Health Research Fundamentals
Dr. Sanjay Mehendale
ICMR-National Institute of Epidemiology, Chennai

Lecture - 20
Conducting clinical trials

Hello. In the course of Health Research Fundamentals, today I am going to discuss the experimental study designs or clinical trials.

(Refer Slide Time: 00:16)

The scenario of clinical trials in India has changed over the last 25 to 30 years. In the late 20th century, what was happening was, mostly the clinical trials that were undertaken were by the research institute and also by the pharmaceutical industry, which were limited in nature. But, towards the beginning of 21st century, in the first decade in particular, the clinical trials industry in India grew and expanded very, very rapidly. But in the present decade, it has been facing some kind of challenges because of various regulatory reforms that have happened recently. But overall, the international community particularly the international investigators and sponsors, who want to undertake high quality clinical trials perceive that there are certain challenges for conducting clinical trials in India.

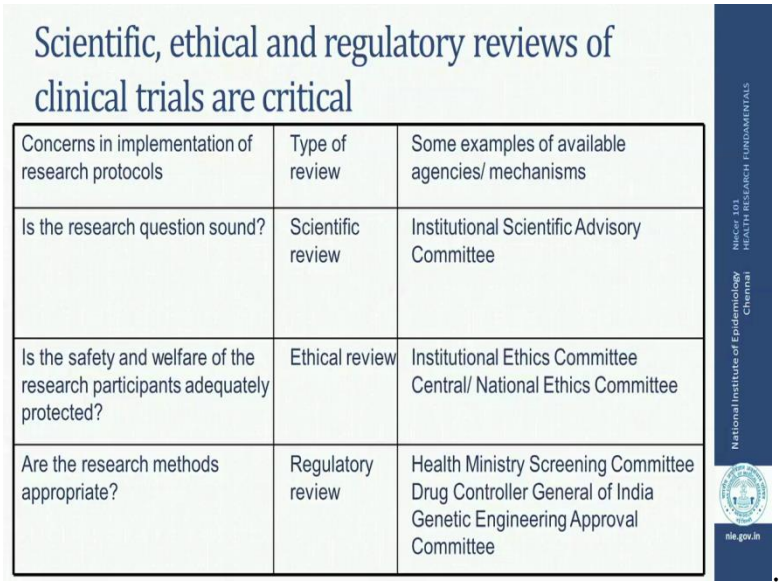
They feel the important ones among them include, the approvals are often delayed;

approvals in terms of the ethical approvals, by the ethics committees as well as the regulatory approvals by the regulatory authorities. There are also concerns about the quality of ethical review that takes place because it has been only in the recent times, a very systematic effort is being taken to improve the performance of various ethics committees of research organizations in particular.

The shipment of samples and transfer of data has always been an issue for international studies in particular because government has some specific restrictions and regulations about transfer of the data as well as samples. It is also felt that, there is an overall lack of duly certified and trained investigators as well as centers in India and again a very systematic effort in this direction is ongoing in the country. What has happened as a part of the regulatory reforms are two important changes suggested now and there is a specific clause of compensation, which has now come up for clinical trial participants and the office of the Drug Controller General of India has given very specific recommendations about how this compensation has to be calculated and up to what period these laws are applicable, that has put in some kind of pressure on the people, who are conducting the trial and there is some kind of haziness around this particular area.

Also, in the area of audio visual recording of informed consent process, all of us will certainly agree that to make ourselves very accountable, to make ourselves very transparent, probably this is the best procedure. If we protect the confidentiality of the trial participant adequately, but carry out audio visual recording that is possibly the best proof of how the consent procedure was actually undertaken here. It is currently applicable to mostly the IND trials, which are Investigational New Drug trials, but again people are confusing this. They are trying to do it in all different kinds of scenario and some kind of thinking, rethinking on this particular matter is happening at the center on this particular thing in India.

(Refer Slide Time: 03:35)



But, for any clinical trial to happen or to start, certain approvals are mandated and they have to be taken in. It all starts with the scientific review; it is a very systematically planned experiment, very meticulously planned. Every step is outlined in detail and basically, what we ensure through the scientific review is whether the research question is sound and usually it is the Institutional Scientific Advisory Committee that decides, whether the study designs that is being proposed here is appropriate. All the methods that are being described under that are accurate and correct.

Then, it goes to the next stage of what is called as the Ethical review. It is done by the Institutional Ethics Committee; sometimes at the national level also it can be done by National Ethics Committee as well. We do it, in our set up of Indian Council of Medical Research and what is really looked at here, is whether the safety and welfare of the research participants is adequately protected or not? This is a very significant aspect of a clinical trial. This review is considered very critical, why? Because, the basic principle is, we should do no harm to research participants by making them participate in a research study and that is a very critical component, which we have to keep in mind.

Another kind of review that happens is that of regulate, which we call it as a Regulatory review. Sometimes it is new drugs, so the setup in our country is the previous Drug Controller General of India, which is now the Standards Control Organization, that we have CDSCO. Sometimes, if the project is getting funded internationally, then there is a

health ministry screening committee, which looks at various regulations around that particular issue. If there are genetically modified or engineered products being used then there is a Genetic Engineering Approval Committee, which looks at that. It is the responsibility of the sponsors and investigators to find out, what kind of regulatory approvals are required for the kind of clinical trial that is being undertaken and all those clinical trial approvals must be taken before initiating the study. Appropriate certification has to be kept on file for ready review by the external monitors or by any other agencies that are authorized.

(Refer Slide Time: 05:57)

But one of the most important things that has to be kept in mind is because it is an experimental study, because we are manipulating the environment, we have to take care of a lot of ethical issues that can arise in this particular scenario. Primarily, the most important thing is have all the approvals been sort for this particular thing, which include the scientific, the ethical as well as the regulatory approval, which is currently the norm in the country at any point of time. Then what? Just getting the initial approvals is not enough; to ensure that the patients or the participants are protected all throughout the trial is also critically important and so some role of ethics committee to monitor this particular process is also important.

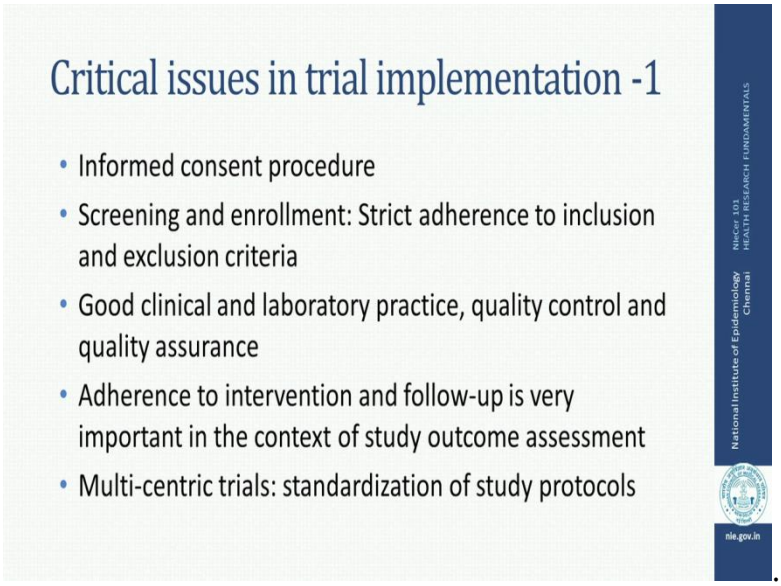
Is there an adequate community engagement and support for this? Somehow, it has so happened that sometime when the people were not made aware of some of the

interventions that where being tried at the national level, there where backlashes because there where something which where believe to be culturally not acceptable and hence it is always important to engage the community and face of the community is visible through many groups. They may be the private practitioners and doctors, they may be the program managers of the country, they may be the doctor attending to the patients, they may be the political people who are taking say, sort of care of the interest of the people and so on and so forth.

One of the important things is to be remembered is every single participant has to sign an informed consent form before participating in a clinical trial. Any trial without an informed consent form is a problem and we have to ensure that this particular process is completed. Also, after the trial gets completed, probably the responsibility of the investigator does not necessarily end. There has to be some kind of a mechanism for providing follow-up care to or post-trial support to the trial participants and that maybe all well thought of right ahead of time and planned in the research protocol.

Use of placebos has raised some questions in the past and it is a topic in itself, but wherever there is a vaccine which we are talking about, where there is no comparable vaccine available earlier of that particular disease, doing use of placebos is considered as justifiable. One of the important things which is an ethical issue, is the confidentiality of the study participants. The study participants sometimes are worried that nobody other than them, even in their own family should know about their research participation and it is our duty as investigators or researchers to protect this interest of the participant and to actually keep all the information totally confidential.

(Refer Slide Time: 08:50)



As I said, the whole process of clinical trials starts with the informed consent process procedure. I have deliberately used this word, it is a procedure and it can be multiple step procedure also. Some patients and some participants may not be able to finish this particular process in one single sitting. You may require multiple sittings to explain the things. The word 'informed consent' here is to be critically looked at, informed is where the duty of the investigator is to explain all the study procedures to the study participant very carefully and also ensure that any question or doubt the person might have is appropriately answered. This has to be now documented, all of us know this. And now, there is also an insistence that for clinical trials it should be, a duplicate copy should be signed and because it is a document, which give some information about the study also. One copy should be kept by the patient and the other should be kept with the investigators team.

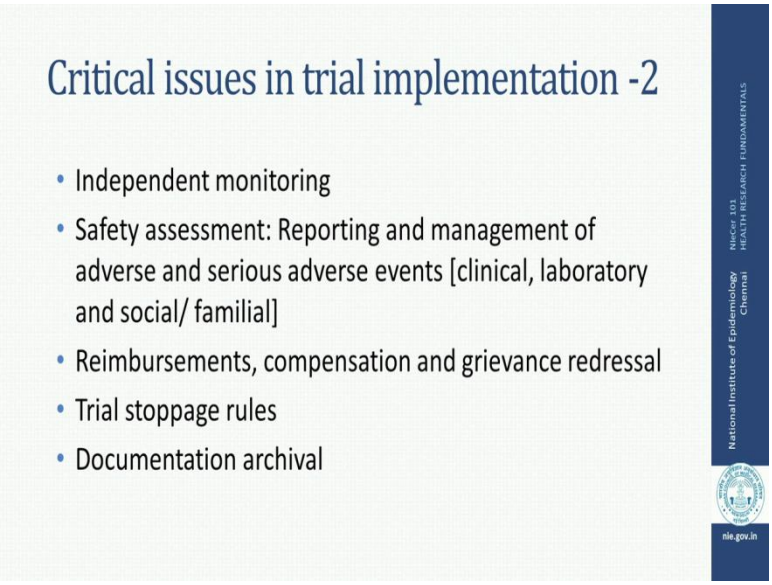
The process of clinical trial participation is generally two step: There is a screening protocol first, wherein those who are interested in participating in the trial undergo some level of screening that is the interview, followed by medical examination, followed by some samples collection and it is ensured that they fit into the eligibility criteria and because as investigators, we have to adhere to the inclusion and exclusion criteria very specifically. It is important that the investigators follow good clinical and laboratory practice. This is absolutely important, this has to be followed all throughout the trial and what this means? This is, although this looks like something like a common sense. Do

the enrollments as exactly as have been defined in the protocol. Do the study procedures as they have been defined in the protocol. Collect the volume of blood as has been defined in the study protocol; ensure that all the visits are made. So, these are the basic procedures, there are responsibilities for the sponsors, there are responsibilities for the investigators. All of them have to follow this.

In clinical trials, one of the most important things, which we have to ensure, is adherence to the intervention. If it is a drug trial, we have to ensure somehow that the patient is taking the drug regularly. If it is adherence with respect to follow-up evaluation, also we have to ensure that the person comes for follow up at the define time intervals. Say for example, we are asking a particular participant to participate in a vaccine trial and if we want to study, periodically up to 2 years from giving that particular dose of vaccine, till what length of time, the vaccine immunogenicity or the antibody levels to that particular vaccine candidate are maintained and if it is decided that once in every 3 months, this evaluation will be done. If patients miss some of these visits, it is very likely that we will miss some of the important data because we may not be able to decide up to what level the antibodies were maintained and beyond which they were not maintained.

There can be a lot of issues which can arise in case of multi-centric trials. Sometimes, trials are conducted in 5, 6, 7, 10, 50 centers in the country and here is where, this is done with the basic purpose is sometimes, it becomes very difficult for a few sites to gather the required number of study participants. So, multiple large number of centers have to be used, but the compromise that we make here is the quality can come down particularly, variations can occur within the procedures that are adopted in various centers and hence, one of the key elements here is the standardization of the study protocols. Training of the people right in the beginning, periodic training of the people and also then using very standard well defined protocols is something which is absolutely important.

(Refer Slide Time: 12:56)



Also in a clinical trial, one of the important prerequisites is to make some kind of an arrangement for an independent monitoring mechanism. This is an agency, which you generally employed by the sponsor and that carries out independent monitoring, looks at for the adherence to GCP, dispensing of study products, how the records are maintained, how informed consent procedure is happening and so on and so forth.

This particular agency has to have a total third party view in doing that particular assessment and should not be influenced either by the sponsors or by the investigators. As we know, as I have been mentioning right from the beginning, safety is one of the most important thing as far as clinical trials are concerned and maintaining or ensuring safety of research participants is of paramount importance and hence, the safety assessments are built in all clinical trials. What is also important is, there are very well defined reporting mechanisms for management of various kinds of adverse and serious adverse events as they happen in, among the clinical trial participants and they have to be timely reported to the regulatory authorities as well as sponsors as well as ethical committees.

We have to remember that all the adverse events may not necessarily be clinical. Sometimes, they can be odd laboratory values or they could be even social or familial problems that are happening as a part of clinical trial participation. All these pieces of information have to be appropriately trapped. Generally, there is an agreement that some

kind of reimbursements should be made to the trial participants. One is for the kind of time they spent in coming over there and the loss of daily wages that might happen as a result of that and also for the travel cost involved, plus maybe some kind of food expenses, which are made particularly, in case of trials which require long term participation of the study participants.

So, but here is where a clear understanding has to be there as to we should know that we are doing reimbursements and we are not doing incentives because sometimes incentives can become coercive. In the sense, the incentives can persuade patients to participate in the trials, even if they are not interested, if the amounts are really large. Recently, some kind of laws and regulation has come in with respect to compensation. We have to be all aware of what is prevalent regulation in the country with respect to the clause of compensation.

It is also important that we have a mechanism for grievance redressal, some of the research participants because it is an experiment and some kind of a experimental intervention is being tried and the some of the people might come up with some kind of complaints, which the investigators may feel are not related to the intervention that is being tried, but the patients keep insisting that it is essentially related to that and hence, there has to be a kind of third party body and it is always believed that grievance redressal team should be there, which is easily available to address these issues in real time.

Every single trial has to have a defined trial stoppage rule right in the beginning itself. Generally, 3 serious adverse events which are defined as maybe; deaths or very serious complications on the previous clinical condition that is what happening, hospitalization due to any cause, these are considered as serious adverse events. So, after any 3 serious adverse events, it is normally decided whether they are related or not related to the trial by a third party body called as Data Safety Monitoring Board, which is an independent entity, which is also predefined earlier and when they allow us to move forward, we move forward in the clinical trial, but these rules have to be defined up front.

Another important thing in a clinical trial is documentation archival. Various sponsors have various expectations with respect to this; some of the trial sponsors require this. All the trial related documents to be stored for a period of 5 years, sometimes 10 years and

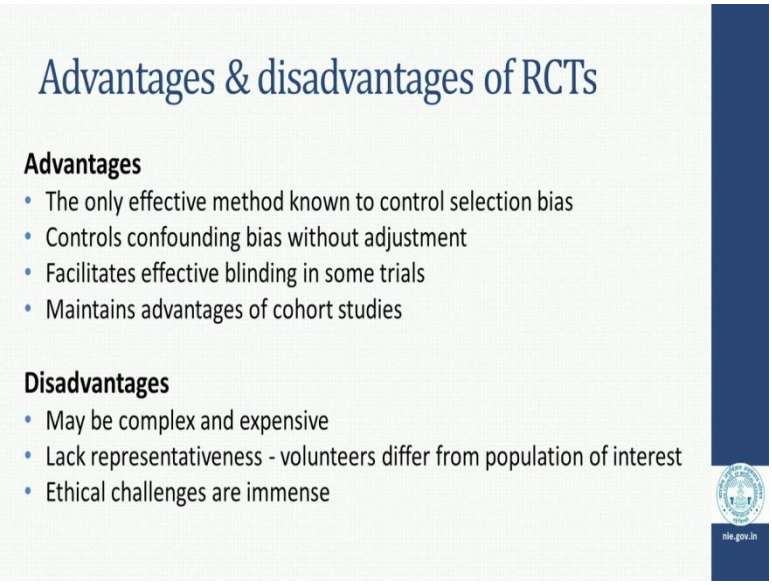
sometimes 15 years, whatever are the regulations we have to comply with that particular expectation.

(Refer Slide Time: 17:30)

There could be some impediments in clinical trial participations. At the patients' level, many times patients do not know about the clinical trials. Sometimes, they do not have access to clinical trials. There is mistrust, suspicion or people are afraid of being participating in clinical trials. Sometimes, they feel there are fees attached to this particular thing. If clinical trials have to succeed, patients have to agree or volunteers have to agree to participate and hence, disseminating this particular information becomes extremely important.

Sometimes, there are some issues at the level of health care providers also. There is a lack of awareness of appropriate clinical trials that sometimes they are unwilling to lose controls of person's care, say for example, a trial is going on in cancer patients, there could be some kind of a fear among health care providers that they would lose their patients to this particular trial once it is referred. Sometimes, they believe that the standard therapy is best and could be also concerned about the administrative burdens that this may add. So, even if there are impediments here the clinical trials are the only way for making a progress in medical science.

(Refer Slide Time: 18:38)



Because, if there are no clinical trials, no new drugs will come, if there are no clinical trials, no new technologies will be tested, no new vaccines will be tested and so they must be supported and the adequate information about clinical trials must be disseminated. Randomized controlled clinical trials have to be carried out in the best possible manner, with the highest possible quality adherence.

Thank you for your attention.