

WHITE PAPER

# **Clinical Monitoring in India - Practical Challenges and Best Practices**

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## Introduction:

Clinical research industry, a fast emerging powerful knowledge based industry, has thrown open a diverse pool of clinical research jobs for professionals from disciplines like medicine, pharmacy, nursing, science, and laboratory technology. This growing industry attracts many such professionals who wish to make a career in clinical research. This article focuses on the clinical monitoring in India - one of the most critical activities in clinical research - and aims to give new entrants a snapshot of what monitoring is all about.

## Monitor / Clinical Research Associate:

The monitor is a representative from the CRO/Sponsor and is the main liaison between the sponsor and the site personnel. The monitor monitors the progress of the study at various sites and verifies whether the study is conducted in compliance with the GCP and the protocol.

## Monitoring:

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).

## Purpose:

The purposes of trial monitoring are to verify that:

- The rights and well being of human subjects are protected.
- The reported trial data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

## Practical Challenges:

### 1) Challenges while dealing with the investigators

- Scheduling Appointment:** Challenges begin right from the time of scheduling an appointment with the investigators - right from the time of first call. Investigators tend to take this casually and are noncommittal about fixing an appointment. They frequently change appointment schedule as per their requirements disrupting planned schedule.
- Priority to regular medical practice:** Investigators prefer to give priority to their medical practice. Even after arriving as per their convenience, CRO/sponsor representative may have to wait for long to have a discussion with the investigator since; investigators put their medical practice on highest priority.
- Lack of process awareness:** The next biggest challenge is making the investigator aware of the need and seriousness of keeping CRO/sponsor informed well in time about any deviations with patient visits, patient medication, reports etc.

### 2) Protocol non-compliance

Site personnel, including investigators, fail to appreciate the importance of adhering to protocol, which frequently results in non-compliance of protocol leading to a possibility of incorrect data thus eventually resulting in marketing a drug with hidden side effects.

Some examples of protocol non-compliance are: The protocol specifies that all subjects should follow up at the site at monthly intervals. However, one of the subjects stays far away and has missed some visits. This results in protocol deviations.

### 3) Informed consent process and documentation

India has a diverse patients' pool. Moreover, there are 26 distinct languages in India and over 250 dialects. Translation of an informed consent form (ICF) into all of these dialects is nearly impossible. Also, it would require the involvement of language expert for ensured accuracy.

**Challenges during informed consent documentation:** The following challenges are sometimes faced during the documentation of informed consent.

- Performance of informed consent documentation by unauthorized personnel.
- Subject signing consent form after treatment is started.
- Subject signing incorrect version of informed consent form.

According to ICH-GCP (4.8.8), Only the investigator or authorized person should sign on the ICF given by the patient - only investigators are authorized to enroll the patient and hence only they can sign on the relevant documents. It is therefore necessary that, Monitor ensure that only the designated persons sign on the relevant documents.

### 4) Patient recruitment in given timelines:

Considering that the investigators are hard pressed for time, they may not review the inclusion and exclusion criteria completely and may promise to recruit certain number of patients within given timelines. However, as study progresses most of the patients may not meet the inclusion and exclusion criteria due to which the recruitment target may not be achieved within the agreed timelines. To convey this information to the sponsors and to devise new strategies to reach the target recruitment rate then becomes a major challenge. This would affect the cost, time and resources of the project.

### 5) Case record forms and source document verification:

Common errors during case record form (CRF) filling:

- CRF is not always filled completely.
- CRF is not always accurately filled.
- Changes in CRF are sometimes not dated and initialed.

The Monitor needs to be more careful and keen while verifying the CRF with the source data of the subjects, as the accuracy rate of the monitor is assessed with the number of data clarification forms (DCF) raised - more the DCFs less the accuracy rate. The verification is directly proportional to the accuracy rate of the monitor, which is again challenge to a monitor.

### 6) Prevention of Errors, Misconduct and Fraud:

Prevention of errors, misconduct and fraud is a challenging task. CRA/Monitor is the first line of defense against errors, misconduct and fraud. Good monitoring and awareness can help in preventing and in detecting misconduct and fraud.

### 7) Queries, errors and issues resolution at the site:

Frequently, Monitor/CRA have to take immediate decision to resolve issues at the site e.g. at a site visit, if CRA/Monitor

find that subjects are enrolled as per inclusion and exclusion criteria then we may have to let this concern know to the investigator without offending him and may have to do the necessary research work to understand the gap in communication based on different scenarios there may be whole lot of situations where in appropriate decision need to be made at the time.

#### **8) Site Performance:**

Some sites perform better but some do not, The CRA/Monitor should focus on low performing sites and visit a site regularly even though enrollment may be slow or not existent. Slow enrollment may indicate a lack of enthusiasm on the part of site personnel regarding the study. In that case, some CRA encouragement may help, which will probably involve visit. Site personnel often view frequent visit by the Monitor as an indication of the importance of their study to the Sponsor. Sometimes a few extra visits are all that necessary to get a study back on track or to re-establish priorities at the site.

#### **9) Time Management:**

Time management is also one of most challenging task being a CRA/Monitor. The monitor's job requires 60-70% traveling of his total job. So he/she should enjoy traveling as this job involves a lot of traveling. Traveling from hotel to hotel and from city to city can become exhausting and all-consuming endeavor, and the repetitiveness of travel is often the most difficult part of this job. Coordinating and attending business meetings nationally or internationally, air travel, rental cars, hotels, and even differences in food from city to city are inherent challenges of the job.

#### **Best Practices:**

Over the years, pharmaceutical companies turned from in-house management of the clinical trials process to a totally outsourced model, relying on CROs to manage entire studies from beginning to end. However, as sponsors' experience with this method of pharmaceutical development matured, many of them identified issues of resource management and quality control, leading them to explore other options such as functional outsourcing. In the functional outsourcing model, the outsourced provider manages specific functions within the study, while the sponsor maintains overall management and control of the study.

#### **Training the study staff before starting the study:**

It's always better to make the study team members aware of the type of the study, the respective sponsors of the study and the timelines of the study. We can go ahead and ask their inputs in regards to their requirements, which would assist them for the study. Similarly, we should have training material and training schedule formulated in advance which would assist the team members to resolve their queries and provide them direction and guidance for the smooth conduct of the study.

- 1) Awareness of Protocol, SOP and GCP Compliance programs at the site:** As per the requirement, Monitors while conducting the pre-study visit usually should assess the site staff's GCP knowledge and gauge their awareness to know whether or not they require the GCP training. Conducting continuous GCP as well Protocol awareness programs may result in the credible and accurate data and effective documentation.
- 2) Good Documentation Practice:** Since, our industry is very critical and sensitive as it deals with people's health it is necessary to have all details reported in the hard copy. As per the country regulations it is also necessary by law to maintain the required documents with the relevant data. Hence, it is always said **"if it is not documented then it is not done"**.

3) **IMP administration and Accountability:** The site personnel should understand the importance of administration and accountability of Investigational Drug. Document 5 R's of Investigational Product:

**Right drug to Right patient at the Right time in the Right Route.**

- 4) There should be regulations requiring intense monitoring, reporting and reviewing of clinical data, especially if a placebo is used.
- 5) There is an acute need for a Government department to oversee the protection of vulnerable populations. Also, a special set of precautions for phase I trials are required.
- 6) In order to conduct need-based trials, a public sector CRO should be set up. This CRO could also be involved in training professionals in the area of clinical research.
- 7) Research subjects need to be insured.
- 8) Dealing with noncompliance issues, evaluate the situation and follow up on corrective action, if further need to notify the regulatory authorities if correction not obtained.
- 9) There is need to develop expertise in approving and monitoring a trial, and also in the enforcement of regulations. Furthermore, there is a need to train people in research design, data management and analysis of clinical trial data by web based or conducting workshops.
- 10) As per the job requirement, Monitor should be SMART.  
S = Spokesperson  
M = Manager  
A = Auditor  
R = Reporter  
T = Trainer/Traveler

## CONCLUSION:

At last I would like to conclude that, to be a SMART monitor one needs several special skills: initiative, confidence, good interpersonal relationship, eye for detail, communication, flexibility, focus, time management, adherence to commitments, problem solving ability, and adaptability to changing environment. The monitor's job is not easy to deliver, since **"it is more art than science, more skill than luck, and more experience-driven than textbook-learned"**.

## References:

- 1) [www.google.com](http://www.google.com)
- 2) [www.centerwatch.com](http://www.centerwatch.com)
- 3) [www.ich.org](http://www.ich.org)

