions rather than the individual patient.

Other cultural factors may affect patient perception of symptoms, and thus the reporting of such clinical data. For example, there are culturally perceived differences in pain

tolerance between Asian populations and many Western cultures. Cancer studies involving Asian American patients have shown that Asians tend to under-report pain due to the cultural belief that it must be accepted as part of their disease (5). These factors must be taken into account for accurate interpretation of patient-reported data.

Finally, traditional herbal medicines and natural therapies have been in use for centuries in Asia. Many are commonly used today to relieve pain, reduce symptoms, and treat diseases ranging from rheumatoid arthritis to gastrointestinal diseases. Two well-known examples, acupuncture and the herbal medicine Ginseng, are common practice in China, Taiwan, and South Korea. In India, Ayurvedic medicine (healing through the use of natural, herbal medicine) is also quite common. In many Southeast Asian countries, the use of local traditional herbal and natural medicines is also well established. Asian patients commonly use traditional medicines and therapies in conjunction with Western medicine. Foreign sponsors must take into account possible interference or synergistic effects with the drug or treatment undergoing testing, and ask clinical investigators to report these practices.

Socio-economic Factors In addition to cultural factors, socio-economic factors play an important role in patient enrolment in many Asian countries. Among Asian countries dominant in clinical research, there is a vast range in healthcare systems and government regulations. These countries can therefore be categorized according to the stage and degree of development of these systems (see Table 1):

1. Category 1: Countries with a well-developed healthcare system and regulatory standards equivalent to Western developed nations (this category includes only Japan – although Japan is the most established clinical trial market in Asia, the cost of research is comparably high due largely to strict government healthcare regulations)
2. Category 2: Countries with well-developed healthcare systems and regulatory standards comparable to Western developed nations (Taiwan, Singapore, South Korea, and Hong Kong – research in these countries is high quality at reduced costs compared to the West)
3. Category 3: Countries whose healthcare systems are not quite as highly developed as those of the wealthier Asian countries in the previous two categories, and whose standards are evolving (India, China, and countries in Southeast Asia including Indonesia, Malaysia, Philippines, and Thailand – the cost of clinical research in these countries is reportedly 2/3 lower than in the West largely due to lower wages).

Especially for countries belonging to the last category, sponsors must be aware of socio-economic factors that affect clinical research. In these Southeast Asian countries, because of low economic status, a large portion of the population does not have adequate access to healthcare. As a result, participation in clinical trials may be the only opportunity for many patients to receive up-to-date treatment, or in some cases, any treatment at all. Foreign sponsors must therefore make an effort to ensure that investigators maintain international ethical standards.

Differences in patient literacy rates are another factor that must be considered, especially in the process of obtaining informed consent. Throughout Asia, there are vast differences in literacy rates (see Table 1). For example, in India, although a wide range of literacy exists depending on the region, there is a relatively high rate of illiteracy. As a result of past problems, the Indian government has implemented procedures to better

protect illiterate patients in foreign-sponsored trials - informed consent forms must have the signatures of the patient's witness, an independent witness, and the site staff. Similarly, several Southeast Asian countries have vast disparities in literacy among their patient populations. Where poverty and illiteracy are prevalent, many countries have initiated efforts to better protect the rights of these individuals by implementing new regulations, training programs, IRBs, and adapting methods to overcome illiteracy.

Conclusions and Recommendations Clinical trials are being pushed across the globe into ascending markets in Asia largely because of timely subject recruitment and cost effectiveness in these regions. Several Asian countries have streamlined their regulatory approval procedures and increased transparency to meet growing demands. A comparison of Asian countries prominent in clinical research, however, reveals remaining regulatory differences, socio-economic disparities, and issues of language and culture.

With respect to language, translation requirements vary depending on the country and patient population. Even with English as a second language in many countries, significant language barriers exist. Linguistic differences among Asian patient populations must be identified, and regulatory documents must be culturally adapted for each target patient population. Furthermore, cultural attitudes that affect medical practices and clinical data must be taken into consideration.

Multinational trials can be conducted successfully in Asia if these issues are properly addressed. The region will continue to provide a solution to the cost and recruitment problem. However, overcoming language and cultural barriers will play a key role in conducting quality clinical research in this region. As many Asian countries improve their regulatory environments and healthcare systems, there is a greater incentive for foreign sponsors to overcome language barriers and gain a better understanding of cultural and socio-economic differences.

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