Introduction

In the recent past the number of clinical trials conducted in India is increasing steadily. However, there are certain practical issues, which may be either major or minor, that needs to be addressed by the investigator, Clinical Research Organization (CRO) and the Sponsor. If we are able to address these issues, then the credibility of the data generated from the clinical trials would be certainly worth and it would be highly appreciated by the regulatory agencies. The objective of this paper is to bring out certain issues in the conduct of the clinical trial and to suggest suitable remedies to prevent such issues in future. This paper would certainly beneficial for the future clinical trial Sponsors, CROs, investigators and those who are involved in the clinical trial profession.

Issue 1: Protocol Violations

Due to over enthusiasm, some investigators tend to admit the patients to the trial before selection criteria is checked fully. Sometimes, this could be due to the delay in getting the results from the laboratory. In this situation, the patients started taking the trial drugs and later on they will be withdrawn from the trial, if selection criteria are not satisfied. The investigators should avoid this kind of situation at any cost. Investigators should be advised to strictly follow the protocol and ensure that all the inclusion and exclusion criteria are satisfied before the subject enrolled in to the trial.

Another possibility is that when there are too many inclusions / exclusion criteria for a particular trial, then there is a possibility of missing one or two in the long run. Hence, the sponsor should try to minimize the number of inclusion / exclusion criteria would reduce the chance for protocol violations.

Yet another tendency among clinical trial investigators is that the borderline values for particular biochemical parameters would be ignored if the parameter were one of the inclusion criteria. For example SGOT > 60 IU/ML is the inclusion criteria for a patient in a particular clinical trial, and then there is a tendency to admit the patients with SGOT value 60 IU/ML. Finally this patient becomes ineligible for the trial as per the protocol. Strict monitoring and motivation are the possible ways to curtail these kinds of protocol violations in a clinical trial.

Issue 2: Lack of Standardization of laboratory procedures

Some times, the standardization of lab procedures are not achieved despite training the personnel in a particular central lab due to various reasons such as non availability of sufficient kits of a particular brand. Yet another reason could be the frequent change of personnel in the lab. Again, the precision of lab estimates varies from lab to lab due to their local lab settings. Some labs report very accurate results whereas the other labs report very less precise estimates for even very highly sensitive tests. Finally, the reporting units may be different for different centers.

In order to achieve the maximum standardization among various laboratories involved in a particular clinical trial is to have a uniform training to be conducted in a particular central lab to ensure that all the personnel involved in the laboratory procedures should follow the same procedures throughout the trial. Also the central lab staff should make a frequent visit to the other participating labs to check the quality and ensure that the lab procedures are same and uniform. If any personnel change is happened in a particular lab, then immediately the same information should be passed on to the central lab and the central lab should make the necessary arrangements to provide the adequate training to the new joinee on the job. It is important to make sure that the adequate kits are available through out the trial period. The sponsor, CRO and investigator should ensure the same during the trial period. Adequate number of kits should be procured before starting the trial.
Some times temperature in the lab could be a concern for good laboratory procedures. It is also important to maintain the constant room temperature in the lab during the trial period. Good quality air conditioner should be installed in the lab to maintain the constant room temperature in the lab. Periodic maintenance should be undertaken to ensure that the air conditioner is working properly.

Finally, the precision of estimates could be achieved by calibrating the machines in the labs with proper periodic maintenance. It is also advisable to make sure that the reporting units are same in all the labs. During the training period, all the trainees must be insisted to report the same units throughout the trial period. It is also important to minimize the change in personnel as far as possible during the trial period. Proper motivation and encouragement should be provided to the personnel to retain them during the trial period.

**Issue 3: Unmet Target and Other Difficulties**

Usually, the site feasibility studies will be conducted to assess the patient population in a particular site before initiating the trial. This information will be given by the PI based on the past attendance of the patients with a particular disease condition. However, in reality, to get the adequate number of patients is very difficult within a stipulated time period especially in case of rare diseases. For instance an individual center could admit only four patients over a period of three years in a particular trial due to stringent inclusion / exclusion criteria. When the recruitment is very slow, then to use the costly drugs before their expiry dates is always a problem. Ultimately, all these suffer the adequate statistical power.

In order to overcome these difficulties, a CRO should be engaged to do site feasibility study in a realistic manner and cross check the results with the peers and pharmacists to confirm that the estimated sample size could be achieved in the stipulated time period. Also it would be ideal to do frequent site visits by the clinical trial monitors and ensure that there is no problem with the patient recruitment. It may be advisable to procure the costly drugs as and when required depends up on the recruitment rate. A dedicated clinical operation team is essential to monitor the progress of the trial. Thus, the CROs play a vital role to ensure that the trial is progressing well in the right direction.

**Issue 4: Specimen Transportation from Trial Centres to the Central Lab**

Some times, the serum samples reach the central laboratory at room temperature from the participating sites while it is necessary to maintain the cool chain. Leakage during transportation is yet another problem while transporting the specimens to the central lab. Delay in sending the specimens from the participating centers to the central laboratory adds the fuel to the burning problem.

In order to avoid the problems related to specimen transportation to the central lab, the sponsor should engage a specialized agency working in the same field with a lot of experience. A CRO would be ideal to engage these kinds of activities to carry out these responsibilities in future. Usually a third party vendor in collaboration with CRO would be ideal to carry out this particular task uninterrupted through out the trial period.

**Issue 5: Drug Inventory**

Maintaining the matching lot is a problem in case of Ayurvedic with Allopathic drugs. These drugs usually have different dates of expiry. Costly drugs are always a problem with respect to procurement. Hence one should be very cautious about the drug procurement. It should be procured on need base and should not purchase whole lot before starting the trial. Clinical Operation team should be sensitized in this issue before starting the trial related activities. Usually the CROs would take care of this aspect while conducting the trials.
Issue 6: Ethical Issues

Based on the positive test results obtained from the site laboratory, the patients are admitted to the trial. While cross checking the results at the central lab by repeating the same tests showed that some of the already admitted patients lab test found negative. Thus the patients who are actually non-diseased based on the laboratory results unnecessarily admitted to the trial, which is unacceptable and unethical. This is very serious issue, which needs to be addressed by the clinical trial society. In order to make sure that only eligible patients are admitted to the trial, there should be some mechanism in which the investigator has to doubly make sure that the lab results are 100% accurate and reliable. No compromise on quality and reliability of the lab tests. The CROs also make sure that labs involved in the clinical trial should be nationally and internationally accredited to National Boards and reliable.

Issue 7: Other Minor Issues

There are certain other minor issues, which need to be addressed while conducting the clinical trials. Irregular follow up by the patients is one of the common issues faced by almost all clinical trial investigators. This could be avoided by sending advance reminders like letters, phone call, email etc. to the patient. There should be good rapport between the patient and the investigator for regular follow up.

Some patients who already admitted to the trial would migrate to distant places and the investigator would not be able to collect the data from these patients. Thus these patients become lost to follow up. This could be avoided by providing some pre-paid stamped envelope to the patient to provide crucial information about the disease condition of the patient at the time of leaving the place. Also it could be advisable to select the patients who would not migrate in the near future.

In multi-centric trials, it is very common that certain sites experience large number of withdrawal / dropouts. This could be due to problems with the poor infrastructure available at the site or it could be due to poor service rendered by the personnel at the site. Remedial action should be taken to minimize the withdrawal / dropouts at the site. Clinical operation team from the CRO could be able to resolve these issues, if they undertake frequent site visits periodically and also conduct surprise visits to assess the situation at the site.

Usually certain Investigators are very enthusiastic in the beginning of the clinical trial. What happens, they usually go for more laboratory tests other than normally prescribed in the protocol. This is unnecessary and unethical. It is also expensive for the site as well as for the sponsor. Investigators should be advised to strictly follow the protocol.

Conclusion and Recommendations

To conduct the clinical trial is a Himalayan task. There are so many people involved in this huge task. The above-mentioned issues are just a few, which could be avoided if we plan properly. Through mutual understanding and by following guidelines such as ICH and US FDA would definitely provide a fruitful result at the end of the trial. The end result is the accumulation of credible data for proper analysis and interpretation. Most of the above tasks could be easily identified by experienced CROs while planning the clinical trial. Hence the sponsors should not only looking for cost-effective clinical trials but also look into the other aspects such as proper site monitoring, smooth conduct of the trial, less drop-outs at individual sites, proper drug inventory, ethical way of patient recruitment etc. needs to be in their mind while initiating a new clinical trial.