ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 8, Issue 1, 2015

ISSN - 0974-2441

Review Article

SITE SELECTION FOR CLINICAL RESEARCH IN INDIA

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Received: 30 August 2014, Revised and Accepted: 20 September 2014

ABSTRACT

For biopharmaceutical companies, in order to prevent excessive expenditure, completing a clinical trial on time is crucial. Selection of the right study site(s), trained investigators and site coordination team are key factors in determining the timely completion of the study. There are few criteria (study and sponsor specific) that have to be met by the study sites to allow them to qualify and participate in the study. By adhering to these, the value of the sponsor's time and money can be enhanced. Though site selection in India is similar to that in other countries, there are a few cultural differences that the sponsors should be aware of. Based on our experiences, here we provide guidance to address practical issues that may be encountered while selecting a site and an investigator in India. Study sites in India have the potential to become world-class study sites, but require an infrastructure and proper training. With an available patient pool along with an unmet health need, Indian sites offer an attractive alternative to their foreign counterparts.

Keywords: Clinical trial, Infrastructure, Investigator, Site selection, Training.

INTRODUCTION

Globalization has opened the gates for the foreign companies to invest, establish and conduct business in India. This has led major foreign biopharmaceutical companies to focus on conducting clinical studies in India, as many are facing challenges for a timely completion of the study in other countries, due to various reasons such as cost and deficiency of eligible subjects.

The Government of India amended the policies and regulatory guidelines (Schedule Y) in 2005 in an attempt to meet global standards, and to facilitate the efficient conduct of clinical trials (CTs) by global pharmaceutical companies. Well trained and qualified medical practitioners (by education and practice), a large treatment-naïve population, unmet health needs and generation of quality data, along with reforms in the regulatory guidelines has turned India into attractive destination for the conduct of CTs. In a survey conducted by Kearney, a consulting firm, India ranked second to China in a scale which used the US market for comparison and was found to be similar in many categories, such as, regulatory systems and timelines [1].

Selecting the right site to conduct a clinical study in a particular therapeutic area and to meet the regulatory requirements is a major task faced by sponsors globally. Proper site selection will not only result in timely completion of the study with minimal data errors (thereby generating a high-quality data) but will also result in reduced drug development costs.

There has been a steady inflow of CTs to India, and simultaneously there has been much debate going on outside India about the quality of sites and the data obtained. Though site selection in India does not differ much from other countries, there are few issues that are crucial and relate to site selection. Even if the responsibilities are delegated to a contract/clinical research organization (CRO), it is advisable for the sponsor to take on the final responsibility of qualifying the site.

CURRENT RESEARCH PRACTICE

Location and patient pool

The majority of CTs are, at present, concentrated in the major cities of India i.e. Mumbai, Bengaluru, Chennai, Kolkata (formerly known as Bombay, Bengaluru, Madras and Calcutta respectively), Delhi, Ahmedabad, Pune and Hyderabad, due to the availability of medical centers equipped with an adequate infrastructure. These cities are also well connected by road and air, thus aiding easy and better transportation. However, there is a gradual shift to the next level of cities and bigger towns that take into account the availability of patient pools.

Until now, unlike the West, there has been no deficiency of patients and the requirement to advertize for patients has been rare, as every physician has an adequate patient pool. The number of treatment naïve patients for any disease is very large in comparison to Europe or USA.

Identifying an investigator

A qualified investigator to conduct the CT is identified, and the study site is selected. In exceptional cases, in well-established institutions, the investigator may be identified later. Selection of the investigator is usually done via one of the following methods.

1. Database: Most Indian sponsors and CROs have databases of investigators. However, a central database of good clinical practice (GCP)-trained investigators in India is not available.
2. Previous experience with an investigator is taken into consideration and whether the proposed study is in the same therapeutic field. However, if the investigator has conducted a previous study properly and completed on time, they will have more probability of being chosen for the next study in the same therapeutic area. This is one of the commonly followed methods in identifying an investigator.
3. Referral: Through contacts and known principal investigators (PIs), a referral is often sought. This has been found to be very reliable on many occasions
4. Internet: Contact details of medical practitioners in a particular therapeutic area and in the required location can be searched for via the internet. This will often be the method of last resort as the contact details may not have been updated, and there is no means of authenticating the information available. One can get the information through the clinical trials registry of India (CTRI) wherein, contact details of the investigators will be listed for a registered study. Based on the therapeutic area, one can identify the investigators. Searches can also be made by looking in local journals to find who has contributed in different therapeutic areas. Few of the medical fraternity (associations) share the contacts of their members on the internet.

Site identification

Investigator

Many well trained medical practitioners are located in major cities due to the availability of good infrastructure; hence, many trials are conducted in these cities. Availability of trained investigators, large drug-naïve patient pool, and good connectivity, as well as effective transport facilities in smaller (tier 2) cities and towns make them an attractive alternative.

There are institutes where pharmacologists and other non-clinicians are principal investigators and internal medicine practitioners (e.g. neurologists, cardiologists, etc.) as sub-investigator!

Since CTs take time to initiate, it would always be best to keep discussing to investigators on fortnightly basis to make sure that they have not resigned or are planning to change institutes or even retire.

Site coordination team

Since the investigator's main focus is on clinical practice and has little time for clinical research, it is important that a qualified and dedicated site coordination team be in place. This could comprise of a sub-investigator, research pharmacist, and a site coordinator.

Infrastructure

The site should have the necessary infrastructure to conduct the study, such as clinical and laboratory facilities, specimen storage facilities and other study specific requirements to conduct the study. Some of the local labs may not have local accreditation to National Accreditation Board for Testing and Calibration Laboratories (NABL). A list of suspended and withdrawn accreditations can be obtained from the NABL website.

Internet facility may not be available for electronic case report form entry. A mobile data card can, therefore, be used as an alternative.

Most cities and towns in India have power outages frequently through the day and night. A back-up power supply is, therefore, always necessary.

Patient pool

Availability of the patient pool is one of the important factors in considering a site. If the site is a tertiary referral hospital in the district headquarters, or consists of a smaller local population where patients visit the site from far off places (due to the availability of physicians, infrastructure and all treatment under one roof), the site may not be feasible, especially if the study demands frequent visits or prolonged follow-up. However, the epidemiology of the disease being studied should also be considered. When the study is long, a lot of patients fail to return for visits because of the distance that they have to travel to a tertiary care center. A site at a tier-2 city would be more appropriate. One should also consider if the patient population is from the residents or the floating population.

Connectivity

Connectivity by road and air is one of the pre-requisites in selecting a site, to save time in travelling when performing frequent monitoring, transport of samples to the central laboratory within the specified time, patients to commute (time spent) and safety of monitors. Currently, as most cities/towns are well connected by road/train, monitors can travel to the nearest place by air and then by road for monitoring. Study sites in the North-Eastern states are not usually selected due to poor connectivity.

Local political issues

At times, there can be long-standing political issues that may call for "city shutdown," which can deviate the visit schedule of the patients and Monitors. Hyderabad is one example. There are states, where CTs are not allowed (for now) e.g. Madhya Pradesh.

Climate

A few cities in India have hot and humid temperature conditions (costal), whereas other cities are just hot (Delhi, Hyderabad, etc.). Room temperature can vary 15°C (59°F) in the winter to 45°C (113°F) in the summer.

Site feasibility

Study site feasibility must be conducted by the sponsor to evaluate the site, before the final selection of the site is made unless the sponsor has previously worked with the investigator or site. Availability of patients in the required therapeutic area should be confirmed prior to site feasibility as the disease under study may not be prevalent in a particular geographic area. Other factors such as congenital enzyme deficiency syndromes, different standards of care (though India mostly follows western textbooks for treatment protocols) and the availability of alternative medicine systems such as Ayurveda, Homeopathy, Siddha, Unani, indigenous medicines, and non-availability of certain drugs for emergency use, should also be verified.

What about the CRO personnel's experience in working with these sites? It is important that CRO personnel should have had experience with the site and at least have confidence in working with them.

Site feasibility may be done initially by telephone and later by visiting the site. Some sites may not have the required infrastructure; visiting the site not only helps to evaluate the existing infrastructure but also in the evaluation of the investigator and the study team.

Pre-visit

Site feasibility questionnaire

- A study specific questionnaire should be prepared including the details about the investigator (and study team), the investigator's willingness to conduct the study, study specific requirements and required infrastructure at the site
- Qualifications and training of the investigator and contact details, whether s/he is GCP trained or not, experience in conducting CTs in the required/related therapeutic area
- Availability of the study team; if available, training, experience and other relevant details regarding the team should be obtained
- Patient pool - Availability of patients in a particular therapeutic area under study
- Ethics committee (EC) - The constitution, operating procedures and frequency of meetings
- Laboratory and clinical facilities, and other infrastructures: If accreditation of the labs is required
- Study specific details such as experience with similar compounds/ the study drug, should also be collected
- Information on whether the investigator has received any warning letters from any regulatory authority or has been disqualified should also be collected in the questionnaire. India does not have a list of disqualified investigators on the internet
- Involvement in any other CTs, similar or unrelated to assess how much time the investigator can devote to this study
- Role and obligation(s) of site management organization if involved, their role also has to be specified.

Establishing a contact

An investigator should be initially contacted via telephone or email to determine their willingness to conduct the study. The investigator may respond immediately, there may be a delayed response, or they may not respond at all. An investigator's interest or disinterest to conduct a study can be identified only if contact is established. Establishing initial contact can sometimes be a very difficult task for many sponsors.

If an investigator is willing to conduct a clinical study, then a study-specific questionnaire can be sent to the site (via e-mail, facsimile, courier or by post), requesting the investigator to return the completed questionnaire. Based on the feedback, received from the investigator, the site may be considered suitable to conduct the study if it fulfills the sponsor requirements.

A protocol (or synopsis) should be sent in advance so that any questions or concerns that the investigator may have can be clarified. If the investigator has read the protocol before the meeting, it shows the investigator's interest.

Sometimes, due to some obligations, an investigator may agree to conduct a study, but subsequently may due to various reasons, such as a busy work schedule, or other technical issues be not so keen to conduct the study.

Fixing an appointment helps to schedule the meetings at a time suitable to both the sponsor and investigator. Investigators should be informed to keep the letterhead, stamp, updated curriculum vitae (CV), a copy of degree certificate, a copy of the registration with Medical Council of India (MCI) handy during the site feasibility visit. Though the majority of the investigators value the appointment, it may sometimes be canceled due to some unforeseen circumstances. Lack of communication from the investigator in such circumstances may result in the loss of valuable time for sponsors. Hence, it is advisable to re-confirm the appointment 1-2 days before attending.

During the site feasibility visit

The pre-study visit (site feasibility visit) must be conducted by the sponsor (even if responsibilities/obligations are transferred to a CRO), provided the investigator is willing to conduct the study.

During this visit, information obtained in the feasibility questionnaire is verified, evaluated and assessed. A site qualification visit by the sponsor's representative is always required to interview and assess the personnel, their experience, capability to conduct the CTs, and also to estimate the available patient pool at the site. The study protocol is discussed, and all concerns should be addressed in this visit. This is the proper time to highlight any limitations at the site and to ensure compliance with criteria required to participate in the study. Most investigators can assess whether they can participate in the proposed study during the site qualification visit. A site is selected only if the sponsor's representative is satisfied that it meets the previously established protocol-specific requirements.

Sponsors will be concerned about the recruitment of trial subjects at the required rate, so that enrollment will be completed within the stipulated period. Similarly, investigators too may have few concerns regarding a foreign sponsor's awareness of India's specific issues and cultural differences. This visit will be a platform during which both can discuss, express their concerns and can resolve any issues, if any, amicably.

Each new investigator has to be evaluated thoroughly, and an assessment can be made done to a certain extent during the initial telephonic contact and later in the site feasibility visit.

In this visit the following activities should be carried out:

- Verification of the investigator's qualifications (education and training) to conduct the CT in the required therapeutic field. It should not happen that a study on hypertension is been conducted by a neurologist. It should also be verified if s/he is eligible to conduct the study in India as some foreign medical degrees are not recognized by the MCI
- Experience in conducting CTs; number of patients recruited and completed in a similar CT should also be ascertained
- Availability of the study team, qualifications and their experience in conducting CTs
- Verification of a patient database if any: Most investigators do not maintain a patient database and even if they did, they may not be willing to share the details. A few investigators may not wish to enroll patients from their database, for fear of losing their clinical practice. The number of patients that can possibly be recruited at the site for the study should also be estimated
- Verification of infrastructure: The site should have study-specific infrastructure such as storage facilities, centrifuge, facilities to conduct clinical investigations, Internet, communication, imaging capabilities, etc. The availability and quality of the infrastructure should be verified physically during the site visit. Some sites may not have the required study specific infrastructure; which may have to be provided by the sponsor
- Institutional EC (IEC): Presence of an IEC should be ascertained. If possible, a copy of the EC standard operating procedure, list of members should be obtained; EC constitution should also be in accordance with the regulatory guidelines (Schedule Y of Drugs and Cosmetics Act); one of the specifications is that the chairperson should not be from the same institution, in order to prevent bias; hence the list of members should be verified. Information regarding the EC, such as its accreditation/registration with any national regulatory agency, processing fee, frequency of meeting, possibility of granting conditional approval pending Drugs Controller General India NOC etc. should be obtained
- Any other study specific requirements should be assessed for the availability and quality
- During the site visit, the study protocol should be discussed after obtaining confidentiality agreement signed, and a copy of the protocol synopsis can be given to the investigator. Less awareness among some new investigators regarding this agreement requires the sponsor to explain the salient features including the legal points before the confidentiality agreement is signed
- If found feasible, and the investigator is willing to conduct the study, an investigator's consent letter to conduct the study (such as statement of investigator, USFDA form 1572), a signed up-to-date copy of their CV may must be obtained; since some of requirement such as letterhead, updated CV, copy of degree certificate and MCI registration details may not be available, these can be collected later.

Schematic representation of site selection process is depicted in Fig. 1.

Utilization of laboratory services

Feasibility of utilizing the central or institutional laboratory for the study specific investigations at the site should be discussed and assessed during the site feasibility visit.

When the facilities of a central laboratory are utilized, problems related to issues such as collection of samples from site, storage, transport to the central laboratory, possibility of repeat tests should be considered and coordinated throughout the study. Using the services of a central laboratory for laboratory investigations though maintains uniformity, but also has practical disadvantages in terms of coordination, insufficient samples, repeat tests etc.; utilizing the institutional laboratories to perform laboratory investigations can be considered as an alternative. However, certain issues such as accreditation, uniformity in test methods can be a concern if the site's laboratory is used, which needs to be addressed and resolved.

Drawbacks

Investigator

Updated contact details of the investigator may not be available via the internet, thereby posing a difficulty in establishing contact. Sometimes, the investigator may not respond to mail/telephone call(s), even though they are interested in conducting the trial; this often happens due to a variety of reasons, such as busy schedule, resulting in repeated, frequent telephone calls until the contact is established. It is advisable to find out a convenient time to contact the investigator as sometimes it is difficult to contact them, even during the course of the study. The reasons they do not respond to an email can vary, from not being

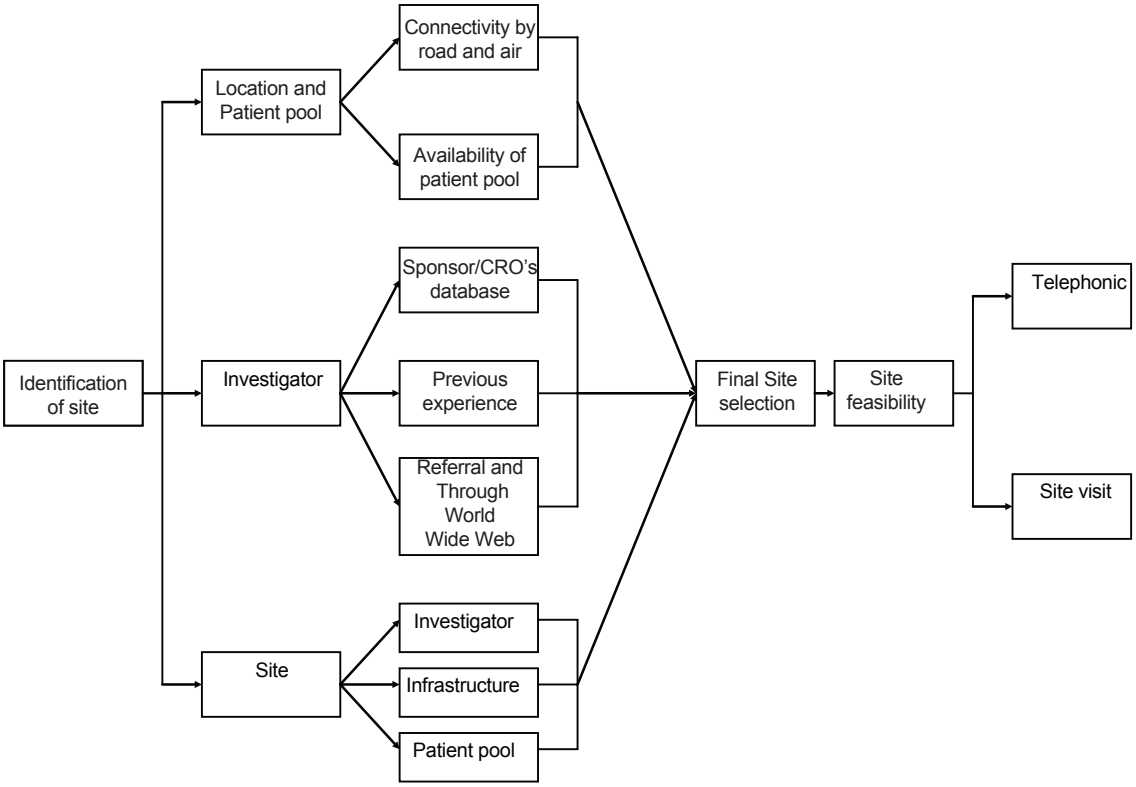

Figure 1: Site selection process in India

well-versed with using a computer, limited technical knowledge and reluctance to check e-mails.

A telephone assessment cannot determine if an investigator can dedicate the time to conduct a study and cannot provide a clear picture of the available patient pool.

Training

Our medical graduates are trained to master the art of clinical practice, rather than clinical research during their training period and preparing them as treatment providers, rather than clinical research scientists. This has resulted in fewer GCP trained investigators capable of conducting global trials in India. Investigators depend on their mentors and sponsors for guidance while conducting a study.

Inadequate funds and infrastructure, overburdened by work, and administrative hurdles, are adding to the problems. Moreover, investigators lack adequate knowledge about the regulatory requirements of India.

Unlike the US, In India, there is no official government website that provides a list of investigators who have received warning letters or have been blacklisted by the regulatory authority. However, now Govt of India has brought major regulatory changes in the Schedule Y of Drugs & Cosmetics Act of 1940 and Rules 1945. Central Drugs Standard Control Organization (CDSCO) headed by Drug Controller General of India (DCGI), is now planning for accreditation EC, Investigator and study sites, of which accreditation of EC is ongoing.

Our observation

Sponsors are concentrating on Hospital/Institutions/Medical Colleges to conduct their studies which are limited in numbers and available GCP-trained investigators are pre-occupied with other studies; hence it is advisable to approach specialist medical practitioners who are working independently in clinics, but experience, qualifications and availability of the support team should be emphasized. In such cases, an independent EC can be utilized for the review of documents. This will help to approach the drug-naïve patients, benefitting large population and also to minimize the commercialization of the CTs.

Addressing the un-met health needs and beneficence to patients are the driving force for investigators to conduct a study. However, sometimes, motivating an investigator and the team by regular contact via telephone, e-mail and site visits will help enhance the pace of recruitment.

Concerns

Investigators in towns and smaller cities without doubt have the required patient pools to conduct a CT, but also have to face challenges such as maintaining quality, enrollment at the required pace and balancing clinical research and patient care. There is also growing concern that poor, illiterate patients may be exploited, thus violating GCP principles. Due to the low literacy rate and usage of many vernacular languages, the informed consent form (ICF) and patient information sheet needs to be kept very simple, easily understandable and should be translated into the local languages (there are 22 languages recognized by the constitution of India [2], depending on the site's location, the ICF and other patient information sheets may have to be translated into at least two or three languages, depending on the region).

According to a market report by Varawalla *et al*. [3], "India has 10,000 GCP-trained clinical research professionals, and 1500 GCP-trained investigative sites" (Varawalla *et al*. 2011), indicating the limitation of selecting experienced investigators in conducting global trials in India.

In smaller cities and towns, availability of GCP-trained study teams will be a concern. Hence, site personnel need to be trained accordingly to study specific needs in order to achieve error free quality data. Government of India is trying to address this issue by training the Investigators. Ministry of Science & Technology has set up Clinical Development Service Agency, an extramural unit of translational Health Science and Technology Institute to cater this need of the hour. This agency is a not for profit organization which facilitates training

of investigators, EC members to ensure they are trained to face the challenges of conducting a clinical trial. This organization focus on the promotion of the scientific research. They also offer other services such as preparation of study documents and other study related activities.

CONCLUSION

Proper site selection is the key factor in determining timely completion of the study, without any major hurdles. Hence, many activities need to be performed and should be done with utmost care. The site has to be evaluated continuously throughout the study since it is not a one-time activity performed at the time of site selection. As problems may be expected to arise at any time during the study, which can delay its completion, continuous and vigilant evaluation of the site is absolutely necessary. Sponsors have to dedicate a lot of time and effort on this aspect. With proper training and supervision, many sites and institutions in towns and districts can be utilized.

A well-defined site selection and site management procedure is required to protect a company's expenditure; successful completion of a study within a budget and timelines and to ensure high performance and competitiveness (not just getting high numbers of patients who do not comply with the protocol specified visits or high screen failures), meeting global and Indian regulations and guidelines generating high quality data. With adequate training, study sites in India can attain world class status.

ACKNOWLEDGMENTS

This article is based on a lecture given by the authors at 34th Annual ACRP Conference and Exhibition held at Tampa, Florida, USA during 24-27 April 2010 and years of clinical research experience in India.

We acknowledge the support of James Thorburn, APCRA Ltd., Hong Kong; Dr. Shantala Bellary, Asst. Manager, Global Medical Affairs, Dr. Reddy's Laboratories Ltd., Hyderabad, India and Dr. Binny Krishnankutty Manager, Global Medical Affairs, Dr. Reddy's Laboratories Ltd., Hyderabad, India, in the preparation of this manuscript.

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