Health Research Fundamentals
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Lecture – 07
Experimental study designs – Clinical trials

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

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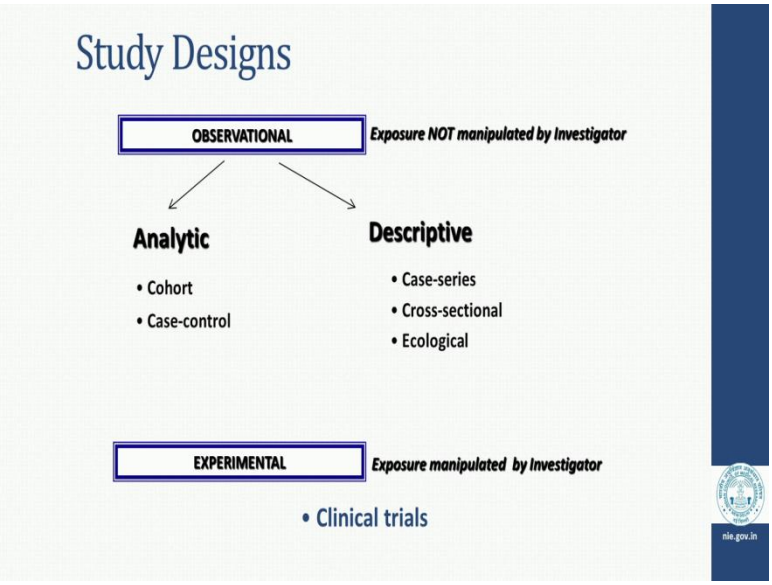

As has been discussed earlier, the various types of epidemiological study designs are classically described as observational designs and experimental study designs. Observational study design is where the exposure is not manipulated by the investigators and there are two different types of observational studies. There could be descriptive studies like a series cross sectional studies or ecological studies and analytical studies include case controls studies, which are retrospective in nature and cohort studies, which are prospective in nature. But, considered as more advanced are the experimental study designs, where the exposure is manipulated by the investigator and a classical example of this is clinical trials.

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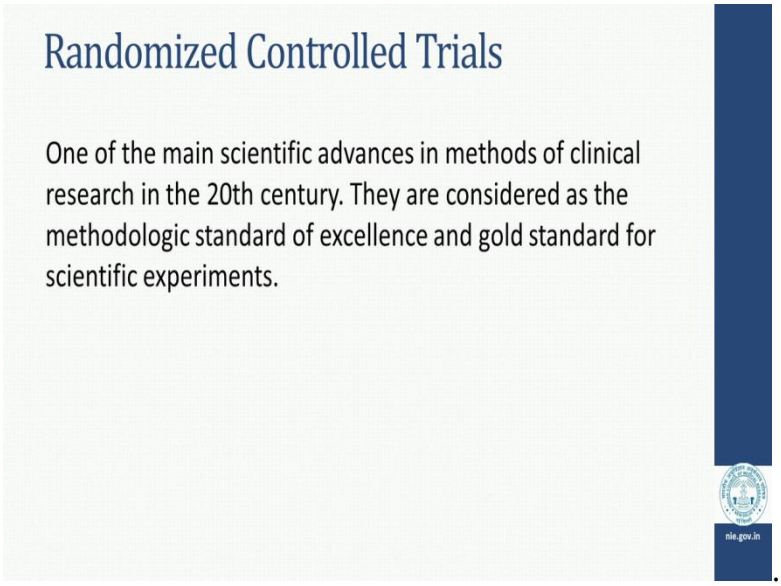

These clinical trials, these kinds of studies were one of the main scientific advances in the last century, they are considered as the methodological standard of excellence, are also described as gold standard for scientific experiments.

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Their main significance is that they are essential for translating the results of basic scientific research into better ways to either prevent the disease, diagnose a disease or a condition or to treat a particular disease and they have a huge translational value. But, primarily randomized controlled clinical trials and we are going to discuss this at length

today.

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These are planned experiments, primarily designed to assess the efficacy of prophylactic, diagnostic or therapeutic agents. It also helps to test out the new devices or different types of drug regimens or new procedures that are being introduced including the investigative procedures, etcetera, particularly in human subjects. Basically, it involves comparing the outcomes in two groups of individuals and when we talk about doing a therapeutic trial, we talk about people suffering from a particular disease, who are grouped into two different groups.

Wherein, one group requires a new kind of a treatment and the other group requires the standard treatment that is being available at that point of time. Then, what is done is over a period of time, they are evaluated, which we call it as a prospective study and we find out how many of them get effectively cured for example. So, this is the prospective nature of the study, all the participants are essentially followed for a certain period of time and that is why it is a planned experiment. Why? Because here is where, as we have discussed earlier in the definition, the environment has been modified, manipulated or modified by the investigator because the investigator has decided that some people will be placed in one particular arm of the clinical trial, wherein the other group will be placed in the other arm of the clinical trial and that is what is the process called randomization, which we will be discussing sometime later.

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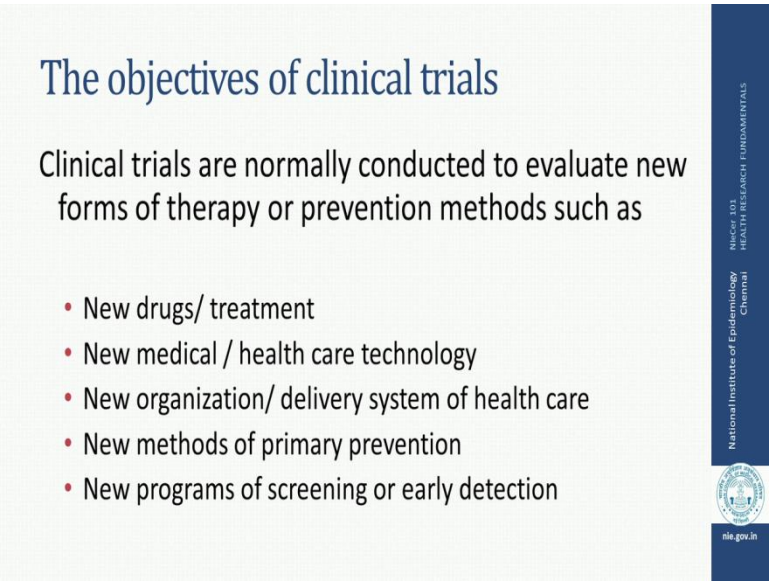

Clinical trials can be broadly used for a variety of reasons as we briefly discussed. New drugs, new treatments, new medical or health care technologies, new organizational or delivery systems of health care, new methods of primary prevention or new programs for screening of early detection of diseases. They could be employed in a variety of scenario.

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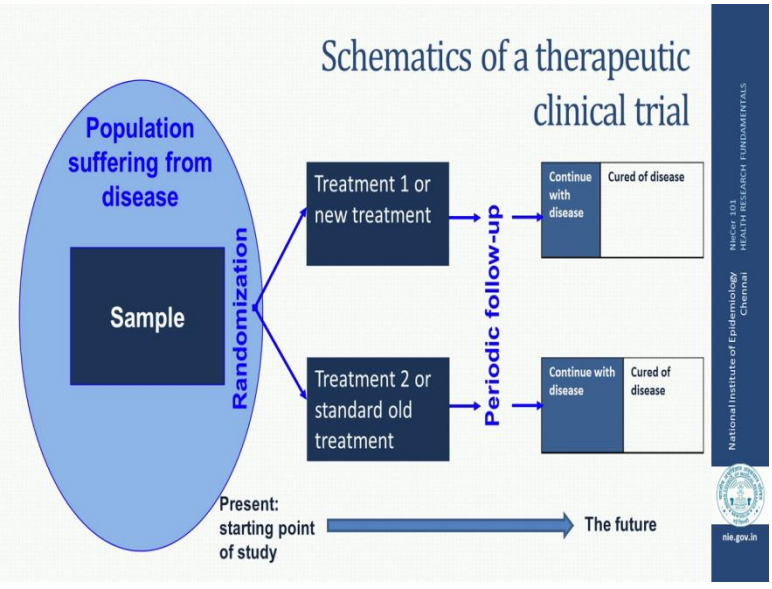

Normally, clinical trials are equated with drugs and pharmaceuticals. So, this essentially have intent of therapeutic benefit. So, if we just think about how this could be done is? We have a large number of individuals, who are actually suffering from a particular

disease. What we do here is? We take out a sample of people, who are, say eligible to apply eligible to, say participate in a clinical trial. Here is where the problem is, that these are the people who should be willing to participant in the study. So, we cannot say that, this particular sample is essentially generalized or it is generally representative of the total population that we are dealing with.

Now, in a process of randomization, which we will talk about they will be sent out to two different arms of the clinical trials. Whereas, one arm will receive the new treatment or one type of treatment, whereas the other arm will receive the standard old treatment or the second type of treatment. Then all these individuals will be prospectively followed up for a defined duration and with a defined frequency. Maybe it is 1 year, once in every 3 months or 2 years, once in every 6 months or whatever and then we assess them again to find out because it is a therapeutic trial. What we want to figure out is how many of them have actually got cured of the disease? And how many continue to have the disease?

The reason why we are testing out a new treatment, we are having an expectation that the newer treatment will have more benefit. So, the number of people being cured of this particular disease would be more compared to that in the other arm and this can be statistically analyzed.

In case of a prevention scenario, say if we talk of new vaccine for example, this can also be tested in a clinical trial design. Here, the type of population will obviously change. Here, we will talk of people or the population, which is susceptible or at risk of developing that particular disease. Here, again we will take out a sample of people who are willing to participate in the study. Like in the therapeutic trial, these will be randomized into two arms, one arm or one group of people in them will receive the vaccine and the other will receive a placebo. This is a critical decision which needs to be really discussed at length, whether it is a placebo or some other type of a vaccine or what can be given in this particular scenario as a comparator arm.

Again, these two groups of individuals are followed for a certain period of time with a certain periodicity and what we try to judge is how many of them in either of the two arms actually acquire the disease? The expectation is that if the vaccine is effective, less number of people in that particular arm who are receiving the vaccine would acquire the disease compared to those who have not received the vaccine in the comparator arm or

the placebo arm. This can also be statistically analyzed and so we decide, whether this particular vaccine has been effective in preventing occurrence of that particular disease in susceptible populations.

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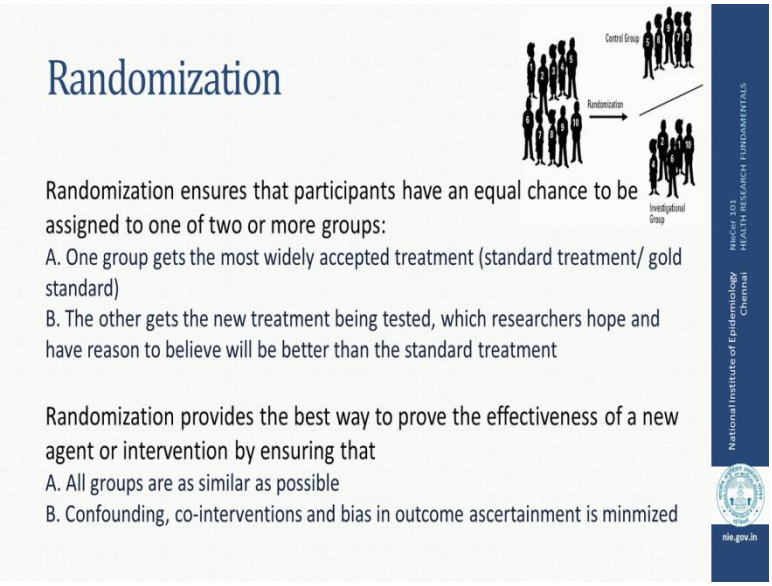

The most critical step in a clinical trial is what we call as randomization. Randomization is a process, where we say that the participants have an equal chance of being assigned to any study group. There may be one study group, there may be two arms in the trial and there may be multiple arms in the trial. Accordingly, the original numbers of participants that are found eligible that get placed into various arms in a pre-decided manner. In the number, in each arm is decided and candidates get assigned or the participants get assigned to different kinds of arms here. What is important here is, the participants do not decide that he or she or they want to participant in a particular arm. It is done through a neutral process. Also, the investigators do not decide, whether a particular participant goes in arm A or arm B or arm 1 or arm 2. It is a process of randomization, which is a third party procedure which decides that.

So, one group gets the most widely accepted treatment, which we call it as the standard treatment or the gold treatment. Whereas, the other group gets the new treatment and here, the hope and expectation is that the newer treatment is better than the standard treatment. This is the process of randomization. So, it ensures that we can test the effectiveness of new agent optimally here because all groups are most likely to be

similar, as similar as possible and confounding, co-interventions and bias in outcome ascertainment can be minimized.

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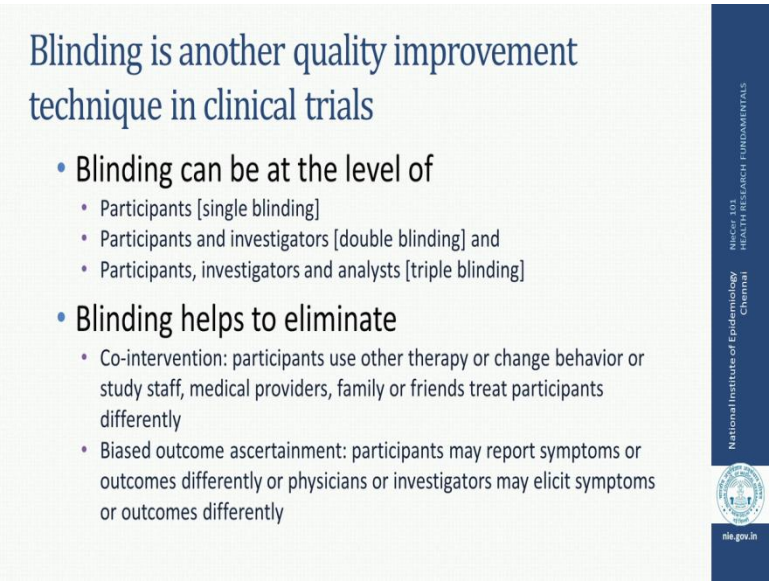

Similarly, blinding is another quality improvement technique, which is often used in clinical trials and blinding is a procedure when participants, if they do not know, what they are getting, whether they are getting drug a or drug b? This is called single blinding that is here participants are not aware as to what kind of drug is being given to them, investigators may be aware.

Sometimes participants as well as investigators do not know what kind of drug allocation is being done because the type of treatments that are been given, the nature, the color and the appearance of the interventions is exactly identical. This is a double blinding procedure and even when the analysts also are kept blinded, while they analyze the results, this is called as triple blinding. Basically, this stepwise blinding from single to double to triple blinding that eliminates the kind of subjectivity in judgment of outcomes in a large number of instances.

There are two problems that generally arise, one is a co-intervention. What happen is participant, if they realize that one particular group is getting a particular type of drug, the other group is getting the other type of drug. They try to do some kind of an exchange and decide something between themselves. Sometimes, this is also facilitated by some kind of study staff or medical providers or family or friends, etcetera and hence

this kind of a co-intervention that takes place can vitiate the results of the study and hence blinding helps to eliminate that.

Also, if for example, if a patient or a study participant knows what he is getting, if he is getting a new drug, may be some of the minor elements he might want to exaggerate as compared to the, if he knows that he is getting the standard treatment, he may not want to report that. Similar thing may happen in case of those, who are actually evaluating that study participant and hence these kinds of biases in outcome ascertainment that can come in, can be minimized in blinding.

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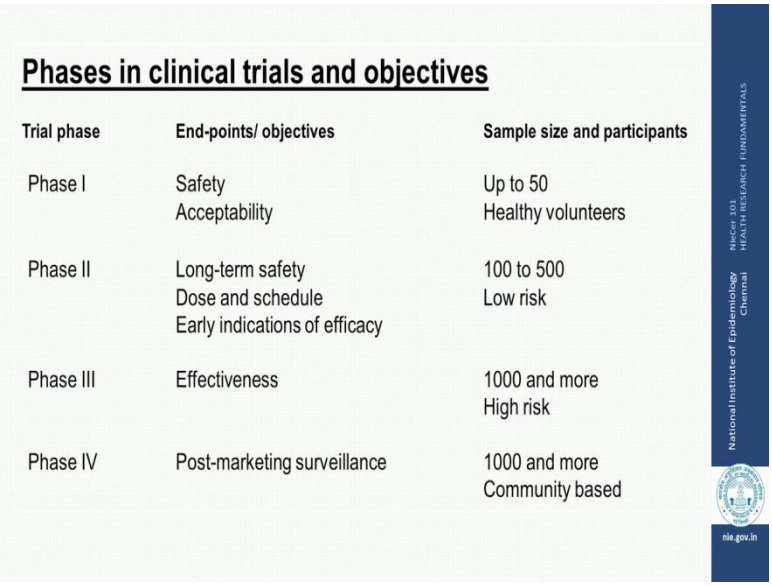

Typically, all the clinical trials are done in 4 phases. The phase I, is the step 1 in clinical evaluation of any new intervention that comes in and here is where the trial is done in a very small number of individuals, generally below 50 and they are mostly the healthy volunteers, who are the part of phase I study and goal is to do safety and acceptability evaluation here. When this particular product is found to be safe and acceptable, it passes on to the phase II trial, which is generally done in larger number of individuals, generally 100 to 500 and who may be having some kind of low risk of a particular disease and here is where we studied the long-term safety. We also try to study the dose and schedule, in case of a vaccine for example or in case of a vaccine again some early indications of efficacy. This is a phase II design.

A phase III design, essentially is a large trial, which looks at the efficacy of a particular

intervention and under controlled clinical conditions, generally they involve thousands of individuals and who are more at risk of acquiring that particular disease or who are suffering from that particular disease and we try to look at in a therapeutic scenario, how that particular drug is effective in curing or in prevention scenario how that particular prevention measure is helpful in preventing the occurrence of that particular disease. Once, all these phases I, II and III are completed, the product goes for licensures in the country, it gets a license and once it gets the license, it gets marketed in the country and then phase IV trials are undertaken, which are considered as post-marketing surveillance and they are done in again thousands and thousands of individuals, but it is generally collection of information in a community based manner not in a thorough clinical kind of a clinical trials set up. This is how clinical trials are conducted.

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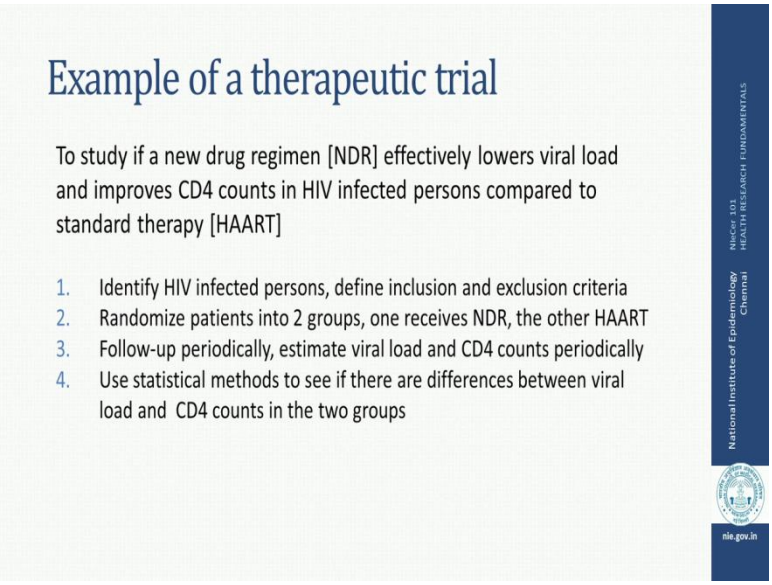

Just, I will give you an example of a therapeutic trial. If you want to study a new drug regimen, whether it can effectively lower the viral load and it also results in an improvement in the CD4 counts in HIV infected persons. So, I am talking about HIV AIDS scenario, where people are eligible for treatment. Now, currently there is a standard HAART, Highly Active Antiretroviral Therapy; which is available, which comprises of 3 drugs, which is being given at ART centers, Antiretroviral Therapy centers, which are run by the government in our country, all of us know that.

Somebody comes up with the new drug regimen, which probably is a cheaper regimen.

Probably where the number of tablets required are much smaller than the standard HAART regimen and so, one wants to evaluate whether this is an optimum regimen to be used in the country or not. So, how would we go about it? We will identify HIV infected individuals and define the inclusion and exclusion criteria for participation, whether they are eligible to be put on antiretroviral therapy. Then they will be randomized, all those who are found to be eligible in screening will be randomized into two groups or arms. One will receive the new drugs regimen, the other will receive the gold standard that is available now; which is the highly active antiretroviral therapy will follow them up periodically.

The expectation will be both these sets of drugs will effectively lower the viral load and help to improve the CD4 counts. This will be evaluated periodically, once in every 6 months for example and if the total period of study is 1 year or 2 years, we just see, how these two groups have reacted or responded to these two different types of the regimens and statically we will try to find an answer, whether this new therapy that we are talking about has provided any kind of an additional benefit. This can be done using standard statistical methods.

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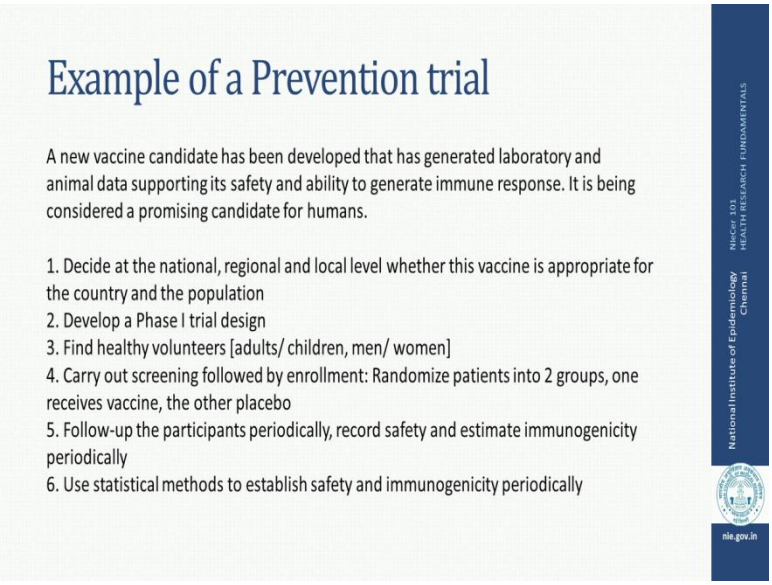

In case of a prevention trial, new vaccine candidate has been developed and there is a generally data available in the laboratory, also in the animal studies which you have, which support that, it is a safe vaccine candidate and it is able to generate some kind of a

immune response against a particular disease and it is felt that it can be used as a candidate in humans for prevention against that particular disease. So, how we will go about this particular thing is, first is essentially to decide at the national, regional or local level, whether this vaccine is appropriate for the country and whether we want to evaluate this or not. Then develop a phase I trial design, here is where because we are talking about a phase I study now. A new vaccine is being developed; we have to start with a phase I trial design. We will have to find healthy adult volunteers, then depends on what type of vaccinate it is. If it is a primarily a disease in children, sometimes children could also be recruited in the study.

With then, we carry out screening to find out whether, who are the people who are willing to participate in the study are actually eligible for enrollment and then we randomize them into two groups. One group will receive the vaccine, the other will receive the placebo and then we will follow them up to find out the safety, how will the safety be evaluated? We will see what kind of reactions are occurring immediately and in the long run, say for a period one to one and half years. What kind of adverse events are reported in both these kinds of individuals and then try to compare between the people who are receiving vaccine verses those who are receiving the placebos. Also, we will do some blood test, to find out what kind of immunogenic response has been stimulated in either as these two groups and compare them using standard statistical methods. So, that is an example of a prevention trial.

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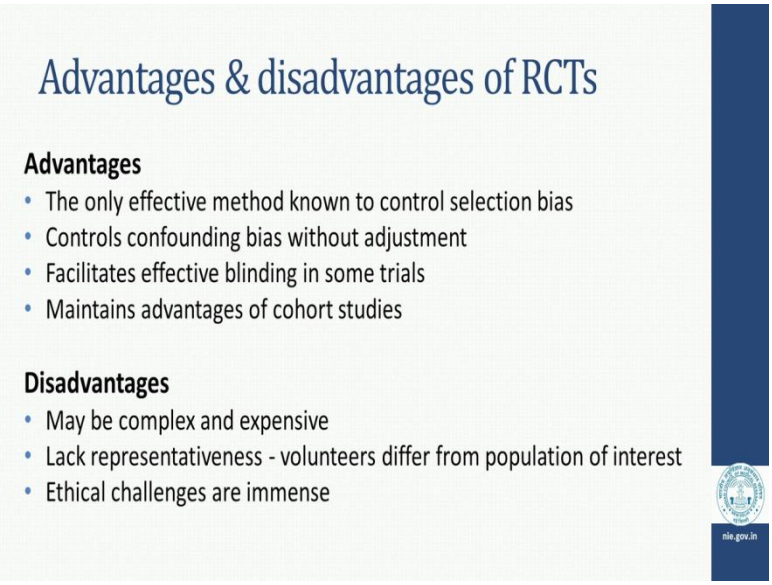

So, even if there are impediments here, the clinical trials are the only way for making a progress in medical science because, if there are no clinical trials, no new drugs will come. If there are no clinical trials, no new technologies will be tested, no new vaccines will be tested and so they must be supported and the adequate information about clinical trials must be disseminated. The advantages of a clinical trial include that this is the only effective method known to control the selection bias of participants. Also, it controls confounding bias without any adjustment, facilitates effective blinding in some trials and maintains advantages of cohort study or a prospective study, but there are certain disadvantages of this. It is a very complex procedure, it requires thorough training of all the investigators and also any clinical trial is very expensive.

As I mentioned earlier, we essentially use a sample from the total population that is eligible to participate in the trial and hence, there is some level of problem with respect to generalizability of this particular finding. But, that is something which one has to accept and there are ethical challenges which are immense. So, we know that this is a difficult study to do, but we also know that progress will essentially be made if we have new drugs, if we have new therapies, if we have new technologies and if we have new interventions.

Thank you for your attention.