MEETINGS IN CLINICAL RESEARCH

Though often derided as a waste of time, meetings do help in business processes. Skeptics have labeled meetings as gatherings where hours are wasted and minutes are kept. Yet at the bottom of the balance sheet of advantages and disadvantages of meetings, the result is in favor of meetings.

A meeting is a gathering of two or more people that has been convened for the purpose of achieving a common goal through verbal interaction, such as sharing information or reaching agreement. Meetings may occur face to face or virtually, as mediated by communications technology, such as a telephone conference call, or a video conference.

Thus, a meeting may be distinguished from other gatherings, such as a chance encounter (not convened), a sports game or a concert (verbal interaction is incidental), a party or the company of friends (no common goal is to be achieved) and a demonstration (whose common goal is achieved mainly through the number of demonstrators present, not verbal interaction).

All meetings should and must follow the same sequence of activities, and they are :

1. Finalizing an agenda for the meeting.
2. Deciding on the date and time as well as the location.
3. Circulation of the agenda.
4. The actual meeting, wherein information is shared, views obtained and decisions taken.
5. Recording of the minutes of the meeting.
6. Taking action on the decisions taken.

An explanation of each of these activities may not be required for many, yet to the uninitiated, these terms might seem daunting. An explanation of each term is therefore being provided.

An agenda is a set of points that need to be discussed at the meeting. If this is prepared well in advance, it helps us decide who is required for the meeting and who is not. Gathering a large number of people usually kills a meeting, yet sometimes senior people need to be called since they can give direction to others, though they may not contribute otherwise.

Date, time and venue of the meeting are an obvious necessity as is circulation of the agenda. When the concerned people have had an opportunity to know what is going to be discussed, they can come prepared with their ideas, suggestions or feedback.

The person who is in the chair generally conducts the meeting. Each chairperson has his/her own style of conducting meetings. Some do not allow any discussion while

some allow every one to discuss everything. Both techniques are obviously wrong, one must allow free exchange of ideas, but disallow members who try to 'hijack' the meeting to discuss something that has no relation to the agenda.

Recording the minutes of the meeting is probably as important as holding the meeting itself. Very often people voice their opinions which they do not own later. Others claim that they were not heard at the meeting or were misinterpreted. Maintaining accurate minutes of the meeting is a very responsible job, most unfortunately it is delegated to the junior most and least experienced member.

Lastly comes the action taken on the meeting (or its minutes). Very often one finds an organization drifting from meeting to meeting without any action being taken on the minutes. However, if the above points are religiously followed, meetings will be as productive as they should be.

In clinical research, as in other businesses, there are a number of both statutory and non-statutory meetings. Statutory meetings are those which must be held as per guidelines for research. There are other meetings which are held periodically to review progress of trials and finally some which are held for trouble shooting.

Investigators' Meeting

Meeting with the investigators is a statutory meeting, which is held before the trial commences. Often after the preparation of the draft protocol, it is discussed with key opinion leaders in the field, to take their advice on the feasibility of the protocol. Here changes may be made in the protocol, and the inclusion exclusion criteria are firmed up. The efficacy and safety variables, to be measured are discussed and firmed up. The opinions of leaders in the field are important since they have the clinical knowledge about the disorder under study, and may have experience in conducting similar trials.

After the finalization of the protocol, the work on site and investigators begins. It might turn out that some of the experts consulted earlier might become investigators, but that is not so always. A fresh investigator's meeting after finalization of the protocol and other trial documents is the one on which the trial hangs.

The main objective of the investigators' meeting is to make all investigators conversant with the trial protocol and procedures. Details like the location, the timing, and the members of the investigators' teams to be invited are secondary to the main objective.

Investigators, though experts in the field of medicine often are ignorant about research methodology. The protocol is for them an alien document, and they must understand it thoroughly if they have to implement it efficiently. A thorough discussion on the protocol is therefore a must during the investigators meeting.

Recruitment procedures need to be discussed during this meeting, and the investigators must be informed about the duration of the trial and the expected rate of recruitment. Subject recruitment is a rate limiting step in clinical research and over 50% of international trials are delayed for varying periods due to slow recruitment. Slow recruitment also means over run of the trial budget and delay in marketing the drug.

Most PIs and their subordinates need to be trained in selection of subjects and the inclusion/exclusion criteria. Some of the inclusion and exclusion criteria are very rigid while some are flexible, and waivers can be granted. The PI must know which of the criteria are rigid and where waivers can be obtained and from whom, this ensures smooth recruitment procedures.

PIs need to be explained the concept of equipoise, that there is genuine lack of knowledge, about which treatment (the new or the standard) is better. In the absence of this, the PI may try to convince the subjects that the new treatment is superior to the standard one. Exaggeration of the benefits of participating in a trial is one of the ethical pitfalls to be avoided.

For a number of investigators, this may be the first trial they are participating in. It is necessary to inform them that they need to approach their Ethics Committee for the approval of the trial. They would have to be informed about the procedure to apply to the EC and the documents to be submitted. An idea about the functioning of the EC would also be useful for new investigators.

Medical specialists conventionally do not bother much about the consent of the patients. They are used to decide on behalf of the patients, what is good for them. PIs therefore need to be made aware of the rights and the well being of subjects, and that free given informed consent is essential for recruiting a subject in the trial.

The PIs need to be explained the financial aspects of the trial, the mode of payment and the need for invoicing the work done. The payment terms must be discussed with the PIs so that there is no confusion or doubt over this.

Reimbursements to subjects are a contentious issue, since investigators often ignore making timely payments. The BBC documentary (The Dark Side of Clinical Research) focuses on this grouse of subjects and this earns a bad name for the PI and the sponsors. Detailed instructions on payments to subjects and a clear understanding and agreement on this issue will ensure that subjects will not have complaints at the end of the trial.

These are the technical aspects of investigators' meeting. Organizers should remember that most PIs are stressed out people and a day or two of relaxation is essential for everyone. Arranging the investigators' meeting in a good and comfortable place has its own intangible benefits, and keeps the PIs in good humor.

The investigators' meeting provides another opportunity to complete the paper work which may not be complete. Collection of signed and dated CVs of investigators, their conflict of interest forms, and other documents may be done when they gather for the meeting. Missing signatures and dates can be added at this time, so that documentation may be completed and trial supplies can be dispatched to the sites.

Initiation Meeting

The main purpose of the initiation meeting is to train the site staff on protocol or trial specific activities. This meeting is necessary since all the site staff does not attend

the investigators' meeting and one cannot rely on the investigators to train their staff on trial specific procedures. Often a long time may have elapsed between the investigators' meeting and the actual initiation of the trial, and all staff may need to be retrained.

Though the responsibilities of the investigator are many, the site staff performs a major part of trial related activities and they need to be well conversant with these procedures. The initiation meeting takes place once all trial supplies have reached the site, and the site is ready to recruit the first subject.

The site staff needs to be trained to play the roles assigned to each of them. Additionally they would need to be trained in the use of randomization procedures, and IVRS if it is used. The pharmacy staff will have to learn the special needs of the investigational product for storage, dispensing and disposal, if necessary. They will have to be instructed in precautions to be taken in case of spillage or breakage of containers.

The staff at the site may need training in recruitment and retention of subjects. Most Indian hospitals are overcrowded and site staff rarely has to go in search of patients. For a trial patient numbers are less important than subject numbers. Site staff must be trained to attract patients towards the trial, by pointing out the benefits of enrolling, without stepping outside ethical limits.

The site staff will have to be instructed in proper usage of the trial drug and the need for accounting every unit of the drug. Other issues that do not appear in regular working at the site such as confidentiality, will have to be discussed, because most site staff are not aware of them. Complete understanding of the staff, on all trial related procedures is essential before the first subject is recruited, since this alone will ensure a smooth conduct of the trial.

The initiation meeting is generally held at the site and usually conducted by a CRA or a member of the project team. It can be held by a conference or a video call, if these facilities are available, but then all site staff should be present. If initiation meetings are not properly held there may be need to retrain the staff midway in the trial.

Periodic Meetings

The sponsor's staff and site staff meet periodically during the trial. These meetings are held when monitoring visits are made to the site. During these visits the monitors (often CRAs) come to check on the progress of the trial. Verification of source data is an important component of monitoring. Site staff should be aware of the process of monitoring and should cooperate with the monitoring.

Meetings are also held when problems arise, and these are trouble shooting meetings. Throughout the study, the site staff would be in touch with the sponsor's representatives, and mutual cooperation is necessary to ensure success of the trial.

Closeout Meeting

At the termination of a trial, a closeout meeting is held. The purpose of this meeting is to signal a formal closeout of the trial. This meeting is organized at the site by the

CRA who has been in regular touch with the site. A number of activities are performed during this meeting, such as :

1. Collection of all CRFs that have been filled in.
2. Collection of all unused trial material and documents.
3. Reconciliation of investigational product and other medication if any.
4. Completion of all financial transactions with the site.
5. Instructing the site about archiving of documents and material.
6. Completion of the site master file (for eventual inspections).
7. Instructing the site about possible inspections by regulators.
8. Formal close of trial.

There are many reasons why a trial is terminated, and they may be positive or negative. Positive reasons include, the logical termination of the trial after the targeted number of subjects have completed the study. In some studies, the trial drug may prove to be superior to the comparator, before the targeted subjects are completed. In this situation, the IRB or the DSMB may signal a closure of the study, since the objectives of the trial have been met. (The objective of a study is not to complete a predetermined number of patients, but to examine whether the null hypothesis is true or false).

Among the negative reasons for terminating the trial, is the gross failure of the investigational drug. Additionally, the IRB or DSMB may signal the end of the trial if the patients were at undue risk or they were not adequately protected. Trials could be stopped if the site fails to recruit the required number of subjects.

In rare situations the sponsor may discontinue the trial due to lack of commercial interest or lack of adequate finance. The marketing of a radically different or more effective and safer drug could also make the sponsor lose interest in the trial. Whatever be the reason, when the trial terminates, a closeout is essential.

The most important job during the closeout is the reconciliation of CRFs. The monitor must review all CRFs before the closeout meeting and go to the site with a list of CRFs which are incomplete or have an unresolved query. The monitor should also carry a list of queries raised and those that have remained unresolved. This is probably the last chance the monitor would get to discuss the CRFs with the PI, since they would then go for storage.

Reconciliation of the trial drug is the next duty of the monitor during closeout. Some amount of trial drugs are bound to remain unused after the trial. The investigators could be tempted to use these in other patients who visit the site. This would be highly irregular since trial medications, by regulations, cannot be used for anyone other than subjects enrolled in the trial. Such a use is fraught with risks, since the sponsor will not pay for the cost of treating adverse events if any were to occur. The insurance companies would also not make any payments should the need arise.

The monitor should carry from the sponsor instruction about the disposal of unused or returned samples of the trial drug/device. A sponsor may choose to recall all the

material for destruction at his own premises or may order the disposal at the site. Which ever be the sponsor's choice the monitor must know the entire procedure for disposal.

The monitor should review the site master file, for its contents. The file must contain the protocol, the ICF, the IB (all the amendments of each) and all the documents that provide a trail to the trial activities.

All administrative issues must be addressed in this meeting, to ensure that all payments have been made, appropriate people paid, and arrangements made for archiving of the trial documents. A checklist helps to ensure that all the necessary activities have been completed before the monitor departs from the site.

The monitor also ensures that the PI sends a report to the IRB about the completion of the study, and prepares a report of the closeout. This report helps the sponsor inform the regulators about the closure of the site. There is no recommended time for the closeout, but it is agreed that the earlier the better. In no case should a closeout be delayed more than 60 days of the last CRF being received in house.

Closeout visits are like filling your "INCOME TAX". If you have done a good job of record keeping all year long you can file your TAX return in a day. If you have been lax in maintaining records, it may take a week.....a month or even more....

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