

Commentary

Challenges of conducting clinical trials in Asia

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ABSTRACT

Unlike North America and European Union (EU), Asian continent appears to be an ideal destination for conducting cost-effective clinical trials utilizing the pool of treatment naïve subjects. With a population approaching 4.5 billion, recruitment of subjects can be done without a fear of limited patient pool across Asia. The burden of infectious and chronic diseases is also higher in Asian countries. The emerging clinical trial markets particularly China, South Korea, and Taiwan offers genetic diversity in population group, thus promoting the quality and generalizability of clinical trial's data. Nonetheless, several challenges also exist for the Western sponsors in majority of the Asian countries; regulatory, operational and infrastructural challenges are at the forefront. Challenges under the heads regulatory, operational, infrastructural, language and cultural, ethics, and future challenges have been discussed. SWOT analysis of Asian clinical trial's market exhibits enormous opportunities for study sponsors with manageable threats.

Keywords: Clinical trials, Asia, Sponsor, Challenges, Regulatory, Population

INTRODUCTION

The clinical trial is an important type of research design in the spectrum of translational research.¹ The extent to which clinical trials are conducted is a reflection of the level of advancement that exists within a healthcare system.¹ Asian countries are going to be the hub of clinical trials due to the presence of heterogeneous population groups unlike other continents.^{2,3} The outsourcing of clinical trials to Asian countries is considered as a sage decision due to the allocation of low budget and easy recruitment of subjects which also provide diversification in the population groups with different disease patterns. Consistent to this notion, management of large clinical trials remains challenging which can be frustrating for the sponsors and other stake holders. Asian countries such as China, India, Malaysia,

Thailand, Singapore, Philippines and Indonesia are recognized as the emerging clinical trial markets. Sponsors can easily conduct clinical trials on several diseases in this continent without any undue issues pertinent to the recruitment and trial cost.²

Asia is also the largest and most populated continent with the population of more than 4 billion (59.69%). Out of world's top 10 most populated cities, eight belong to Asia. China (1.38 billion population) and India (1.34 billion population) are currently leading in the ranking of Asian countries population.⁴⁻⁶ The most important part of clinical trials is the recruitment of study subjects and study power increases with the large sample size. The incidence of diseases such as liver cancer in Korea, cardiovascular diseases in Philippines, and gastric and esophageal cancer in China, is high that is also

considered as a stimulator for conducting clinical trials in this continent.^{2,7} The availability of treatment naïve patients makes Asia an ideal destination for clinical trials. Moreover, trial cost in Asia is relatively 30-40% lower than United States (US) and European Union (EU).⁷ The combined cost of each patient per visit in China, India and Thailand is nearly equivalent to per patient per visit cost in US alone. Likewise, the cost of electrocardiography (ECG) in China, India and South Korea costs 4, 5 and 50\$, respectively. On the contrary, cost of ECG procedure in US is 110\$.⁷

There are several challenges that are faced by researchers, regulatory agencies and sponsors in Asia such as cultural, ethical, operational, regulatory and infrastructural factors. There is also a shortage of skillful researchers and essential equipment which eventually affect the quality of data. Moreover, sponsors need to send biological samples to developed countries for laboratory reports which reflects their lack of confidence on Asian labs. Subjects' attrition in clinical trial is deemed to be a major issue in Asian countries which adversely affect the power of a clinical study.

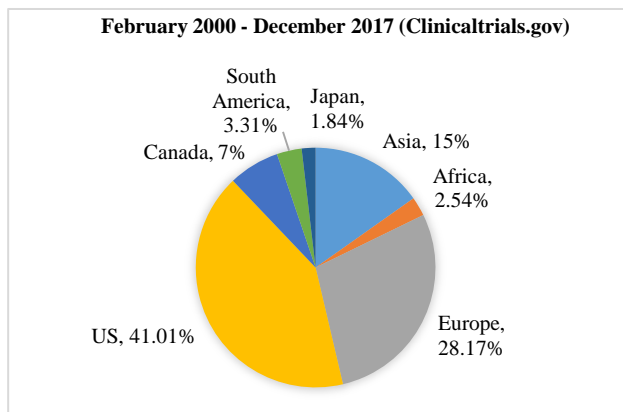


Figure 1: Percentage of total clinical trials.³¹

As per current statistics (Figure 1), 39,424 clinical trials are being carried out in Asia which is 15% of overall clinical trials registered in ClinicalTrials.gov. US is leading in the ranking of clinical trials with a share of 41.01%. High clinical trials cost, financial crises, limited patient pool, and other administrative expenses have prompted the study sponsors of North America and Western Europe to look for an alternative destination in order to cope with this dilemma.⁶ It is prudent to conduct feasibility for clinical trials that eventually provides optimum results; it's not deemed viable to conduct a clinical trial without looking at the incidence of the target disease in a selected country. Likewise, Asian countries provides more study subjects for an oncology trials while the pool of an oncology patients have already been consumed in the west. It was earlier reported that approximately thirty-five percent of the delay occurs due to the patient recruitment in the US and EU and one-fifth of their study sites neither enroll any subject.⁸ Western clinical trials are also conducted in collaboration with

developed countries for expediting the recruitment process and avoiding delays in drug approvals.⁹

CLINICAL TRIALS IN ASIA

Figure 2 shows that China is leading with a share of 27% trials followed by South Korea (22%) and Taiwan (13%). In comparison to earlier data, there has been a decline in the total number of clinical studies in India, Thailand, Singapore, and Malaysia during the last 5 years; this decline trend is disconcerting which occurred due to the collective fall of phase 3 trials.⁶ Fabricated data and uncertain regulatory environment have jolted India's clinical trial market despite of having an enormous potential for the recruitment of treatment naïve patients, thus prompting pharmaceutical companies to conduct clinical trials in other Asian countries.¹⁰

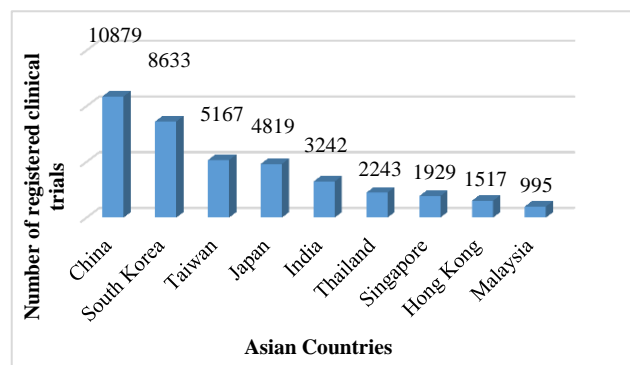


Figure 2: Clinical trials in Asia - ClinicalTrials.gov (February 2000 to December 2017).³¹

The concept of four color light strategy was introduced by China Food and Drug Administration (CFDA) in 2015 that streamlined the drug approval process, thus encouraging sponsors to conduct clinical trials in China without facing delays in site initiation that usually occurs owing to lengthy ethical and regulatory approvals.¹¹ Study proposals that focus on treating severe or life threatening conditions such as AIDS and cancer, are granted a fast track designation for getting early approvals.¹¹ CFDA has also recently introduced penalties for unethical practices during the conductance of clinical trial in order to tackle the issue of data falsification.^{10,12} These measures were taken after the release of investigation report regarding fraudulent data submitted by pharmaceutical companies to CFDA.¹³

Clinical trial's market in South Korea has performed well in the last decade, predominantly due to the support of Korean government. Korea National Enterprise for Clinical Trials (KoNECT) was established in 2007 for fostering clinical research in Korea and there has been a surge in clinical trials since its inception. KoNECT follows an integrated collaborative approach by involving all stake holders such as academia, pharmaceutical sector and government. The prime objectives of KoNECT are: to develop robust clinical trial infrastructure, to produce

competent and qualified workforce for clinical trials, and fostering global clinical trials in Korea.¹⁴

REGULATORY AND ETHICAL COMMITTEE APPROVAL TIMELINES

Table 1 presents regulatory and ethical approval timelines in Asian countries. These timelines were taken from the websites of regulatory authorities and George Clinical which may vary as delay in approval is quite common;

applicants need to be realistic during the submission of study proposals to the regulatory authorities.¹⁶ As shown in Table 1, the proposal submission process in most of the Asian countries is parallel, and some countries such as Thailand, Indonesia and Japan, follows sequential process for the approval of clinical trials. Moreover, regulatory process in China is comparatively long-drawn than other countries, while Singapore and South Korea appears to be some ideal destinations in terms of getting early approvals for conducting clinical trials.

Table 1: Regulatory and ethical approval timelines in Asian countries.

| Country | Process | Regulatory process | Ethical committees process |
|-------------|------------|----------------------------|----------------------------|
| Singapore | Parallel | 30 days | 30 days |
| Malaysia | Parallel | 30 days | 50 days (MREC) |
| Thailand | Sequential | 30 days | 90+ days |
| South Korea | Parallel | 30 days | 30 days |
| Taiwan | Parallel | 30-60 days (+10 for local) | 30 days |
| Philippines | Parallel | 180 days | 60 days |
| Indonesia | Sequential | 4-8 weeks + time for MTA! | 4-8 weeks |
| Vietnam | Parallel | 60 days | 30-45 days |
| China | Parallel | 12-16 months | 30-60 days |
| India | Parallel | Approx. 180 working days | Approx. 3-4 months |
| Japan | Sequential | 30-60 days | 30 days |

The delay in an attainment of regulatory and ethical approvals for therapeutic agents exerts an enormous impact on the availability of drugs particular for patients suffering from life threatening conditions. In China, clinical trials on immune-checkpoint inhibitors, including nivolumab and pembrolizumab, were initiated in the third and fourth quarter of 2015.¹¹ On the contrary, the first ever regulatory approvals for nivolumab and pembrolizumab were granted by other regulatory authorities in 2014 for cancer treatment.¹⁵ Therefore, a delay in clinical trial's approval by Asian regulatory and ethical committees creates a gap as compare to other western countries in publicizing the clinical data of Asian population.

SWOT ANALYSIS OF ASIAN CLINICAL TRIALS MARKET

SWOT analysis exhibits that strengths outweigh the weaknesses, and there are huge opportunities for sponsors with manageable threats in emerging Asian markets (Table 2). During 2015-2010, compound annual growth rate (CAGR) of Asian contract research organizations (CROs) is forecasted to be 19.9% while the CAGR of global clinical trials is projected to be 12%.⁷ CAGR of Asian CROs depicts robust growth of emerging clinical trial market in upcoming years, and prime determinants of this growth are fast recruitment, worldwide data acceptability and cost-effectives. Moreover, similarity in disease patterns provides competitive environment compared to the Western market for conducting clinical trials.

Regulatory factor

Regulatory authorities in Asia take long time for granting study approval as regulatory approval by CFDA is given after following several internal procedures. Time to decision is usually based on the total number of submitted application to CFDA and the efficiency of National Centre for Drug Evaluation (CDE). A large number of clinical trials applications were submitted to CFDA during 2010-2013, while resources and regulatory staff for handling these application were not adequate, thus delaying approval process. As per previous CFDA regulations, approximate approval time was 7 months compared to the recent timeline of 12-16 months. In 2015, more than 21000 applications were pending due to the delay in review process by CDE.¹¹ Recently implemented four color light strategy by Chinese regulatory authority will certainly expedite the review process in future; this strategy has prioritized the approval of certain drug classes for granting timely approvals.

Some restrictions also exist in Asian regulatory environment as first-in-man studies are not permitted in India, China and Malaysia. Consistent to this notion, applicants cannot get approval for preventive vaccine trials in China unless registration approval issued by other country is provided to the CFDA. In US, EU and Australia, patient's insurance companies and government organizations pay for standard of care, while sponsors are required to pay standard of care in most of the Asian countries such as Taiwan, Korea, Japan, China and India.⁷ Moreover, import permit for drugs is also required

in some Asian countries. Material Transfer Agreement (MTA) required in some countries for export of biological materials such as in Indonesia you need a MTA to transport biological samples outside the country.

Translation of clinical trial documents into local languages also affect time and cost in this emerging market.

Table 2: SWOT analysis of Asian clinical trials market.

| Strengths | Weaknesses |
|--|--|
| <ul style="list-style-type: none"> • Low operational costs compared to Western markets • Large population i.e. 60% of world’s population lives in Asia. Enormous potential for recruiting study subjects • Vast treatment-naive patient pool • Diversification in population group • Rising incidence of Western diseases. Or High incidence of infectious and chronic diseases in Asian countries • Disease patterns similar of Western countries • Presence of multinational pharma’s research centers in major Asian countries • Large, state-of-the-art clinical trial centers generate high-quality data • Regulatory environment improving and robust | <ul style="list-style-type: none"> • Low research awareness exists at public, health care professionals and regulatory levels • Shortage of experienced and competent investigators and other research staff • Lack of accredited clinical labs • Lack of GCP compliant trial sites • Inadequate facilities for conducting clinical trials particularly in small health care settings • Government spending on healthcare is lower than in US and western Europe • Medical system does not pay for certain drugs • Varying and delayed regulatory and ethical approval timelines • Lack of harmonization in regulatory systems of Asian countries |
| Opportunities | Threats |
| <ul style="list-style-type: none"> • Emerging clinical trial market • Growing pharmaceutical market • Interested international pharmaceutical and biotech organizations • Large government/private tertiary care settings • Less investment on subject’s recruitment • Good patient accrual | <ul style="list-style-type: none"> • Lack of experienced regulatory staff • Limited experienced talent pool at CRO, sponsor and site level • Political instability • Fraudulent data • Cultural issues |

Infrastructure issues

Good Laboratory Practices are suboptimal which obligate sponsors to send biological samples to accredited laboratories located in developed countries. Logistic complexities also exist; congested road transport in metropolitan Asian cities. Diagnostic specimens are temperature sensitive and lack of well-established transportation network may exert negative impact on the stability of study samples. Sponsors usually have to outsource these activities to local logistic companies for safe handling of these samples particularly for the trial sites located in rural areas. Hospitals also lack necessary infrastructure that is crucial for running successful clinical trials except in South Korea, Japan, Singapore and Hong Kong, which are equipped with basic necessities for conducting clinical trials. Lack of well-trained research personnel is also considered as one of the challenge in emerging trial market.

Operational issues

There is a limited awareness of clinical trials as a treatment option at both subject and physician level. Malaysian and Japanese Good Clinical Practice (ICH-GCP) guidelines differs from standard ICH-GCP document on some points.¹⁷⁻¹⁹ Sponsors need to be

familiar with existing differences of these guidelines before operating clinical trials in Asian countries. It is crucial to know the local requirements during medical writing of clinical regulatory documents, thus avoiding delays in the submission and approval process. Besides following the standard GCP guidelines, there are also additional local requirements for conducting clinical trials in Korea, Taiwan, and Philippines.¹⁹ Other operational issues include: limited experience at CROs, limited experiences at sites, limited experienced talent pool at CRO, sponsor and site level.

Language and cultural issues

Lack of translations for certain words, phrases or concepts in the local language; several local languages are spoken in India, and it’s mandatory to translate clinical trials documents into local languages. Rank and status are important in Asian countries as experienced or senior health care professionals usually play their role to resolve disputes and non-compliance issues during the conductance of clinical trials. It is prevalent among Asian trial participants to discuss with their close relatives regarding their participation in clinical trials.²⁰ There are also hurdles in the collection of an informed consent as one of the study in India revealed that community leaders could influence the decision of local residents before consenting for clinical trials. Moreover, study

investigators need to show patience during the consenting process and give ample time to participants before taking final decision.²¹ Another cultural issue in Asian population is stigma which is associated with disease conditions such as HIV/AIDS and TB.²²⁻²⁵

Ethical issues

Fraudulent data is one of the important ethical issue in some Asian countries. In 2016, Chinese authorities' revealed huge amount of fabricated clinical trial data which was submitted to CFDA for acquiring drug approvals.¹³ World health Organization's bulletin highlighted disconcerting fact regarding the establishment of hospitals by pharmaceutical companies in India.²⁶ Several reports have already been published regarding the unethical practices by study investigators and ethical committees in this emerging clinical trial market.^{27,28} Human research protection programs for health care settings are crucial for conducting ethically sound clinical trials and encouraging sponsors and patients; merely 8 hospitals each in China and Taiwan, 6 hospitals in India, and one setting in South Korea, have accredited human research protection programs.²⁹

Limitations

The statistics of clinical trials is solely based upon the information as registered in ClinicalTrials.gov which is the oldest and largest database of clinical trials from 201 countries. There is the possibility that other trials not registered could exist in other registries. Moreover, we couldn't filter the details of clinical trial's sponsorship due to an extensive database of Asian clinical trials.

CONCLUSION AND FUTURE CHALLENGES

Political unrest may jeopardize the clinical research environment and discourage sponsors, thus reducing sponsor's inclination to invest in politically unstable countries. Further, political disruptions adversely affect routine medical care and conducting clinical research appears futile during this disconcerting situation.³⁰ Another key challenge is the competition in the recruitment of study subjects predominantly in densely populated countries such as India, China, Indonesia, Japan, Thailand and Malaysia.

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