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Research Article

BRINGING PHASE I TRIALS IN HEALTHY SUBJECTS TO JAPAN: CURRENT PRACTICES AND FUTURE DIRECTIONS

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ABSTRACT

Objective: Recently, the number of phase I trials being conducted in different regions has been changing. From the pharmaceutical industry's point of view, it is important to focus on selection of the appropriate study country. This study was conducted to investigate Japan's capabilities in conducting phase I studies in healthy subjects.

Methods: A structured questionnaire survey was performed to identify unique features of phase I sites in Japan. The questionnaires were administered to 15 phase I sites in Japan, sites at which over 90% of all phase I studies of new molecular entities in healthy subjects in Japan are conducted each year.

Results: 165 phase I trials of new molecular entities in healthy subjects are conducted per year. This survey revealed three features of phase I sites in Japan: (1) subjects are recruited quickly, (2) sites can perform studies with both New Molecular Entities and Generic Entities, (3) the majority of these phase I sites have adopted the requirements outlined in the Medicines and Healthcare Products Regulatory Agency accreditation scheme that is practiced in the UK.

Conclusions: Our survey suggests that Japan currently has highly qualified phase I sites, in terms of quality, speed, cost and experience. However, improvements must still be made in order to gain global recognition and to promote Japan's capabilities in early stage clinical trials.

Keywords: Drug development, Phase I trial, Phase I site, Healthy subjects.

INTRODUCTION

Phase I trials have been defined in the following way: "A clinical trial to study the pharmacology of an investigational medicinal product when administered to humans, where the sponsor and investigator have no knowledge of any evidence that the product has effects likely to be beneficial to the subjects of the trial" [1]. According to this definition, the phase I trial can be classified into three categories: the first-in-man, subsequent, and bioequivalence trials (Table 1).

Table 1: Types of Phase I Trials

Type	Definition/Objectives	Design/Examples [2]
First-in-man trial	The first trial of investigational medicinal products (IMP) in humans to assess the tolerability, safety, pharmacokinetics and, if possible, pharmacodynamic effects of the IMP, and to compare the results with those from pre-clinical studies	Single ascending dose
Subsequent trial	After the first-in-man trial	Multiple ascending doses to assess the effects of factors such as food, gender, age and genetic differences, on the efficacy of the IMP
Bioequivalence trial for Generic Entities	Bioequivalence between a commercial drug and a generic drug	Cross-over

In drug development, phase I trials, such as the first-in-man (FIM) trial and the subsequent trial, which both typically include healthy volunteers, are the key steps in bringing novel drug candidates from the research laboratory to the clinical setting. The phase I trial falls within the realm of experimental science, and requires a range of skills and expertise, including the highest level of medical knowledge [3]. It is important that a study site conducting such research has highly-experienced staff, advanced infrastructure, and high quality operational standards for conducting a phase I trial.

For the pharmaceutical companies developing new molecular entity (NMEs), efficient management of phase I trials is extremely important, and selecting the appropriate countries in which the studies will be conducted is paramount [4]. Since phase I studies are performed without any evidence that the product is likely to be beneficial to the subjects in the trial, country and site selection for phase I studies is arguably more complex than for Phase II and III.

Globally, the number of the phase I trials being conducted varies depending on the region [5]. The number of phase I trials conducted in the US is currently the largest in the world, but, in recent years, has been declining. On the other hand, even though the number of phase I trials conducted in Asia is currently less than that of the US, it is rising rapidly. This trend is largely attributed to the fact that pharmaceutical companies have started to choose more diverse countries for phase I trials.

Despite the fact that Japan has the second largest pharmaceutical market [6] and is one of a handful of countries that possess the ability to conduct drug development from scientific research all the way through to post-marketing development [7], it is extremely rare for Japan to participate in a global clinical trial in the early stages of development, even if the compound was originally discovered in Japan [8]. This "hollowing out" (i.e. industry relocation abroad) phenomenon occurring in Japan leaves the nation unable to participate in concurrent global development, which can result in "drug lag" [9], [10].

In this paper, we focused on the performance of study sites operating phase I trials in Japan. A survey was conducted to analyze

the current capabilities of Japanese sites in conducting phase I trials in healthy subjects. Based on the results of that survey, we propose below a vision for bringing global standards to the conduct of phase I trials in healthy subjects to Japan.

MATERIALS AND METHODS

The questionnaires were administered to 15 phase I sites in Japan, at which more than 90% of the total phase I studies each year in Japan are conducted. Most of these phase I study sites had membership to the Japan Association of Contract Institutes for Clinical Pharmacology (JACIC); all 15 questionnaires were returned. The survey was conducted during the period from April 2010 to October 2010 and from January 2012 to February 2012. The questionnaire was designed specifically for this study and was composed of a series of questions including how many phase I studies are conducted in each year, the type of clinical studies conducted, the number of research personnel, the volunteer database, the total operational period of a study, the cost of conducting a study, and quality as assessed by the Medicines and Healthcare products Regulatory Agency (MHRA) phase I accreditation scheme. All responses were self-reported and the completed questionnaire forms were returned directly to us for analysis.

RESULTS

The study sample size consisted of 15 institutions, of which 53% (8 of 15) were clinics, 20% (3 of 15) were general hospitals, 13% (2 of 15) were academic medical centers and 13% (2 of 15) were others (a hospital specializing in clinical trials and a university-affiliated research institute). Sites had been actively engaged in phase I research for a mean period of 13.7 years through 2009. The mean subject capacity for phase I studies (number of subjects capable of being hospitalized at the same time) was 43.8 subjects.

The mean number of investigational staff at a single institution was 71.1, which consisted of: 12.3 medical doctors; 20.1 nurses; 8.7 pharmacists; 12.3 laboratory technicians; 6.2 administrators for study subjects (participants); 2.1 dietician; 6.9 general administrative staff; and 2.5 others. The mean number of total supportive staff (all staff excluding medical doctors) for one medical doctor was 4.8. A summary of the survey results is shown in Table 2.

Table 2: Summary of statistical data and distribution characteristics of responses to the survey

	N	Mean	Median	Min	Max
Experience of Phase 1 study (/year)	15	13.7	10.8	4.5	28.8
Capacity of admission (number of bed)	12	43.8	35.0	15	151
Number of staff	13	71.1	42.0	14	314
Medical doctor		12.3	5.0	2	38
Nurse		20.1	14.0	2	104
Pharmacist		8.7	4.0	1	52
Laboratory technician		12.3	6.0	2	52
Subject database management		6.2	2.0	0	31
Dieticians		2.1	2.0	0	10
General administrative staff		6.9	5.0	0	27
Other		2.5	0.0	0	21
Number of registered volunteer	7	6,408	3,181	1,951	19,293
Male		5,256	2,518	1,222	16,557
Female		1,152	729	54	2,736
> 65 years old		386	142	0	1,198
Ratior of scneening subject/taeget number	12	2.9	2.8	2	5
Ratio of informed consent subject/target number	14	2.4	2.4	1.8	3.5
Speed (timeline)					
Contract - FPI (Day)	11	7.5	7.0	1	15
LPO - CRF completion (Day)	11	12.7	14.0	7	21
Deviation from agreed timeline (Day)	7	14.3	3.0	0	120
Estimated cost/subject (JPY)	9	1,315,000	118,800	775,000	2,748,000
Number of protocol (/year)[1)]	15	21.4	14.7	1	87
NME (/year)[2)]	12	10.5	4.1	0	38
GE (/year)[2)]	12	11.5	6.1	1	38

First-patient-in (FPI), Last-patient-out (LPO), Case report form (CRF), New molecular entity (NME), Generic entity (GE)
1) 2007-2009, 2) 2005-2009

Figure 1 shows the presence or absence of a volunteer database maintained by each study site. 73% (11 of 15) of the sites had a database of registered healthy volunteers. Several sites had volunteer databases for special populations (e.g. elderly, ethnicity or other particular demographics). However, only a few sites had a database for volunteers with renal impairment or children. No study site had a database of volunteers with hepatic function impairment.

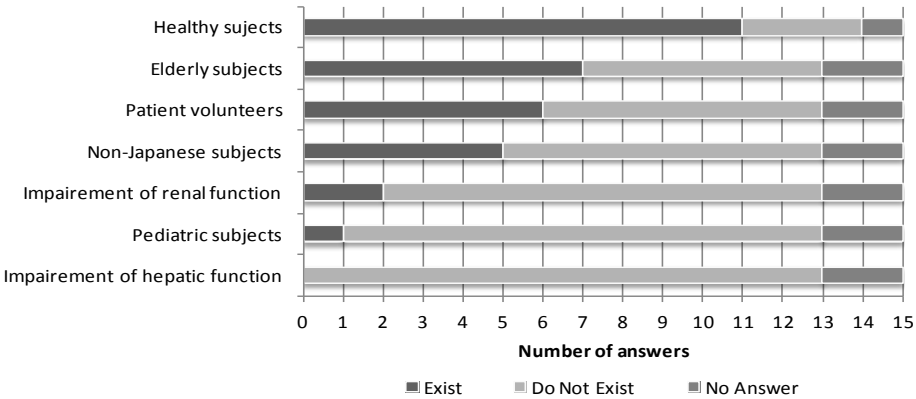

Fig. 1: Presence of Volunteer Database by Category

The mean size of the volunteer database owned by each study site was about 6,408 subjects, which consisted of 5,256 men and 1,152 women.

On average, research sites recruited 2.9 times more subject candidates than the target subject number, and attempts to obtain informed consent occurred 2.4 times more frequently than the target number. The percentage of discontinuation or early withdrawal from any given trial was less than 10% throughout all sites.

The mean period from final execution of a contract to written informed consent of the first subject was 7.5 days. The mean period from the final observation point of the last subject to completion of the final case report form (CRF) was 12.7 days. The mean time lag from the planned timeline agreed to by the sponsor and investigator to actual time required was 14.3 days.

The mean estimated cost of a trial (per subject) in an initially proposed study design was 1,315,000 JPY. Factors in the trial that had the highest impact on the cost were whether subjects were hospitalized and institutionalization period as well as the total number of subjects enrolled.

The quality of the phase I study sites was evaluated according to the MHRA phase I accreditation scheme. In March 2006, a FIM trial was conducted in healthy volunteers for a superagonist antibody against CD28, TGN1412. The first infusion was given to six volunteers and all six faced life-threatening adverse events requiring care in the intensive care site. This particular incident initiated many discussions, and ultimately led the MHRA to publish an accreditation scheme for phase I sites in 2007 [11]. The scheme stipulates requirements for facilities and staff conducting phase I trials and consists of two types of accreditation: (1) standard accreditation, for sites that wish to conduct phase I trials other than FIM trials with risk factors that require review by UK experts from the Clinical Trial Expert Advisory Group of the Commission on Human Medicines (CTEAG), and (2) supplementary accreditation, for sites that wish to conduct all phase I trials with compounds at all levels of risk, including those that require review of risk factors by the CTEAG. Although this accreditation is not mandatory, 15 study sites have been approved in the UK as of January 18, 2010 [12]. Most of the sites surveyed here indicated they "satisfy" or "nearly satisfy (i.e. do not completely meet the criteria but can compensate in other ways)" the criteria for standard accreditation, while 3 out of the 15 study sites (including 3 that did not respond to questions in this section) did not meet the criteria with regard to subject identification procedures, bed specifications, and documentation of standard operating procedures (SOPs) for handling common medical emergencies and unblinding in an emergency situation. Three out of 15 study sites (including 3 that did not respond to questions in this section) also did not meet 2 out of the 3 main criteria for supplementary accreditation. In the remaining 12 study sites (including 3 that did not respond to questions in this section), 3 sites did not meet the requirement that "research physicians employed by phase I sites seeking supplementary accreditation must be able to demonstrate appropriate training and experience in handing medical emergencies. A procedure must be in place to address the assessment of continuing competency in this area and may be achieved by peer review, audit or other means." 2 study sites each did not meet the requirements "Phase I sites may be located within a hospital; with critical care facilities" and "Appropriately trained clinicians with up-to-date emergency medicine experience may be brought in to the site on a contract basis during dosing days. These contract staff must also be trained in ALS, the study protocol, site procedures and GCP. The contractor would not be expected to take on the role of the principal investigator and must be appropriately supervised whilst in the site. Indemnity arrangements made by the sponsor and/or site must also apply to the contract medic" and 1 site did not meet the requirement stipulating that "There must be a procedure in place for contingency planning." Nevertheless, some sites took countermeasures such as contracting with other hospitals to deal with an emergency resulting from a clinical trial. All study sites had undergone inspections by domestic or foreign health authorities.

The mean number of phase I trials conducted from 2005 to 2007 at a site was 21 per year. In terms of molecular entities, 10.5 studies were carried out for NMEs while 11.5 studies were done for GEs. Figure 2 shows experience with non-phase I studies with subjects other than healthy volunteers. Over 50% of the sites have performed clinical studies in patients, postmenopausal women, or elderly people or drug-drug interaction studies. Less than 20% of the sites had experience with thorough QT studies, pediatric studies, or studies in subjects with hepatic impairment. Our survey revealed that the type of studies conducted closely coincided with the type of volunteer database maintained by the study site.

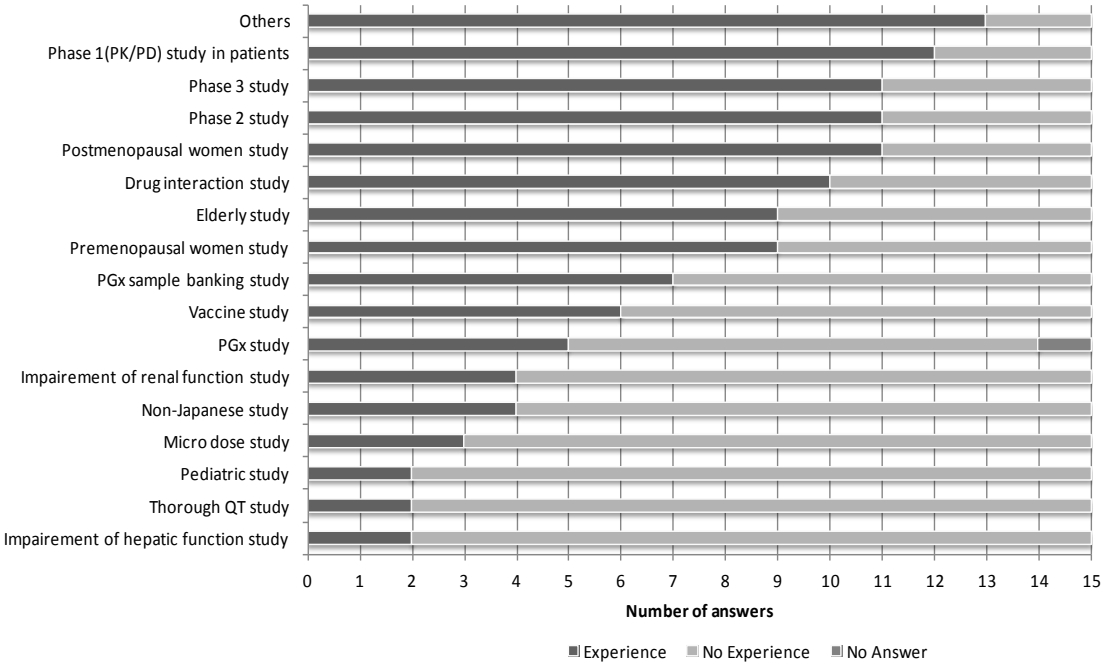

Fig. 2: Types of Clinical Studies Conducted

DISCUSSION

This survey revealed three features of phase I sites in Japan

- Plenty of volunteers (corresponding to over 50 people per trial) registered in each site, which allows for speedy subject recruitment. In addition, CRF documentation is promptly completed as the study sites are well-staffed.
- All study sites conduct trials with both NMEs and GEs. But only a limited number of FIM trials have been done.
- In terms of infrastructure, including facilities and other resources, some of the study sites satisfied the MHRA accreditation scheme that is practiced in the UK while others did not. There is still room for improvement in emergency response for FIM studies, which would improve the capabilities of these sites in handling high-risk compounds and stay abreast with global development.

The performance of each site is shown in Table 2. The speed (from the conclusion of a final executed contract to the completion of CRF of the last subject) is notable. This speed could be attributable to appropriate selection and management of subjects suggests, which is very likely a result of the large size of the volunteer databases compared to the number of volunteers required by each trial and a low study drop-out rate. Recently, duplicative registration of healthy volunteers has been raised as a challenge when finding appropriate subjects for phase I studies [13]. In 1991, the JACIC, in which the phase I trial sites participate, introduced a verification system to prevent volunteers from duplicate registration [14]. Therefore, we believe that Japan possesses a sophisticated volunteer registration system that gives access to for a large volunteer database, which in turn allows for speedy and high-quality clinical trials.

In foreign countries, NME trials and GE trials are generally conducted in separate sites as the requirements from the sponsors differ between the trials [15]. In contrast, according to our survey, all of the phase I study sites in Japan accepted both NME trials and GE trials. One possible reason for this is that the sites cannot fully utilize their available capacity with NME trials or GE trials alone, and thus accept both to improve their trial turnover rate. In sites with less than 10 years of experience, more GE trials were conducted than NME trials (5 of 7 sites). The sites with over 10 years of experience tend to take on more NME trials than GE trials (7 of 8 sites). These data suggested that sponsors prefer experienced study sites for NME trials.

According to our survey results, even for study sites with a long history of experience, the commissioned trials, including FIM trials, were not exclusively NME trials. This phenomenon could be attributed to the study site's needs for business efficiency and effective utilization of their assets. This may also reflect the fundamental background in Japan that the growth of the number of phase I trial is stagnant, which resulted from oversupply of sites conducting NME trials. On the other hand, this also suggests that if demand for NME trials increased, then phase I trial sites could take on more NME trials.

Only four sites had experience conducting phase I trials in foreign (non-Japanese) subjects. This may reflect the current regulatory requirement that phase I studies generally have to be done in Japanese subjects for New Drug Applications (NDA) in Japan [9], and as a consequence, phase I sites in Japan tend to focus on trials for domestic NDAs. After the China-Korea-Japan Tripartite Health Ministers Meeting (THMM) in 2007 [16], interest in sharing clinical data in order to investigate ethnic differences in drug pharmacokinetics between East Asian people has risen. If enough clinical data can be gathered regarding the ethnic factors affecting pharmacokinetics, efficacy and safety, inter-East Asian sharing of phase I study results could become a reality. In addition, countries such as South Korea and Singapore have established policies to promote clinical trial implementation in their own countries [17], [18]. As a result, the number of phase I trials being conducted in the Asian region (except for Japan) is increasing, giving rise to a global shift in where phase I trials are conducted. This may mean a possible decline in the demand for phase I trials in Japan.

The quality assessment based on the MHRA phase I accreditation scheme revealed that most of the sites met the Standard Accreditation criteria. The remaining unfulfilled criteria are generally thought to be manageable if necessary. In terms of supplementary accreditation which has more strict criteria, 3 out of 11 sites did not meet most of them and hence were unlikely to be accredited. On the other hand, the other 8 sites could receive accreditation if procedures and institutional training are implemented as a part of their contingency planning. Most phase I study sites in Japan were not set up in a hospital with critical care facilities. Nonetheless, a certain number of sites took countermeasures such as contracting with other hospitals to deal with medical emergency situations resulting from a clinical trial. Each site had undergone an inspection by either domestic or foreign health authorities. Approximately 70% of the sites were aware of the MHRA accreditation scheme. On the other hand, our investigation of official websites of the sites revealed that 67% of the study sites (10 of 15) did not have an English page link that transmits the information to sponsors abroad (as of 28 June 2012).

Recently, the Ministry of Health, Labour and Welfare released their decision to initiate a project to improve early and investigational clinical trial sites, which aims to build a new structure in which FIM trials and Proof-of-Concept trials in Japan for medical compounds discovered by Japanese academia and biotech companies can be conducted widely [19]. The purpose of this project is to identify needs within the early stage clinical trial area in Japan and encourage growth of the market for early stage trials by establishing additional new sites that can conduct early stage clinical trials. In order to make Japan a "primary option" for early phase I trials, it is critical to facilitate work in this area and improve institutional capabilities in conducting trials such as FIM studies that can handle high-risk compounds, and to improve the mindset toward globalization.

As discussed so far, our survey revealed that currently Japan has globally-qualified trial sites from a quality, cost, speed and experience standpoint, and are very capable in implementing phase I trials. However, there still is a need for verification of the sites' compliance with standards in order to appropriately conduct FIM trials in high-risk compounds. More measures should be taken to gain global recognition regarding the high capability of the phase I trial sites in Japan.

Limitations

This study has several limitations. The subjects of this survey were primarily sites that are members of the JACIC and own phase I study facilities. Recent report revealed that approximately 200 new phase I trials are registered every year in Japan [8]. This number includes approximately 24 phase I trials for oncology [20]. Based on our survey results, that means, on average, 165 phase I trials of NMEs are conducted per year. It is very likely, therefore, that this survey accurately captures the overall trends in phase I trials in Japan, as the institutions surveyed conduct over 90% of the 165 registered phase I trials. In the actual certification process defined by the MHRA phase I accreditation scheme, accreditation is determined based on objective evaluation by third-party auditors, whereas, in this survey, the same scheme was used, but the results were self-reported by the phase I trial sites in Japan.

CONCLUSIONS

Despite a recent trend toward moving clinical trials outside of Japan, this study revealed Japanese research sites possess many qualities that make them attractive phase I study sites. Our data show that the sites surveyed possess three features in particular that demonstrate why Japan is an attractive location for phase I studies: (1) quick recruitment of subjects, (2) experience in handling both NMEs and GEs, and (3) most have adopted the requirements outlined in the MHRA accreditation scheme that is practiced in the UK. There are, however, a few improvements that can still be made, such as more training, greater experience in handing emergencies, and creating English websites. Once these areas have been strengthened, Japan's capabilities in handling early stage clinical trials will truly be at the forefront, and this will pave the way for these sites to gain global recognition as leading early stage clinical research sites.

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