CLINICAL TRIALS: GOODS CLINICAL PRACTICE [GCP] CONSIDERATIONS

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INTRODUCTION

A clinical trial is an experiment designed to answer specific questions regarding some observations in the natural history of disease process, or the effect of an active intervention on the same.

A *well designed* and *properly conducted* clinical trial is now considered essential before any new therapeutic modality gains wider acceptance. In the age evidence based medicine the controlled clinical trial presumably provides the final conclusive proof of the utility (or lack of it) of the proposed new mode of therapy. Several advances and refinements in clinical trial methodology have taken place over the last half a century. These have been evolved in response to the need to evaluate the burgeoning list new chemicals discovered to have therapeutic effects and additionally by ethical, legal and good practice requirements.

Observing 'good clinical practice' (GCP) in clinical trials is necessary in order to ensure that:

- Rights and safety of trials subjects are protected, especially with regards to withholdings of the most appropriate treatments, avoidable drug toxicity and failure to compensate in case of serious adverse events and/or disability following trials drug administration.

- The data collected are reliable, accurate, precise and facilitate a decision making process e.g. a legal decision such as permitting the sale of a new drug; or a therapeutic decision to use a drug in preference to other drug/s with similar activity.

Elements of GCP

1. Clinical trial design
   -- Should be appropriate to answer important question/s
   -- Should minimise bias and other errors
   -- Should state the level of significance

2. Proper selection of investigator and trial centre in order to ensure that
   -- The investigator is a person of adequate stature and scientific merit,
   -- Interested in finding an answer to the question that the trial is designed to answer
   -- Has adequate time and resources to devote to the conduct of the trial
   -- Is well equipped with a laboratory and other infrastructure required to collect, store and analyse samples of biological fluids

3. Informed consent by trial subjects including
   -- The nature of the drug and its probable utility
   -- Information regarding potential toxic or side effects of the drug information
   -- That the trial subject can opt out of the trial at any time without having to give any reasons whatsoever

4. Compensation guidelines in case of adverse event occurrence

5. Proper labelling of trial supplies

6. Statement of responsibility and confidentiality

Monitoring Clinical Trials

Once the GCP elements in the planning have been properly taken care of, proper monitoring of the trials assumes the utmost importance. Clinical Trial Monitoring is a science and an art. Trials are monitored, primarily with the protection of the patient's interest in mind. The accuracy, completeness and verifiability of the data is ensured by a diligent monitor. The monitoring procedures ensure compliance to the trials protocol and to local regulatory requirements. Monitoring is thus the act of overseeing the process of a clinical trial, and of ensuring that it is conducted and reported in accordance with the protocol, standard operating procedures (SOPs), GCP and applicable regulatory requirements.

The monitor is the principal communication link between the investigator and the sponsor. Among the vast range of skills required by the monitor the most important by far is his/her enthusiasm about their role in the study. Monitors must be good motivators. They must be observant, diligent, sympathetic and assertive and have an eye for details. The monitor is frequently looked upon by investigators doing clinical trials as some kind of a

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policeman. The monitor is both a friend and a policeman. It is difficult for a very friendly monitor to put things right when they start to go wrong. On the other hand, a very formal approach will not elicit the co-operation of the investigator and his team. A fine balance should be struck, preferably at an early stage.

Pre-trial Monitoring

The selection of the right investigator is important in ensuring the success of the clinical trial. Companies spend vast amounts of money and time in the planning and conduct of a clinical trial and it is understandable why they are often very choosy about the investigator they select for trials. Having the right attitude (specifically towards GCP) and the time to do the job properly are important. The investigator must have enough patients (the type required for the specific trials in question) for example a primary referral centres may not recruit as many refractory patients as a tertiary centre and if you are looking for newly diagnosed patients the tertiary referral centres may not be appropriate. An investigator who gets on well with his colleagues will get more patients referred to him. An estimate of the rate of patient recruitment should be made before the trial actually begins. The inclusion exclusion criteria must be discussed beforehand. It is good idea for the investigator to use it for a week and see how may of his patients satisfy these requirements. Other competitive studies that the investigator may be doing will definitely slow down the estimated rate of patient recruitment. Investigators often underestimate the time required in conduction a clinical trial. *Doing a trial in accordance with GCP requirements is time consuming and tedious and so check out your schedules.*

Although the suitability of the investigator is primary to the trial, the centre and the facilities therein are essential for the smooth running of the trial. Companies sponsoring clinical studies look not only for institutes and centre of repute but also the logistics of carrying on the trial in that centre. The centre must have adequate staff who will be able to devote sufficient time to the trial. Staff involved in the trial should be appropriately qualified and the centre must have a good work culture. Observational skills of the monitors during the pre-trial visits may have meaningful inputs in judging the suitability of the centre for the trial. Is the practice busy, is it too busy, do the staff look over worked and stressed? Do they have enough and appropriate storage space? For example do they have a cupboard or room that can be locked? If the trial drug needs specific storage conditions, does the centre face frequent power cuts, do they have alternative arrangements when power supply has been cut off? This could affect the stability of the drug that needs to be stored at low temperatures or refrigerated. Does the study involve plasma or other biological samples to be stored? Does the centre have these facilities? The list is long and it is important for a monitor to identify beforehand what he is looking for.

Trial personnel should be fully conversant with the protocol and the investigative drug reports. There should be a written log stating each persons responsibilities clearly in conducting the trial. The monitor must ensure that they understand their duties and responsibilities. The selection of suitable research assistant and the study nurse/counsellor/social worker are important as they are people whom the monitor will frequently meet and spend time with.

Monitoring during the trial

Monitoring during the trial involves frequent visits to the centres as well as telephonic follow up. The frequency of monitoring visit is usually decided and agreed upon by the investigator and sponsor. It is a good idea to visit centres after prior intimation of the proposed monitoring visit. A proper planning of the agenda will go a long way in making the visit a success.

Checking all entries in the clinical record forms (CRF) is done against source data or the patient's hospital notes and laboratory and other reports. Informed consent procedures must be visit an inventory of drug supplies should be made. Reconciliation of the amount of drug given to each visit as well as overall drug accountability should be made. It is also important to check if the drug is properly stored. Monitoring also involves a vigilant approach to reporting of adverse events in compliance with the companies SOP's as well as the local regulatory requirements.

End of study

Diligent monitoring throughout the trial is essential to avoid errors in CRF, missing data, illegible data, inconsistencies and unreliable data, Every piece of missing information leads to delay in data analyses and thus the publication of the final report. At the end of the trial all outstanding queries must be resolved. All adverse events must be followed up till they are stabilised. Unused trial supplies, trial drug (after reconciliation) and other equipments is

collected. The investigator should be kept informed of the developments till the final report is ready for review. Archiving arrangements should be inspected and organised if necessary.

If the trial has been monitored diligently and objectively it will show in the quality of data collected, in minimum delay during data entry and analyses and in the timely and smooth management of the trial.

Conclusion

A proper planning and monitoring of a trial is important from the point of view of the sponsor, the investigation and the regulatory authorities. GCP is here to stay and it is important for clinicians to perceive its implications. Documentation is an important part of conforming to GCP- the punch line being "if something is not written, it was not done at all !!"