

# Early Phase Japanese Bridging Studies; Their Global Significance and What to Look for when Selecting a Suitable Contract Research Organisation to Conduct these Studies

**As the pharmaceutical and biotechnology industries are forced to continue to introduce internal efficiencies, companies within these industries must equally ensure they enforce these efficiencies on their external providers to maximise their return on investment (ROI) in their R&D spend.**

Subject recruitment for clinical trials is high on the agenda of pharmaceutical and biotechnology companies when deciding to which country and which clinical research organisation (CRO) to award the conduct of their study. Delays in the conduct of clinical trials are more often than not a result of insufficient subject recruitment, classically resulting in delays in compound development timelines, leading to increased R&D spend. Thus it is essential that outsourcing managers and project teams choose their third party providers carefully.

Healthy volunteer trials can readily be conducted by any number of CROs across the globe, however healthy volunteer trials in specific populations, typically trials of Japanese healthy volunteers, need to be carefully considered in terms of geographic and CRO-specific placement.

The Japanese pharmaceutical market is the second largest behind the US, and changes by the Japanese regulators for developing and introducing new chemical entities (NCEs) for the Japanese market heralded a change in the development process of NCEs within this population demographic. This was and is still seen

as essential for pharmaceutical and biotechnology sponsors seeking to expand their presence in the Japanese market. Prior to these changes, NCEs reached market in Japan often much later than other countries, primarily due to reluctance to conduct these trials in Japan on Japanese subjects because of the perceived lack of availability of potential volunteers, and the cost associated with this research.

In 1998 Japan's Pharmaceutical and Medical Devices Agency (PMDA), adopted the International Conference on Harmonisation (ICH) "Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data" (E5). This recognised procedures under which clinical trial data gathered in one region could be used to fulfil certain regulatory requirements in other regions. This change in approach began the drive towards studies involving Japanese subjects conducted outside of Japan. This, coupled with the acceptance by the PMDA in 2007 of clinical data from non-Japanese patients, has helped to bring NCEs to the Japanese pharmaceutical market in both a cost- and time-efficient manner.

Nevertheless the requirements of the PMDA are expectedly very strict regarding clinical data generated from clinical trials conducted outside of Japan on Japanese and non-Japanese subjects. It is therefore the ability to adhere to the strict regulations, coupled with the ability to find suitable subjects and conduct the clinical trials in a cost- and time-efficient manner, that makes some CROs stand out in the minds of

Japanese- and non-Japanese-based pharmaceutical and biotechnology sponsors, when considering placing clinical studies outside Japan with the intention of submitting the data to the PMDA.

## Global Recruitment of Japanese Subjects for Clinical Trials

ClinicalTrials.gov cites 129 Phase I clinical studies enrolling or due to enroll healthy volunteer Japanese subjects globally since 1998<sup>1</sup>. The data available demonstrates that a dramatic rise has occurred globally since 1998 with regard to the conduct of Phase I studies involving healthy volunteer subjects (peaking at 27% in 2008), in line with the changes in requirements by the PMDA (Figure 1).

As one might expect, Japan still accounts for ~50% of listed Phase I trials involving Japanese healthy volunteers, with the USA accounting for 29.46% and Europe 12.40% (UK 10.07% overall)<sup>1</sup> - see Figure 2.

In line with this is the number of Japanese subjects entered/entering trials, with ~45% in Japan, and ~34% in the US and UK (Figure 3)<sup>1</sup>. However, what is interesting is the ratio of population sizes versus those enrolled or to be enrolled.

Worldwide, approximately 130 million people are of Japanese descent; of these, approximately 127 million are residents of Japan<sup>2</sup>. According to the 2001 UK Census, 37,535 Japanese-born people were residing in the UK<sup>3</sup>. The Office for National Statistics estimates that, in 2009, 34,000 people

## CLINICAL RESEARCH

born in Japan were resident in the UK<sup>4</sup>. In the USA, according to the 2000 Census there were circa 796,700 people of Japanese descent residing in the US, with large percentages of the Japanese population residing in California and New York State<sup>5</sup>.

Interestingly, the UK stands out as the highest recruiter of Japanese subjects into Phase I trials per capita based on the data provided above, with 1.521% of Japanese subjects born in Japan taking part in clinical trials, compared to Japan - 0.002%, and the USA - 0.212%. One must note that not all of the population are either suitable for, or interested in, taking part in clinical studies, and thus although the UK accounts for just 10% of clinical Phase I studies of Japanese volunteers, the data demonstrates the UK is an essential participant in clinical development of NCEs designated for release in the Japanese market.

### What Sponsors Require for the PMDA

All clinical studies require a number of criteria to be met in order for the study to be deemed as valid, and the requirements of the PMDA are no different. The regulations regarding subject selection will differ from study to study, however the PMDA have some strict criteria that must be adhered to if the data is to be accepted by the PMDA.

Japanese volunteers taking part in clinical trials in Japan must be a minimum of 20 years of age at the time of randomisation, and thus this most basic of criteria must be met in clinical trials conducted in Japanese subjects outside of Japan. In addition, in order for a subject to be described as an eligible Japanese subject, both of the volunteer's parents and all grandparents must be Japanese. The volunteer must have been born in Japan, have a valid Japanese passport and must not have lived outside Japan for more than five years.

However, most important is the issue of ethics. As with all subjects involved in clinical studies, each person randomised must fully understand the conditions of the study and what is expected of them, and what they might expect during participation in a clinical study. With Japanese subjects it is essential that the study is explained

to them in detail (ideally by a native-speaking Japanese person), and that the patient information sheet and informed consent are provided to them in Japanese so that each subject can make a valid and informed decision.

The above criteria do not form a comprehensive list of requirements of Japanese subjects becoming involved in clinical studies outside of Japan, in which data will be presented to the PMDA, but they are essential and should be the minimum a CRO with experience of conducting studies on Japanese subjects outside of Japan should expect when reviewing a clinical study protocol involving this demographic of subjects.

### What to Look For when Choosing a Suitable CRO for Studies Involving Japanese Subjects

*"We are world leaders...we are the best...experts in our field..."*

These are all throwaway slogans employed by CROs and clinical trial recruitment "specialists" time and time again - on websites, at conferences and at presentations given to many of you. However, what does this mean? More often than not, a CRO will promote the virtues of why they are better than their competitors via these bold statements, however as the old adage goes, a picture speaks a thousand words. As with all clinical studies, the recruitment of enough suitable subjects in the timeframe provided by sponsors is more often than not the critical factor in preventing delays to the development of a sponsor's compound. As such, the merits of a CRO with regard to

recruitment and subject retention must be evaluated with at least the same care and attention as is given to a CRO's ability to conduct a study clinically and produce good quality viable data.

When choosing a CRO or recruitment specialist to conduct the recruitment of specialist subject populations, which Japanese subjects certainly are, sponsors must consider a number of factors, namely;

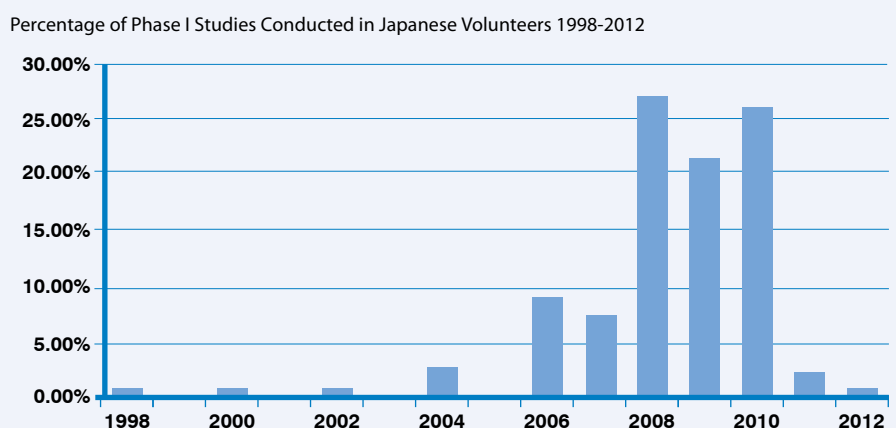
- Company culture and structure
- Track record
- Safety record
- Approaches to recruitment
  - Advertising
  - Attraction
  - Retention
- Safeguard against over-volunteering

### Company culture and structure –

Significant placement on the importance of appropriate company culture and infrastructure is very important both to sponsors and subjects considering taking part (especially for the first time) in a clinical study. A good CRO will understand this and ensure that their staff are appropriately trained to deal with a variety of populations, understanding small but sometimes very important nuances that can show that the CRO is really able to appropriately integrate within the target population with success. A company involved in the conduct of clinical trials involving Japanese subjects can only be taken seriously if they place the appropriate degree of significance on bridging the cultural gap.

Naturally the clinical trial environment subjects enter is foreign to them if this

**Figure 1.** Illustrating the year on year conduct of Phase I trials involving Japanese subjects as documented on clinicaltrials.gov



## CLINICAL RESEARCH

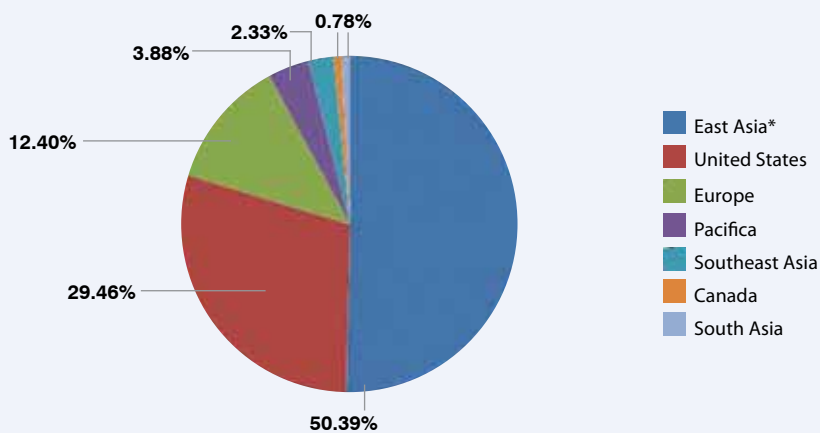
is the first trial they have decided to participate in. This environment can be even more daunting for Japanese subjects, and thus it is vital that a CRO ensures a cultural blend within its employees to meet the needs of its volunteers. This blend must be evident throughout the company, originating from the first point of contact (within the marketing arm) that a potential Japanese subject has with the company, through to its interaction with the subject recruitment agents and clinical staff. Ensuring the company has a core group of professional and well-trained Japanese employees will typically ease initial concerns a Japanese subject may have about becoming involved in clinical research, and their presence in all facets of the company is the extended infrastructure to the Japanese subjects, and helps to cement the bond of trust that is necessary to be successful in specialist research.

When looking for a good indicator of how well a CRO has done in integrating itself appropriately within the target recruitment population, one typically does not need to look further than the repeat rate of Japanese trial participants, and the extent to which previous trial participants recommend friends and colleagues to take part in a trial with a CRO. This is more readily achievable with an inbuilt Japanese infrastructure within the CRO, as it demonstrates to existing and potential Japanese clinical trial participants the importance of these subjects to new drug development within the Japanese population. This inbuilt culture and infrastructure coupled with the trust that still must be worked on continuously, routinely translates into a CRO on which a sponsor can confidently depend.

**Track record** - As previously stated, in today's environment it is not simply good enough to say "we are the best" or "we are world leaders"; these very bold statements need to be backed up with a strong record of achievement. This can more readily be achieved in simpler to recruit standard non-Japanese studies. However, when building up a reputation within a community where reputation is critical to success, as is the case within the Japanese community, a stand-out track record is essential. Sponsors must look at similar previous studies

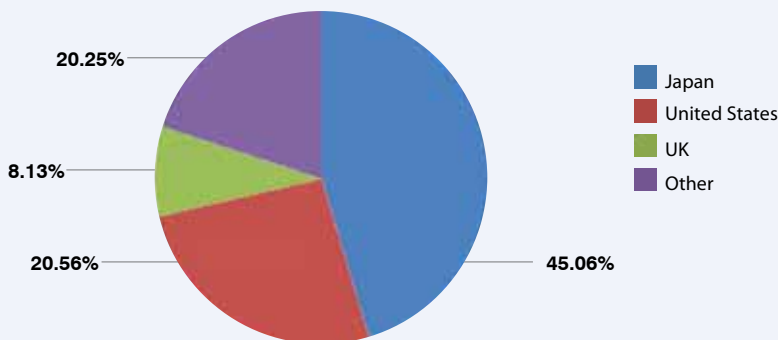
**Figure 2.** Global placement of Phase I trials as documented on clinicaltrials.gov

Geographical Location of Phase I Trials Involving Healthy Volunteer Japanese Subjects (1998-2012)



**Figure 3.** Demonstrates the enrolment ratio of Japanese subjects by geographical location as documented on clinicaltrials.gov

Number of Healthy Volunteer Japanese Subjects to be/already enrolled in Phase I Studies (1998-2012)



conducted by a CRO or recruitment specialist, and scrutinise how well that company performed in terms of conduct and delivery, and most importantly how a company has adapted at times when changes have needed to be made to ensure delivery. This final point is significant to the success of a company, and the delivery of promises made to a sponsor. Typically, a CRO with an in-house specialist recruitment team will have the advantage over a standalone recruitment specialist working with a CRO without the necessary recruitment infrastructure, as they will be able to more readily adapt to change via early warning signals that would have been displayed in the early stages of the recruitment and screening process. If this process is disjointed, with the CRO and recruitment team working in different geographical locations,

necessary and sometimes time-critical changes cannot be effected as quickly as one would like, to ensure the continued smooth provision of service.

**Safety record** – This must not simply be interpreted by the number of incidences of adverse events seen within a CRO, or simply by the safety accreditation a CRO has received from its regulatory bodies. Clinical trial participants understand there is an element of risk associated with taking part in clinical studies, hence the significance placed on providing adequate and ethically approved patient information sheets. However it is about the general care given by a CRO to its trial participants, whether they are at the screening stage of a study, currently enrolled in a clinical study, or are at the follow-up stage. This level of care for a trial participant's

## CLINICAL RESEARCH

medical wellbeing is one major factor that distinguishes a CRO with an inbuilt recruitment team from companies offering standalone recruitment of potential trial subjects. Recruitment companies commissioned to work with CROs or trial sites may never meet a potential trial participant face to face, and may only ever communicate with subjects “on their books” via telephone, SMS and email. Whilst this is efficient in terms of being able to scan greater numbers of potential volunteers in a shorter period of time, with an associated lower initial cost, it does not allow for the development of a relationship between the potential trial subject and the company. In addition, this little (if any) direct contact does not allow for “care” to be established between the potential trial subject and the company asking them to take part in a trial, and thus the level of initial and aftercare, especially if the need for medical care is limited. Whilst this may not be important to many populations, it is clearly evident from the experience of the authors that this is very important to Japanese subjects who are considering becoming involved in clinical trials.

**Recruitment** – Whilst company culture and infrastructure and a good safety record are all important when providing clinical trial services involving specialist populations, a good understanding of the recruitment process required to identify and enrol the correct number of clinically suitable subjects is critical when choosing a supplier of Japanese bridging studies.

Within recruitment, specialist recruitment companies are, as one might expect, usually as adept as the next at setting up marketing strategies to identify and attract subjects to respond to the various advertising activities they employ compared to CROs who have an inbuilt recruitment team. In some cases, where the CRO has not carefully built a solid internal recruitment infrastructure, these specialist recruitment companies are the better option to reduce the risk of not meeting recruitment objectives. This approach may involve more work for the sponsor, as they now have two separate suppliers to interact with and control, but this method clearly can and does often work. The potential problem that a sponsor must consider if taking



this approach is that of responsibility for tasks. For example, if a recruitment company is responsible for generating marketing strategies that translate into ‘interested’ subjects of an adequate number, but the CRO does not handle these interested subjects in the same manner in which the recruitment company set about recruiting them, this may lead to a shortfall in the final number of ‘interested’ subjects. Conversely, if a recruitment specialist does not target the population correctly, this may lead to a number of ‘interested’ yet ‘unsuitable’ subjects whom the CRO has to deal with, once again potentially leading to a recruitment shortfall.

Whilst the above may not have too negative an impact on a large and readily available target population, potential issues as exemplified above will have an amplified impact on smaller populations, such as the Japanese community outside of Japan. A small miscalculation can have an enormous resultant effect, which invariably leads in the short term to delays to a trial, and in the mid to long term to a distrust within the target community, who will think twice about returning to a situation

where they have had a bad experience, but will not think twice about expressing the poor experience to friends and colleagues. As such, a sponsor must cautiously consider how the recruitment of their clinical study will be conducted, by whom, and with whom the ultimate responsibility for both success and failure lies.

A sponsor should ensure that a provider of Japanese recruitment and clinical services can show a realistic and detailed recruitment strategy, with numerous examples of ethically approved past advertising material. A tell-tale sign of lack of experience in conducting clinical studies involving Japanese subjects outside of Japan is the promise of being able to include with ease more than 20 Japanese subjects into a trial in a month. In addition, the volume of material a company can show is more often than not a reflection of how active the company is within the recruitment of Japanese subjects for trials.

Nevertheless, do not just rely on quantity; quality is equally, if not more, important. It should always be the intent of a CRO to be conservative with a

## CLINICAL RESEARCH

recruitment budget and use it sparingly, ensuring a maximum return on investment. A good CRO or recruitment specialist will know which forms of media, and more specifically, which publications, internet and paper-based sites work best for this population, and in what quantity. One must understand that within the Japanese community, saturating the market with advertising can have as negative an effect as not placing enough advertising material in the chosen media. One must be subtle, assured in one's approach, and inventive, to capture the attention of the sub-population of Japanese subjects that would take part in clinical trials.

Once attracted to an offering, many CROs and recruitment specialists who do not employ Japanese employees within subject recruitment do not appreciate the time this population require to make a considered decision. This process can be time-consuming, leaving little time to undertake screening before the intended enrolment date, and this is where a CRO with an inbuilt and suitably equipped recruitment team comes into its own. A CRO offering the full recruitment function is able to adapt quickly and deal with any unexpected needs of the potential subjects, as the recruitment team is always on site to assist the clinical team in ensuring that an adequate number of suitable subjects are available for inclusion at the time prescribed by the sponsor, by being able to cater to the needs of the potential subjects whilst the clinical team go about their business. The key here is that within a CRO offering the full service, the responsibility is shared equally and felt by the whole team, as it is their collective efforts that determine success. These combined efforts, as discussed previously, are also essential in ensuring subject retention within the study, thus minimising the risk of self-withdrawal by the enrolled subjects, which reduces the risk of having to find additional subjects for the study, in turn minimising study timelines and cost.

**Over-volunteering** – It is not the existence of over-volunteering that a sponsor should be concerned with, but more importantly how companies involved in research of Japanese subjects outside of Japan deal with this problem. Numerous over-

volunteering prevention systems are used globally to safeguard against volunteers attempting to take part in more than one trial at any one time. Whilst this problem is not widespread, it must still be dealt with as if it were, to prevent this problem from growing. How a company safeguards against what is a relatively small problem day to day is indicative of the attention to detail they place on all aspects of the work they conduct. Those who take this problem seriously are more likely to have all aspects of their working process in order, compared to those who deem this to be a small problem not worth much investment in time and personnel.

### Summary and Conclusions

The conduct of clinical studies of Japanese subjects outside of Japan is an expanding arena, and a necessity to limit the 'lag' time observed in the past in the approval of new medicines intended for the Japanese market.

Whilst the PMDA appreciate it is necessary to conduct these studies outside of Japan, the PMDA still maintain a very strict set of requirements if the data produced is to be accepted by the Japanese regulators.

Whilst there are numerous countries conducting clinical trials in Japanese subjects outside of Japan, sponsors must be cautious in their approach about the country into which these often intricate studies are placed. The UK and the US stand out as the major contributors of this type of research in the early phases, with no sign that this is due to change in the short to mid term future.

Geographical selection is only half the task when choosing where to place a study of this nature. Fortunately for sponsors, as regulations have tightened globally and CROs have evolved to provide a more tightly regulated and professional service, so the conduct of trials in Japanese subjects has evolved. A number of key factors one should look out for when choosing a site have been identified in this paper, hopefully helping sponsors' decision-making that little bit easier.

### References and Data Sources

- 1 www.clinicaltrials.gov
- 2 Internal Affairs and Communications

Ministry, August 11, 2009 cited in The Daily Yomiuri, August 13, 2009

3 Country-of-birth Database.

Organisation for Economic Co-operation and Development.

4 Office for National Statistics. September 2009

5 Le, C.N. 2011. "Population Statistics & Demographics" Asian-Nation: The Landscape of Asian America.

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