

## Feasibility Analysis: The First Crucial Phase of Startup in Clinical Research

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### Abstract

*This review article presents the standard requirements and processes for activities which need attention during the collection of a Confidentiality agreement (CDA)/ Non-Disclosure Agreement (NDA) & Feasibility analysis from a potential investigator during the startup phase of the study. This article presents the roles and responsibilities of participants, and the importance of communication and flexibility during this phase of a study. This article is written in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonized Tripartite Guideline for Good Clinical Practice (ICH GCP Topic E6).*

**Keywords:** Start-up, data, Protocol, Sponsor, Investigator, Site, Synopsis

### Introduction

Clinical Research refers to a systematic investigation in human subjects for evaluating the safety and efficacy of any new drug. In today's scientific era, research is taking a major stride in all streams and newer and better drugs are being introduced to cure ailments, which are difficult to treat. Clinical trials are the mainstay for bringing out new drugs to the market and constitute approximately 70% of the total time and money spent in drug discovery process<sup>1</sup> under which, Sponsor provides the funding, investigational product and the protocol with the objective of getting a Regulatory approved drug or device onto the market<sup>2</sup>; and the Investigator at the site is the qualified and trained individual who accepts full responsibility to conduct the trial according to the protocol, to protect the subjects right and safety and to collect and submit credible data to the Sponsor<sup>2</sup>.

Implementation and conduct of a clinical study can be a complex process that involves a team from various disciplines and multiple steps that are dependent on one another. This article offers guidance for navigating the study start-up and activation process.

The study start-up and activation process begins with the development of a clinical research study plan in the form of a protocol. Other study documents such as informed consent and assent documents, data collection or case report forms, Manual of Procedures, data management instructions, monitoring plans, statistical analysis plans, and study aids for the approval of the institutional ethics committees at each of the study sites, checklists and logs will be helpful, if not already required, to implement a clinical study. The Regulatory submission and follow-up for its approval and, the contract process between sites and Sponsor is often done in parallel with obtaining institutional ethics committees approval; if not, the series of contracting and institutional ethics committees approval activities can add even more time to the startup phase<sup>2</sup>.

The startup phase can be one of the most critical intervals in the conduct of the trial, as it requires targeted strategies from both the Sponsor and the site. Regardless of which strategies are chosen to accomplish these tasks, clear and transparent communication and flexibility to accommodate changes are some of the keys to a successful study startup. This article will identify which documents and steps need to be completed during the collection of a

Confidentiality agreement (CDA)/ Non-Disclosure Agreement (NDA) & Feasibility analysis from a potential investigator and also attempts to discuss in detail the activities undertaken by different parties involved in each of above milestones so as to begin the conduct of clinical research in compliance with Good Clinical Practice. Both Sponsors and sites need to be flexible while completing below study startup activities<sup>2</sup>

## **Discussion**

### **Identification of clinical site**

When a Sponsor or contract research organization (CRO) is looking for investigative sites for a protocol; they will begin the process of identifying suitable sites by different means.

A clinical/ investigative site is a medical facility, staffed with a clinical investigator, qualified for performing clinical research. To be qualified as a clinical site, strict regulations are to be adhered to. The foundations for these regulations are defined by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and regulatory authorities, which set the guidelines for Good Clinical Practice (GCP) at clinical sites<sup>3</sup>.

There are many types of clinical/ investigative sites conducting studies. It is useful to have an understanding of these different organizations when looking for and assessing potential places to work. Some of the more common investigative site organizational types are listed below:

#### **Part-time sites**

Investigators at part-time sites participate in research studies but also maintain their regular medical practice. Sometimes these investigators do only one or two studies at a time, while others may participate in research to a greater degree, depending on their interest and the resources they have for doing studies. Most Sponsors like this kind of site because there is greater potential for having study subjects readily available and because the physicians chosen for a study will become familiar with the drug, so that by the time it is marketed, they will be more likely to prescribe it to their patients.

#### **Dedicated sites**

These sites are dedicated only to conducting studies; they do not have any other patients as no other medical practice is carried out at these sites. These sites are generally very experienced, very productive, and have the advantage of being consistent in their practices. They also tend to be aware of which studies they can do successfully and are less apt to accept studies for which they do not think they can enroll sufficient subjects within the given time period.

#### **Academic sites**

Academic sites are those sites, located in universities and teaching hospitals. They tend to do a mix of investigator-initiated research and government-Sponsored clinical trials, as well as industry-Sponsored clinical trials. Often these organizations are headed by "thought leaders," the top specialists in their fields. Clinical trials may or may not be the academic site's primary interest. It is sometimes the industry trials that provide added funding to allow these sites to carry on other research. It is desirable for a Sponsor to use some academic sites in their development programs. This allows thought leaders to become familiar with the new compounds and, hopefully, to become spokespersons in favor of the compound when it is marketed.

#### **Site management organizations (SMOs)**

Site management organizations (SMOs) bring together a group of sites and organize them centrally to do studies. They standardize procedures across sites and often provide standardized materials (standard operating procedures (SOPs), source documents, etc.) to each site. Many SMOs also provide training for their sites and assist the site in compiling and submitting the required regulatory documents. There are several types of SMOs, from those that own the sites

to those with other partnership agreements. They provide investigators to do trials and then place an experienced CRC, Project Manager and Quality Manager in the investigator's site to manage and help conduct the trial. These SMOs usually act as the interface with the Sponsor/CRO and manage the operational aspects of the trial; the physician is utilized for his or her medical expertise and patient base. In this case, the SMO is the main contact for all business aspects of the trial, including grant payments and the investigator is usually paid a fee by the SMO. The main advantage for a CRA when using an SMO is that control over study process may not reside at the site and may be handled centrally if working with multiple sites in the SMO because of the consistency on study practices.<sup>4</sup>

### **The process flow for identification of investigator is as follows**

When a Sponsor/ CRO are looking for potential investigator for a protocol; they will begin the process of identifying potential investigator by different means.

The following recommendations to identify potential investigators are the most frequently used:

- Some of the best ways to locate potential investigators are asking: within own company, for suggestions from current investigators colleagues and from other companies.
- Experience with investigators who conducted other studies for the Sponsor's in the therapeutic area or disease state under study.
- Referrals from other investigators with whom a Sponsor company is already working on a particular product
- Disease foundations and database (e.g., the American Cancer Society, the Lymphoma Research Foundation).
- Site Management Organization—these are organizations that act as helping hand for investigators for certain therapeutic areas and often have a large geographic selection of investigators available<sup>5</sup>.

### **Methods**

1. Once the Investigator is identified by any of the resources; Sponsor/ CRO representative approaches the new Investigator directly for discussing a clinical trial proposal in order to assess their interest for the study/ trial or they may approach the SMO to identify and approach a suitable investigator. The first contact is usually by telephone or sometimes it is a face to face meeting also.
2. Potential investigator shows willingness to initiate the discussion
3. Once an investigator is identified and interested, it is entered in the database for that particular therapeutic area
4. Whenever an investigator site is being approached for participation in a clinical trial, the first step is execution of a CDA/ NDA between the Sponsor/CRO and the Investigator prior to the release of study information. This agreement establishes the obligation on the part of investigator for maintaining the confidentiality of information being provided to him/discussed with him by the Sponsor/ CRO designee. As most of the companies require a signed CDA/ NDA before sharing a protocol summary; in this case, they will fax or mail a confidentiality agreement to the site and have it completed and returned before sending the materials.
5. Once CDA/ NDA is executed, Sponsor/ CRO designee forwards the study feasibility questionnaire/ protocol synopsis/ brief study outline to the Investigator or discusses it over phone to assess their suitability for a particular clinical trial. Investigator provides his response on the study feasibility questionnaire as well as enrollment time-lines. If needed, Sponsor/ CRO designee assists the investigator with questionnaires so that paperwork flows quickly. From Feasibility response, potential sites which meet the study requirements for the study are short listed and communicated to the Sponsor/ CRO Managers.

## **Feasibility analysis/ process**

Upon receiving the protocol/ protocol synopsis/ brief study outline, the investigator can review and determine whether the study merits participation and whether the site has the appropriate resources to successfully conduct the study. This review is referred to as a feasibility analysis.

Feasibility analysis involves considering all of the elements affecting the decision to accept a trial. The Feasibility analysis provides points to consider regarding site enrollment potential, study protocol, and requirements including staff, facility, study grant, equipment and supplies.

Conducting feasibility analysis prior to Site evaluation visit reduces the time and money, as based on the feasibility response, different sites are evaluated and short listed, which facilitates to plan the visits to the most favorable sites to the study protocol.

The Sponsor is not the only entity that needs to determine if a study should be done at a site. It is equally important for the site personnel to make assessment of whether or not a proposed study is a good fit for their capabilities. It is always better to turn down a study that is not a good fit for site than to accept it and fail.

Just as Sponsors have checklists and specific items they need to assess a site, the site should have specific things to assess before accepting a study. The clinical research coordinator, the investigator, and any other people who will be involved in the study should read the protocol and supporting materials before making assessment.

Following is a list of some of the questions; site should refer before agreeing to participate:

- Have we worked with this Sponsor before and was it a successful partnership?
- Are the number of subjects to be enrolled and the timeline realistic?
- Will our patients benefit from this study?
- Do we have the required resources to do the study within given time period?
- Are we interested in the study?
- Do we have access to the right kind of patients for this study?
- How difficult will the protocol be to execute?
- Is the study budget reasonable?

It is recommended that the site use a checklist when evaluating a potential study. After each involved person has made his or her assessment, a group discussion is valuable in reaching a decision. Again, it is much better for a site to pass on a protocol than to take on a project and fail at it. It is always be better off telling a Sponsor that the study can't be done at the site. Most Sponsors will respect decision not to participate when it is based on a thorough analysis, and will come back to the site with other studies that may be a better fit. However once a site has failed at a study, most Sponsors can't afford to try and want to use the site again. Consequently, study feasibility is one of the most important pre-study tasks to be performed<sup>4</sup>.

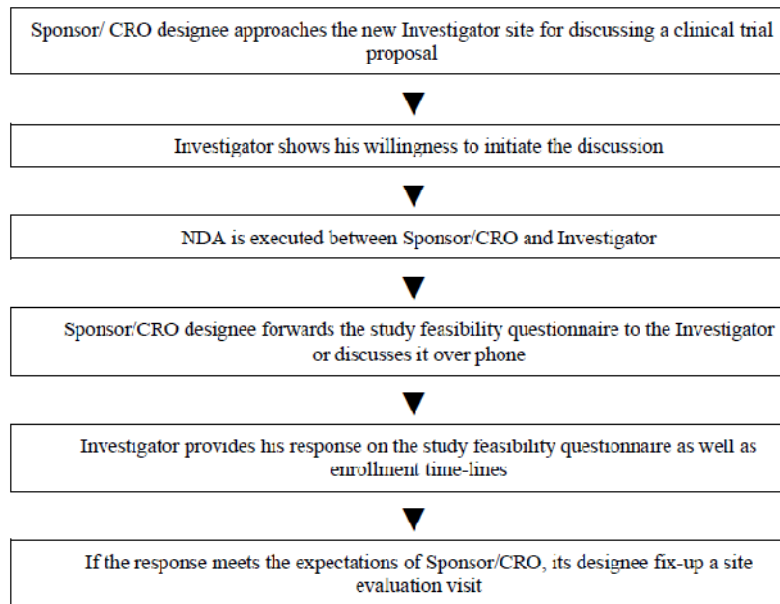
Sites and Sponsors need to share realistic evaluations of past enrollment experiences in order to understand potential enrollment numbers during feasibility discussions. Feasibility discussions may include estimates of previous recruitment numbers, internal and external expert discussions, and investigator surveys detailing research experiences. Whichever strategies are employed, sites should provide Sponsors with realistic data from their prior recruitment experiences. Neither sites nor Sponsors benefit from falsely inflated subject enrollment projections<sup>2</sup>. The investigator, clinical research coordinator and site personnel should always assess the feasibility of doing each particular protocol before agreeing to participate. It is better to decline to do a study than to accept a study and not be able to do it well.

6. If the response of the investigator on the study feasibility questionnaire meets the expectations of the Sponsor/ CRO, and if it appears that there is a high level of interest in the protocol on the part of the potential investigator, and if the Sponsor feels there is good potential for placing a study at the site, it will arrange a time to visit the site in person. This will enable the Sponsor to better evaluate the investigator's capability to do the project. A site evaluation visit is organized by the Sponsor/ CRO representative at the investigator site by getting the prior appointment from the Investigator.

7. Sponsor/CRO designee undertakes the site evaluation visit and reviews the qualification of study team members, composition and operating procedure of institutional ethics committees, source documentation practices and infrastructure etc. and completes the site evaluation visit report. Based on the outcome of the visit, an investigator site is either selected or rejected for participation in a clinical trial. However, if the site meets all the pre-requisite requirements it is highly unlikely that it gets rejected<sup>6</sup>.

**The process flow for selecting the site for site evaluation is as follows**

Whenever a new investigator site is being approached for participation in a clinical trial, the first step is an execution of a CDA/ NDA between the Sponsor/CRO and the Investigator. This agreement establishes the obligation on the part of investigator for maintaining the confidentiality of information being provided to him/discussed with him by the Sponsor/ CRO designee. Once CDA/ NDA is executed, Sponsor/CRO designee forwards a study feasibility questionnaire/ protocol synopsis/ brief study outline to the Investigator or discusses it over phone. If the response of the investigator on the study feasibility questionnaire meets the expectations of the Sponsor/ CRO, a site evaluation visit is organized at the investigator site. Based on the outcome of the visit, an investigator site is either selected or rejected for participation in a clinical trial. However, if the site meets all the pre-requisite requirements it is highly unlikely that it gets rejected.



**Conclusion**

In conclusion, both sites and Sponsors benefit from intentional relationship building, especially during the study startup phase. Building good relationships can lead to positive and productive interactions and successful trials with a minimum of stress. The process should include key strategies, such as clear and meaningful communication, transparency in the data being exchanged, and flexibility to adapt to the ever-changing flow of the study during all of its phases. Being mindful of these strategies and accountable for their implementation can contribute to the success of a trial that goes far beyond a metrics spreadsheet. New Product development contributes not only to science and medicine but to the improvement of the overall health of the world population.

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- [6.] Karen E. Woodin & John C. Schneider. Monitoring Clinical Research; Second Edition; Page 106-111.

## Important websites

<http://www.ich.org>. ICH Guideline for Good Clinical Practice on Good Clinical Practice  
<http://www.cdsc.nic.in/html/GCP.html>. Good Clinical Practices for Clinical Research in India  
[http://www.cdsc.nic.in/html/D & C\\_Rules\\_Schedule-Y](http://www.cdsc.nic.in/html/D & C_Rules_Schedule-Y) (Amended version 2005)  
[www.fda.gov](http://www.fda.gov)

## Author



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Vinod serves Global Drug Development Experts as Country Head- Clinical Operations. Vinod holds a Master's in Business Administration and a Bachelor in Pharmacy and pursuing Ph. D in Clinical Research from Texila American University.

During a career in pharmaceutical industry spanning 18 years, Vinod started his professional career with GlaxoSmithKline in Sales & Marketing and finally decided to enjoy the exciting world of clinical development and made clinical research as a core area of interest. Vinod has been in the field of clinical research for over 10 years now and has expertise in almost all major therapeutic areas in different capacities viz. Asst. CRM, Sr. CRA, Clinical Research Manager at GlaxoSmithKline.

In current profile, Vinod heads finance, business development, human resource and clinical operations in India. His team is involved in phase I to IV clinical trials. He is passionate about clinical project management, and likes to develop, refine and implement the classic project management principles for successful conduct of clinical trials.

Vinod has been a DIA member for about 6 years and lifetime member of Indian Society for Clinical Research.

Vinod resides in Nagpur with his wife Priya, sons Yash & Harsh. Vinod enjoys swimming, reading and playing chess and regularly contributes his time and resources to provide medicines and educational material to needy people via various NGOs.