

Analysis on productivity of clinical studies across Asian countries — a case comparison

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ABSTRACT: In an era of increasing global competition and an increased interest in global clinical studies Japan has been concerned with the risk of losing its attractiveness due to perceived longer execution times and higher cost structure. In contrast, other Asian countries particularly China and Singapore are widely recognized as potential key centers for fast conduction of global clinical studies. We conducted a case comparison based on two clinical studies performed by a multinational pharmaceutical company in order to measure the productivity of clinical studies by region and country. We focused on the site-related study cost which constituted the largest portion of the cost breakdown and also impacted both time and quality management. For investigation of the productivity we propose a breakdown model with two Key Performance Indicators (KPIs), enrollment efficiency and site-related cost efficiency, for the comparison of the number of enrolled subject per site and cost, respectively. Through the comparative analysis we found that the Asian countries (excluding Japan) on average achieved higher efficiency than Japan in both indicators. In the Asian group, China and Singapore stood out as the most efficient on both speed and site-related cost. However, when the site-related cost efficiency was adjusted for Purchasing Power Parity (PPP) the cost advantage in China disappeared, implying the price level was critical for productivity management. Although quality aspects remain to be investigated we postulate that introducing a comparative approach based on a productivity framework would be useful for an accurate productivity comparison.

Key Words: Productivity, clinical development, clinical study, regulatory science

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Introduction

It is a critical issue for large pharmaceutical companies to achieve competitive cost and speed in clinical study execution. Recently the principles of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human use (ICH) have been embraced by most Asian countries for the facilitation of global alignment of clinical studies. Through the globalization of pharmaceutical and medical products for the past decades Japan has been one of the centers of pharmaceutical clinical studies by virtue of its large market potential. However, Japan has received a reputation that clinical study-related cost is high in comparison with that in other countries (1-3). The underlying reasons have not been fully understood, however, site-related inefficiency was suggested as one of reasons for the high cost level. Particularly, over-quality in execution of clinical studies, which creates laborious work processes leading to longer time to completion, has been pointed out through comparative observations (4). This, in turn, resulted in a decrease in the number of clinical studies conducted in Japan over the last decade (1-3).

In order to address the issue of low productivity in clinical studies the government and its affiliates have been implementing various actions. For example, Japanese Pharmaceuticals and Medical Devices Agency (PMDA) endorses global clinical studies involving Japan and Asian countries, as well as Asian clinical studies including Japan and other Asian countries. To design and conduct Asian-wide uniformed clinical studies in an effective way it is essential to capture precise information of cost and subject enrollment efficiencies in Asian countries. However, such basal information has not been readily available, although some limited information exists (1-3,5). Thus, quantitative investigations need to be initiated. For better understanding of the current situation it is necessary to provide qualified case examples which are eligible for cross-regional comparison and exploration of essential underlying mechanisms to describe identified differences.

In this report we present a case comparison of

two clinical studies with a considerable focus on the site-related study cost, which was spent by the pharmaceutical company to fund and support the studies at each study site. One of the studies was conducted globally and involved representative Asian countries including Greater China, Singapore, Taiwan, Hong Kong and Thailand. The other study was conducted in Japan with the study protocol almost identical to the global trial. We here present the results of a quantitative comparison on specific cost items and describe potential underlying explanations for the typical differences observed.

Materials and Methods

Cost related information on both the Japanese and global study was kindly provided by Novo Nordisk A/S and its Japanese affiliate, Novo Nordisk Pharma Limited. The information of cost was external payment from Novo Nordisk and available from the start of the program in 2004 to its completion in 2007. Since study-related payment is requested sometimes even long after completing a study we adopted forecasted figures for the uncovered period of study to keep to the difference an absolute minimal. Site-related study cost in Japan was calculated for the separate clinical trial executed in parallel to the global trial with the almost identical study protocol. The studies performed to document safety and efficacy for treatment of an acute disease in a new therapeutic area of drug development. Very few similar studies have been conducted globally and the study in Japan was a novel case.

In each clinical study investigators were carefully nominated from a pool of similar background and expertise. In the actual clinical studies the medicine (or placebo) was administered to each subject in a very short period of time after disease onset soon after informed consent was obtained from a patient or his/her legally accepted representative. The enrolled subjects were followed-up for three months after drug administration. Inclusion/exclusion criteria, treatment period, follow-up period, evaluation items and visit intervals were almost identical between the Japanese study and the global study. Both cases were placebo-controlled, double blind studies. The Japan study was a three-tier dose escalation trial, while the global study had a three-arm parallel design.

Twenty two countries or areas (the USA and Canada from North America, Spain, Germany, France, Netherlands, Sweden, Finland, Denmark, Italy, Austria, Belgium, Norway and Croatia from Europe, China, Singapore, Taiwan, Hong Kong and Thailand from Asia, Australia from Oceania, Israel and Brazil) participated into the said global study. Top level clinical study sites in each country were involved in both of the clinical studies. However, only two to three study sites in each Asian country were involved in the global study, while in total 29 study sites participated into the

Japan Study.

The number of subjects enrolled in the global study was in total 821 consisting of 282 from North America, 380 from Europe, 113 from Asia, 21 from Oceania and 25 from other countries. In the Japan study 91 subjects were enrolled. The enrollment period of the global study from the first-patient-in to the last-patient-in was 18 months. That for the Japan study was nine months by adjusting total three months of enrollment suspension for dose tier up evaluation and decision. Both of the studies were compliant with Good Clinical Practice (GCP) of ICH (ICH-GCP). The quality in the trials was secured through monitoring activities, which fulfilled the requirements for regulatory submission to Food and Drug Agency (FDA), European Medicines Evaluation Agency (EMA), PMDA and other regulatory authorities. Therefore, comparison of investigator site-related study costs was able to be done with negligible bias.

For the comparative analysis we defined site-related study cost as consisting of investigator grant, clinical research coordinators' (research nurses') cost, indirect cost charged by the site, Institutional Review Board (IRB)/Ethics Committee (EC) cost, study specific examination cost, study specific equipment cost, patient allowance, printing cost, translation cost, courier cost and investigator related information and education cost. For comparison amongst countries in the Asian region, Japan, China, Singapore and Taiwan were selected whereas Hong Kong and Thailand were eliminated due to few enrolled subjects ($n = 2$ and 1 , respectively).

For the analysis of site-related cost efficiency adjusted with comparative price levels, the figures of Purchasing Power Parity (PPP) in 2005 for each country were obtained from annual report from World Bank and International Monetary Fund (for Taiwan).

Results and Discussion

The breakdown of external clinical study costs of the Japanese and the global clinical studies paid by the pharmaceutical company were as follows. The external cost of the global study consisted of site-related study cost (32.0%), outsourced monitoring cost (17.5%), external laboratory cost (14.8%), other outsourcing cost such as data management (11.9%), drug and packaging cost (3.1%) and others (20.6%). The external cost of the Japan study consisted of outsourced monitoring cost (59.0%), site-related study cost (21.2%), other outsourcing cost such as data management (9.0%), external laboratory cost (8.0%), drug and packaging cost (0.2%) and others (2.6%). Since execution of the Japan study was fully outsourced whereas the global study was performed basically by internal resource, the ratio of monitoring cost and other cost varied between them. However, it was obvious that the site-related study cost was the predominant cost portion of a clinical study when the study was managed by

internal resource. This observation showed good correspondence to a previous report (3).

A productivity breakdown model and the results of the enrollment efficiency, site-related cost efficiency, site-related cost efficiency adjusted with PPP, and speed of enrollment are summarized in the Figure 1 and Table 1, respectively. As for relative enrollment efficiency (indices of subjects per site), the numbers for Japan, global average (ex-Japan), Asian average (ex-Japan), North American average, European average, Oceania and others were 1.00, 1.60, 3.27, 1.38, 2.52, 1.67 and 1.99, respectively. Thus, Asian countries (ex-Japan) were on average 3.3 times more efficient than Japan which had the lowest enrollment efficiency of all the regions. Regarding site-related cost efficiency (indices of subject per cost), the figures for Japan, global average (ex-Japan), Asian average (ex-Japan), North American average, European average, Oceanian average and others were 1.00, 1.89, 3.50, 1.22, 2.28, 2.42 and 1.97, respectively. Thus, the Asian average (ex-Japan) was the most cost-efficient in the world and 3.5 times more efficient than Japan.

Considering differences in price levels across countries, we also tested to adjust site-related cost efficiency with PPP. This method utilizes the long-run equilibrium exchange rate of two currencies to equalize the currencies' purchasing power. PPP-adjusted site-related cost efficiency is considered to be useful from perspective of governments, study sites and companies to evaluate real cost efficiency of the study execution at each study site by eliminating impact of price level although only nominal site-related cost efficiency is usually discussed. Through this adjustment we obtained relative ratios of 1.00, 1.53, 1.02, 1.04, 2.19, 2.15 and 1.10 for Japan, global average (ex-Japan), Asian average (ex-Japan), North American average, European average, Oceanian average and others, respectively. This indicated that PPP-adjusted site-related cost efficiency of Japan was at an almost similar level to those of Asian average (ex-Japan), North American average and others, while those of European average and Oceanian average were about 2.2 times higher than

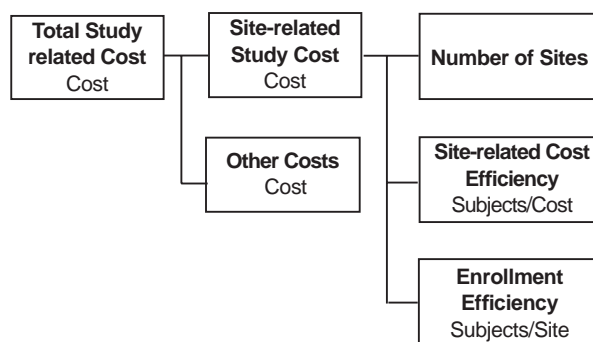


Figure 1. Productivity breakdown model of clinical studies. For comparative analysis we newly synthesized a breakdown model for the measurement of clinical study productivity. Two performance indicators, so called enrollment efficiency and site-related cost efficiency correspond to the number of subjects per site and the number of subjects per cost, respectively. Dividing enrollment efficiency by site-related cost efficiency and multiplying it by number of sites makes site-related study cost.

that of Japan.

When we compared speed of enrollment (subjects per site per month) across regions, these were 1.00, 0.80, 1.64, 0.69, 1.26, 0.84 and 0.99 for Japan, global average (ex-Japan), Asian average (ex-Japan), North American average, European average, Oceania and others respectively, demonstrating clear advantage of Asian countries compared to other regions. Speed of enrollment in Japan was higher than in North American average and Oceanian average, as well as in the global trial as a whole.

To obtain more precise understanding of site performance in Japan we selected top 10% performing study sites for comparison. When these three sites were analyzed, the indices of average enrollment efficiency and speed of enrollment were 3.01, and the site-related cost efficiency index was 1.39. These results indicated that the higher performing Japanese sites were fairly competitive in speed of enrollment. This indicates that with careful site selection Japan can be a notable contributor to global and Asian-wide clinical studies.

We then conducted a country-level comparison in the same manner in the Asian region for the indices of enrollment efficiency, site-related cost efficiency, PPP-adjusted site-related cost efficiency and speed of

Table 1. Comparison of selected performance indicators for clinical study efficiency (Unit: Index (Japan = 1.00))

Items	Definition	Japan Study		Global Study (ex-Japan)								
		Japan		Global	Asia			North America	Europe	Oceania	Others	
		Total	Top 10%		Total	China	Singapore					Taiwan
Number of Subjects	Subjects	91	28	821	113	81	20	9	282	380	21	25
Site-related Cost Efficiency	Subjects/Cost	1.00	1.39	1.89	3.50	4.55	2.70	1.68	1.22	2.28	2.42	1.97
Site-related Cost Efficiency adjusted with PPP		1.00	1.39	1.53	1.02	0.77	2.00	0.76	1.04	2.19	2.15	1.10
Enrollment Efficiency	Subjects/Site	1.00	3.01	1.60	3.27	8.60	3.19	0.96	1.38	2.52	1.67	1.99
Speed of Enrollment	Subjects/Site/Month	1.00	3.01	0.80	1.64	4.30	1.59	0.48	0.69	1.26	0.84	0.99
Comparative Price Levels (PPP)		1.00	1.00	0.81	0.29	0.17	0.74	0.45	0.85	0.96	0.89	0.56

Based on the shown in Figure 1 enrollment efficiency, site-related cost efficiency (nominal and PPP-adjusted) and speed of enrollment were selected as representative efficiency indicators for the clinical studies. All indicators were transformed indices (here Japan was set to 1.00) due to a confidentiality requirement from the information provider. Along with this manner the global and Asian average (ex-Japan) were calculated. North American average, European average, Oceanian average and other countries' average were also deduced herewith for reference. To compare speed of enrollment the indexed figures were calculated by dividing enrollment efficiency of each country by the number of enrollment period of each study and setting that of Japan to 1.00.

enrollment. All comparative data were transformed into indices, setting the Japanese case to 1.00.

In the Chinese case 81 subjects were enrolled to the global study. Here we observed 4.55 and 0.77 for nominal and PPP-adjusted site-related cost efficiencies, respectively, and the speed of enrollment was 4.30. These results indicated that China retained a strong potential to contribute to global studies in terms of speed and site-related cost even in a new therapeutic area of drug development with challenges in preparing and implementing studies. However, the PPP-adjusted site-related cost efficiency suggested that the current Chinese sites' cost efficiency was sustained by virtue of low price levels compared to other regions and countries.

As per other countries, the Singaporean sites ($n=20$ for subject enrollment) showed well balanced performance with regard to nominal and PPP-adjusted site-related cost efficiencies and speed of enrollment (2.70, 2.00 and 1.59, respectively), implying that Singapore was another excellent contributor to global studies. Taiwan's nominal and PPP-adjusted site-related cost efficiencies and speed of enrollment indices were 1.68, 0.76 and 0.48, respectively. We do not have clear rationale for the low level of speed of enrollment, but anticipating that these performance indicators could be influenced with conditional factors such as nomination of clinical investigators and selection of sites due to relatively smaller number of subject ($n = 9$).

Among Asian countries the Chinese and Singaporean sites demonstrated excellent nominal site-related cost efficiency and speed of enrollment profiles. Furthermore, Asian average site-related cost efficiency and speed of enrollment were greater than North American and European average, which strongly suggested further contribution of Asian regions as a driver of global studies for new drugs and the potential for running competitive Asian-wide drug development programs. From the series of comparison we concluded that Japanese sites were not as efficient on execution and site-related cost as Asian sites. This supported our initial hypothesis that Japan was facing challenges and needed to improve its capabilities from both speed and cost aspects.

Chinese and Singaporean sites showed higher performance in speed and site-related cost compared to any other regions. The high enrolment efficiency in China could be due to a centralization of clinical research and development functions to a few medical institutions. Furthermore, the two studies of analyzed required a high level of specialization within the relevant therapeutic area, which might further facilitate a concentration to specific study sites. This explanation also fit to the observed lower PPP-adjusted site-related cost efficiency. Hypothesizing that a high level of specialization is required, there would be an associated increase in the need for medical tasks and expenses. In Singapore, institutional development of clinical research

has prospered under the government's initiative for the last few years. This national approach generates a strong infrastructure for clinical studies, for instance, cross-border invitation of clinical researchers and key investigators, intensive investment in information technology systems and, subsequently, enhanced on-line networking of medical institutions. Although we need further investigation in order to fully understand the observed differences, there are clearly better practices in the Asian region that could be used for the improvement of Japanese study sites' competitiveness.

Around year 2000 Japanese study sites had obtained the following reputation: clinical study cost in Japan was by far more expensive than in other countries; Japanese standard was still not fully aligned with ICH-GCP; Japanese clinical studies often required a longer period of time to completion. However, in our analysis these high performing Japanese study sites exhibited almost competitive performance to sites in other Asian countries and in the rest of the world. This result strongly endorses the importance of the uptake and diffusion of domestic best practices in parallel with benchmarking approaches to other countries. Indeed, it was recently communicated that the quality issues of clinical studies and floundering speed of enrollment were being resolved while the high cost structure still remained as an issue (4). The result of our comparative analysis supports these statements and was in accordance with reported improvement in speed of enrollment over global studies.

Comparison of the PPP-adjusted site-related cost efficiency provided a different perspective on the study cost management. The PPP-adjusted cost efficiency of the Japanese sites was comparable to the Asian, North American and other regions' study sites, taking differences in the price level of each country into account. This observation also revealed a potential risk for future clinical studies. An increase in a price level in China may lead significant increase in level of site-related cost in a longer term. When looking at Japan it is clear that the price level keeps impacting site-related study costs despite internal efforts for improvement. A nation-wide, systemic approach to reduce structural costs, for instance, compensating sunk cost for investment, subsidies, would be required to restore Japan's competitive position in the Asian region and globally.

From the sponsor company's perspective the quality of Asian sites including Chinese sites' performance was comparable to North American and European sites. However, there are still quality-related issues especially in some Asian countries that remain as a concern.

For instance, there are still local practices that differ from international practices and there are still barriers to overcome for example in China. Several precedent observations (6) including what Liang Kong highlighted (7) also have suggested the following quality-related issues in Chinese clinical trials: 1) the overall clinical

study levels lag behind the requirements of ICH-GCP, 2) compared to developed countries GCP history in China is quite short and there are few people with GCP knowledge and experience, 3) the regulatory approval process is lengthy and the local language and hardware can present challenges for multi-national companies, and 4) sponsors conducting studies in China must be prepared to devote substantial resources to understanding the nuances of the distinct system in which they are operating. Therefore, quality aspects of Asian sites should be considered in detail when plans are made to a clinical study in these countries. We may also need to explore ways of evaluating quality-adjusted study productivity.

In this report the site-related study cost was investigated using several performance indicators. This cost item constituted 21.2% of the total external study cost in the Japanese study as described above. On the other hand, approximately over half of the total study cost was spent for monitoring tasks, which was a much larger portion than in the global study. This can be explained by the fact that monitoring work in Japan was fully outsourced to a Contract Research Organization (CRO). If the monitoring activities in both of the clinical studies had been fully outsourced to CROs we could have discussed difference in cost and price of monitoring outsourcing between Japan and other countries. The difference in project team structure made it difficult to compare the monitoring cost across regions. However, in general, there is an issue with high costs for monitoring activities in Japan. This concern has also been raised by Japanese pharmaceutical industry and by the government.

To address this issue a questionnaire survey-based research was conducted in 2006 in order to investigate current condition of Japanese study sites (8). The survey unraveled following findings: 1) there were not enough number of Clinical Research Coordinators (CRCs), research nurses or medical doctors who were educated and experienced well about clinical studies and GCP, 2) Japanese investigators were often too busy to supervise clinical study activities, 3) motivation of Japanese investigators was relatively low due to lack of incentives and mind-set on punctuality for company-sponsored clinical studies, and 4) study application formats differed amongst sites. Another observation, a questionnaire-based surveillance over 24 clinical research associates (CRAs) of a Japanese subsidiary of a foreign affiliated pharmaceutical company, pointed out pursuit of excessive goal of company-sponsored clinical studies in Japan (4). This was potentially due to a requirement of the Japanese GCP guideline and a strict attitude of Japanese regulatory authority. Therefore, it seems that pharmaceutical companies are forced to support and motivate investigators and clinical research coordinators in Japan which may require considerable incremental labor cost. This point needs to be clarified in further cross-regional research

on the dynamics of study sites, investigators, CRCs and CRAs.

In conclusion, we obtained the following findings throughout this comparative case example by analyzing enrollment and site-related cost efficiencies following a proposed productivity framework. Asian sites, particularly the Chinese and Singaporean sites, were shown to be achieving much higher efficiency in both speed and site-related cost than other regions. A comparison of PPP-adjusted site-related cost efficiency provided a different interpretation projecting a significant reduction in site-related cost efficiency when price in these Asian countries may increase. Finally, Japanese study sites should consider adoption of internal and other countries' best practices to be competitive going forward. These initiatives may require a concerted action between investigators, medical societies, regulators, and pharmaceutical industry organizations. Although quality aspects remain to be investigated further, we believe that this approach should be effective to accurately forecast effectiveness of execution and cost across regions and countries.

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