CLINICAL TRIAL DOCUMENTS

There is a subtle difference between medical practice and medical research. In medical practice the duty of the physician is to treat the patient, to cure or control the disease or disorder and help the patient get along with life. After the patient has left the hospital or clinic, there is little record other than the patient's case file.

In medical research the physician's responsibility is wider, the physician wants to assess the safety and efficacy of a new medication or therapy in comparison with a control one, and with the knowledge gained, established a new (or better) method to treat other patients presenting the same symptoms or disease.

In research it becomes necessary to record the basic physiology or pathology of the patient, and the changes brought about by the therapy. In fact, every thing that the patient experiences during the course of the trial needs to be documented. The regulators would study these documents to assess whether the new medication is better than the control one or not. All documents providing evidence of the patient's response to treatments are known as trial documents.

The Protocol

One of the most important documents in clinical research is the protocol. It is a document that describes the objective(s), design, methodology, statistical considerations, and organization of a clinical trial. The protocol usually also gives the background and reason for which the trial is being conducted, but these could be provided in other documents referenced in the protocol (such as an Investigator's Brochure).

The protocol contains a study plan on which the clinical trial is based. The plan is designed to safeguard the health of the participants as well as answer specific research questions. The protocol describes, among other things, what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study.

The format and content of clinical trial protocols sponsored by pharmaceutical, biotechnology or medical device companies in the United States, European Union, or Japan has been standardized: they are written to follow the Good Clinical Practice guidance issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Regulatory authorities in Canada and Australia also follow the ICH guidance.

Often during the pre-trial phase and sometimes during the trial there may arise a need to revise the protocol. These revisions are known as amendments and the final revision or the latest amendment is the one to be followed during the trial. It is, therefore, essential to identify the protocol by its version or revision number and date.

Deviation from the protocol constitutes a violation, yet sometimes some deviation is allowed, if it is considered not to interfere with the quality of data obtained. One of the sponsor's teams (generally the Medical Monitor) is given the authority to permit protocol deviations.

Prior to initiating the trial all the investigators are provided with a copy of the protocol and they are asked to sign the document to demonstrate their understanding and willingness to follow the protocol.

The protocol contains information about the statistical analysis of the data obtained, and the methods to be used. Generally, no deviation from this is permissible. The protocol also has a statement about the publication policy and unless the policy violates any important law or guideline it has to be adhered to.

Though the contents of the protocol may vary from trial to trial, in general the protocol should contain the following information:

1. Introduction (brief description of the problem and treatment regimen(s)).
2. Objectives and purposes of the study.
3. Study duration.
4. Number of subjects.
5. Informed Consent.
6. Opinion of the Ethics Committee.
7. Subject selection criteria :
    a. Inclusion criteria
    b. Exclusion criteria
8. Methodology :
    a. Study Plan
    b. Study schedule
    c. Study Visits
    d. Study Assessments / Procedures
    e. Definition of efficacy endpoints
    f. Treatment cycles
9. Safety Reporting:
    a. Adverse events (AEs)
    b. Serious adverse events (SAEs)
    c. Abnormal laboratory test values
    d. Abnormal values of other safety parameters
    e. Withdrawal from the Study
10. Clinical laboratory parameters.
11. Other safety parameters.
12. Concomitant medications.

13. Data analysis.
14. Appendixes.

Preparation of the Protocol

Protocols are trial specific and preparation of a good protocol requires inputs from experts in a variety of fields such as domain experts, clinical pharmacologists, statisticians, laboratory personnel, medical writers etc. The job of preparing the protocol is usually assigned to a group of individuals who meet the above requirements.

After the protocol is written it may be discussed with more domain experts who have conducted trials on similar products. Following due consultation, the protocol may be discussed with potential investigators to achieve agreement over the protocol and method of conducting the trial.

Obviously, there will be a number of versions of the protocol, and this document needs to be version controlled. Each copy must therefore contain, the version and date along with the short name or identity of the protocol. This document is a highly confidential document and should not fall in unauthorized hands, even after the trial is complete.

The protocol actually used in the trial must be approved by the regulators and the Ethics Committee. Version control ensures that no old or unapproved protocol falls in the hands of investigators who may use it. If any amendment takes place to the protocol, the document must be resent to the regulators and Ethics Committee for approval.

After the site and investigator have bee chosen the PI must sign the protocol, to indicate his/her willingness to conduct the trial as per the protocol. Since the Declaration of Helsinki is the document to which the PI has to adhere to, sometimes the Declaration is reproduced at the end of the protocol. The investigator signs below the Declaration, indicating that the document has been read and will be adhered to.

Informed Consent Forms

The Nuremberg Code was formulated in 1947, as a direct response to the atrocities committed by the Nazis, in the name of clinical research. The code made 'voluntariness' a precondition to participation in clinical research. This meant that no individual, (free citizen or a prisoner) could be forced to participate in research. In order to document this free choice of participants the form designed and used today is the Informed Consent Form (ICF).

The Nuremberg Code also states that the participant may volunteer to participate in a study only after thoroughly understanding the advantages and disadvantages, the burdens and the likelihood of injury. The ICF used now therefore contains all elements required to give the participant full information about the study before the participant signs it.

In order to protect the participants, their rights and well being, the Institutional Review Boards (IRB) were brought in to oversee research. This body made up of both technically qualified and lay members, is required to review trial related documents

before granting approval for the study. One of the documents essential for review is the ICF.

IRB members review the ICF to ensure that:

1. The subject is provided with all information required to take a decision of participating in the study.
2. There is no misrepresentation of likely benefits or burdens on the patients.
3. The patients are not ever required to volunteer and if they choose not to, they would still get all treatment required for them.
4. They are allowed to leave the trial, even midway if they feel so.
5. There is a due channel for appeal in case they feel that their rights are violated.

The informed consent of a subject is recorded using an informed consent form. This form is the written record of what the subject has been told and what he has not been told. This is the documentary evidence that the subject's participation was voluntary and not otherwise.

Some additional features of the ICF are that it can be used even if the subject is illiterate, by having a witness in whose presence the contents of the document are explained to the subject. For subjects who are legally or otherwise incompetent to sign the ICF, there is a provision for the ICF to be signed by their legal representatives.

This would raise the obvious question as to how the information should be passed on to the subject and in what form the consent must be recorded. For years now this is done by using a document known at the Patient Information Sheet (PIS) and the Informed Consent Form. These two documents may be merged into a large single document or could be considered as two documents, the consent one being short and the other one being larger and detailed.

The first question is what should be included in the Informed Consent Form (ICF) for it to be considered adequate. Guidelines have detailed out all the essential elements of the ICF and the IRBs check the document against the check list of essential elements before accepting the ICF as adequate.

Since ICF is the most important document that ensures safety and well being of trial subjects, it must be clearly understood by the subjects before they provide their consent. Many patients in our country may not be able to read and understand English; hence the ICF has to be translated in a language with which the patients are comfortable. In order to ensure that the translation really conveys the same meaning as the original document, it is back translated into English by another translator, and this is compared with the original document.

In any case the ICF has to be written in a way that it can be understood by just literate people and does not require medical knowledge for comprehension. Purity of language is not essential in this translation; the objective is to make the translated copy easily understood. Thus if the word heart attack is understood by the subjects, there is no need to find the accurate term describing the condition in regional languages.

It must be understood that Informed Consent is not merely a document that is to be signed, but it is a process by which the subject is informed of the trial and the individuals consent is then taken. The subject must be given freedom and time to take the document home and discuss the same with the family.

The ICF one of the most important documents assuring the right so the subjects and needs to be treated with respect that is due to it.

Investigator's Brochure

Investigational Product (IP) or the drug under clinical trials is usually a patented compound, the details of which are not available in public domain. As a result, the investigators have little or no information about the drug, and the same has to be supplied by the sponsor in the form of the Investigator's Brochure (IB).

When a sponsor applies for permission to conduct clinical studies on a compound, the regulators have to be provided with detailed pre-clinical data which includes toxicological and pharmacological data. These data obtained from studies on cell lines, tissue cultures and animals provide the basis for the claim of safety and efficacy for a given indication. The preclinical data are provided to the investigators in an abbreviated (and/or simplified) form, so that they have an understanding of the compound they are studying. This is the Investigator's Brochure, and unlike the Informed Consent Form(s), or Patient Brochure, this document need not be translated in regional languages as most investigators know English.

As the clinical trials progress from Phase I to Phase II and then to Phase III, more and more information becomes available about the compound which is incorporated in the Investigator's Brochure. Though the Phase I investigator has very limited data to go by, investigators at the Phase III have a large amount of human data on the compound.

The IB is an important document for the investigators since it gives all the available information on safety and efficacy of the drug. The main purpose of this brochure is to inform the investigator, what adverse events may be expected during their study. It also helps them to decide whether the AE or SAE observed is likely to be related to the trial drug (IP) or not. If the AE observed has been mentioned in the IB, then the AE is classified as 'expected'. If the AE does not find mention in the IB the AE is classified as 'unexpected'.

The Investigator's Brochure must contain the following information:

- List of Abbreviations.
- Contents.
- Summary – a brief description of significant physical, chemical and pharmaceutical properties of the investigational product, and also pharmacological, toxicological, pharmacokinetic, metabolic and therapeutic information that is relevant to the appropriate stage of clinical trial.
- Introduction provides the chemical name (and generic and trade names, if approved) of the investigational product, all active components, pharmacological class, the rationale for performing further research with the investigational product and anticipated indications for its use. This section

should provide the general approach to be followed in evaluating the investigational product.

- Physical, chemical and pharmaceutical properties and formulation of the medicinal product.
- Non-clinical studies - this section provides the data from animal studies regarding non-clinical pharmacological, pharmacokinetic, metabolic and toxicological characteristics of the investigational drug.
- Clinical studies – this section provides information on pharmacokinetics, biotransformation, safety and efficacy in humans; data on post-marketing experience if the product under investigation has been already approved for use for other indications.
- Conclusions and Guidance for the Investigator.
- References (the references should be provided at the end of each section).

Patient Information Brochure

The other document that carries information, of the trial drug and the clinical study is the Patient Brochure (more commonly known as the Patient Information Sheet). This document provides the relevant information to the patients that would help the participant in understanding the reason for conducting the trial and the methodology in brief. Since this document is meant for subjects who are not medically qualified; the document is written in a simple language that can be understood by lay persons.

The patient information sheet, in addition to specific information on the trial, should contain the following general information:

1. What is a clinical trial?
2. Why are clinical trials needed?
3. How are trials approved?
4. Who conducts a clinical trial?
5. What are the benefits of participating in a trial?
6. How can a person participate in a trial?
7. What happens when side effects occur during a trial?
8. What happens to the results of a trial?
9. What else do I need to know about a trial?

Additionally, what is known about the drug under trial is explained in simple words. The PIB should make it a clear that the trial is comparative and the subject may get the trial drug or the comparator. A brief idea about the method of allocating the patients to the trial arms should be given.

It is common to translate the PIS in the language which the subject understands, and to ensure that the translation carries the same meaning, a back translation is also done. There is generally no such requirement for translation of the IB, since most investigators understand English, however if the original IB is in another language

(French or German) then it would be reasonable to supply the investigators with a document translated into English.

Certain guidelines recommend that the PIS be written in such a way that a class VIII student understands it. Indian guidelines make no such suggestion, but only say that it should be comprehensible for a lay person. In any case the level of understanding differs considerably from person to person and it would therefore be superfluous to make such recommendations.

While translating the PIS in regional languages, generally the aim is to achieve understanding among the subjects. The purity of language is not the aim; hence, it is permissible to use an English word if it is understood well in lay parlance.

The two documents IB and PIS are of great importance in a clinical trial, since the first provides the investigator all necessary information about the trial drug and the second provides the participants all relevant information about the trial. Both these documents are reviewed by the IRB to ensure that they meet the purpose for which they are designed. These documents are also reviewed by the regulators before a trial receives regulatory sanction.

Case Record Form

Case record form is a paper or electronic document designed to record all the information for an individual study subject required by the Study protocol.

The Case record form is used for several purposes:

- to ensure data collection in accordance with the Study protocol;
- to ensure fulfilling of the regulatory authorities' requirements for data collection;
- to facilitate the effective, comprehensive data processing and analysis, results reporting,
- and to promote the sharing of safety data sharing between the study team and other departments of the institution.

The data collected in the study site during the course of a study should be comprehensive and provide true and fair information on what happened to each study subject. Only if the above criteria are met, the study will reliably answer the questions concerning the efficacy and safety of the investigational drug.

All CRF's should include the following data:

1. study title and number;
2. Investigator's name;
3. study subject/patient ID (number and initials);
4. inclusion / exclusion criteria;
5. demographic data;
6. detailed description of dosage regimens of investigational drug;
7. concomitant treatment;
8. adverse events (sideeffects and intercurrent diseases);
9. conclusion on subject's health;

10. Investigator's signature and date.

Additionally, the CRFs should include special pages to record the following information:

1. past medical history;
2. results of physical examination;
3. primary and secondary diagnoses;
4. relevant previous treatment;
5. baseline characteristics, results of interim assessments, evaluation of efficacy endpoints, laboratory tests, description of study procedures etc.

All CRF entries should be legible and suitable for duplication and possible additional sharing.

Generally, each page of the CRF has three or four copies, and it is arranged visit wise. After a visit is over, pages concerning the visit are filled and copies are sent to the CRO, sponsor and data management group with one copy being retained at the site. This process is repeated after every visit.

Such a method prevents changes being made in the CRF at a later stage without the knowledge of the CRO, sponsor or the data management group. If any changes are required, the site must make a note to file and then make changes to the data already entered in the CRF, and send copies of the revised CRF to each party that received the original CRF.

Changes in the CRF should be made without obliterating the original entry. The original value must be crossed by a simple line and the new value entered. Each such change should be initialed and dated by the person who makes the change

Source Documents

After patients have been treated with an investigational product or a standard product, and the trial is completed, all that remains behind are the documents. These documents, if well prepared and maintained can tell the tale of the entire trial. In hospital parlance all these documents form a part of the patients' files. These are known as source documents.

The ICH GCP defines source documents as follows, "Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiche, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial)."

Source documents get created during the trial, and are a record of everything that happens to the patients during the trial. They record the changes in various parameters of the patient, such as temperature or blood pressure, or laboratory test results. They

also record all medical events that occur and all drugs and medications taken or procedures undergone by the patient in the trial period.

The three main types of information that must go into the source documents thus are:

- Detailed information of drugs, medications given to the patient (this includes life support or even Ryle's tube used to aid feeding the patient) along with route, dose and dosage schedules.
- Record all medical events that occur with the patient, along with severity, seriousness, and chronological sequence.
- Changes in physiological and other parameters, as required by the protocol.
- Original reports of laboratories, X-rays or ECG records that belong to the patient.

The site staff transfers data from the source documents to the Case Record Forms (CRF), and these CRFs are then transferred to the data management group for data entry and analysis. Obviously, the transfer of the data from the source documents to the CRFs must be free from errors.

The first level of checks to ensure that errors do not take place while transcribing data from the source documents to CRFs, is by the site staff responsible for filling CRFs. This job is often entrusted to Clinical Research Coordinators (CRC). During monitoring a source data verification of a few or all subjects is done by the monitors. Finally, the auditors recheck the verification, thus leaving little room for errors to enter trial results.

Source documents need to be preserved long after the trial is complete, since if there is an issue even after marketing the drug, the regulators may need to access the original documents of the subjects, to verify the authenticity of data submitted to them. Different guidelines suggest different periods for which the data must be stored or archived. ICH guidelines suggest that source documents be archived for two years after the last marketing approval has been granted, and the sponsor does not intend to make any other application in an ICH region.

Since the investigator has little idea what the sponsor intends to do, the safe option is never to destroy source documents. Alternatively, destroy the source documents after the sponsor issues a written instruction to do so. The written instruction of the sponsor should, however, be preserved forever.

Essential Documents

ICH GCP defines essential documents as "Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced". These documents need to be maintained during the trial at places specified in the guideline.

At the sponsor's location these documents are located in the Trial Master File and at the site they are stored in the Site Master File. The sponsor and the investigator

delegate the responsibility of maintaining these files to one of their employees and document the delegation in the responsibility logs.

Essential documents are classified in three classes, those that pertain to activities before the commencement of the trial, those pertaining to the trial and those which pertain to the phase after the end of the trial.

The following documents are considered as essential documents:

1. Before the Commencement of the Trial

1. Investigator's brochure.
2. Signed protocol and amendments, if any, and sample case report form (CRF).
3. Information given to trial subject.
   - informed consent form.
   - any other written information to document given to subjects.
   - advertisement for subject recruitment.
4. Financial aspects of the trial.
5. Insurance statement.
6. Signed agreement between involved parties.
7. Dated, documented approval/favorable opinion of Institutional Review Board (IRB) /Independent Ethics Committee (IEC).
8. Institutional Review Board/Independent Ethics Committee composition.
9. Regulatory authority authorization/approval/ notification of protocol.
10. Curriculum vitae and/or other relevant documents evidencing qualifications of investigator and sub-investigators.
11. Normal values/ranges for medical/ laboratory/technical procedures and/or tests included in the protocol.
12. Medical/Laboratory/Technical Procedures /Tests.
13. Sample of labels attached to investigational product containers.
14. Instructions for handling of investigational products and trial-related materials.
15. Shipping records for investigational products and trial-related materials.
16. Certificates of analysis of investigational products shipped.
17. Decoding procedures for blinded trials.
18. Master randomization list.
19. Pre-trial monitoring report.
20. Trial initiation monitoring report.

2. During the Clinical Conduct of the Trial

1. Investigator's brochure updates.
2. Monitoring visit reports.
3. Relevant communications other than site visits.

4. Signed informed consent forms.
5. Source documents.
6. Signed, dated and completed case report forms (CRF).
7. Documentation of CRF corrections.
8. Notification by originating investigator to sponsor of serious adverse events and related reports.
9. Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB/IEC of unexpected serious adverse drug reactions and of other safety information.
10. Notification by sponsor to investigators of safety information.
11. Interim or annual reports to IRB/IEC and authorities.
12. Subject Screening Log.
13. Subject Identification Code List.
14. Subject Enrollment Log.
15. Investigational products accountability at the site.
16. Signature sheet.
17. Record of retained body fluids/ tissue samples (if any).

3. After Completion or Termination of the Trial

1. Investigational product accountability at site.
2. Documentation of investigational product destruction.
3. Completed subject identification code list.
4. Audit certificate.
5. Final trial close-out monitoring report.
6. Treatment allocation and decoding documentation.
7. Final report by investigator to IRB/IEC where required, and where applicable, to the regulatory authorities.
8. Clinical Study Report.

Translation of Trial Documents

In a multi-lingual country like ours, people speak different languages and all are not comfortable with English. Patients need to be provided with information in a language with which they are comfortable, though investigators and their staff can be relied upon to read and understand English.

Documents which are meant for subjects, such as the Informed Consent Form and the Patient Information Sheet need to be translated into regional languages for use of patients. These translations should be made with the objective of making the patient understand and purity of language is not the main issue. Thus, common words like Blood Pressure, Heart attack or Diabetes need not be translated since these words are understood by most patients.

It may happen that members of an investigation team or CRO may not be able to understand a particular language in which the documents have been translated. It is therefore a practice to back translate the documents in English and comparing this document with the original one to check if the translation meets the requirement. Obviously, translation and back translation should not be done by the same individual, but different agencies should be used for this purpose.

It is necessary to record the name of the individual/agency which has performed the task of translation in trial files. Translations of documents are a necessary part of Informed Consent and subjects must be given choice to read the consent document in the language they are comfortable with before they consent to participate in the trial.

Filing of Documents

Documents are both a resource for and a product of clinical research. Conduct of trials compliant with GCP is not possible without documents, and every trial would generate documents which bear witness to the fact that the trial was compliant with the GCP. After a subject is treated during a trial, he/she may return to health or otherwise, all that remains behind is documents, and the regulators are going to recreate the trial through these papers.

If not for any other reason, then for regulators alone, the trialists must record everything that happens during the trial. These documents are stored both in the sponsor's (or CRO's) premises and the investigator's premises. The ICH Guideline E6 lists the documents to be stored at each of these places.

Though the guideline lists out each document by name, and specifies where it should be available, this list is guided by mere common sense. The general principle on which storage recommendations are based is given below:

The sponsor, supports the trial at multiple sites, hence the sponsor must maintain a record of the documents which provide details of trial in progress at each of the sites. The investigator must store those documents which provide details of the trial at the clinical site. The file maintained at the sponsor's office is known as the Trial Master File, and the one maintained by the investigator is known as the Site Master File.