Biomaterials for Bone Tissue Engineering Applications
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Module 5
Lecture No 26

In this module I will discuss about the clinical trials. I will introduce you to this important important aspect of the biomaterials research that is clinical trials.

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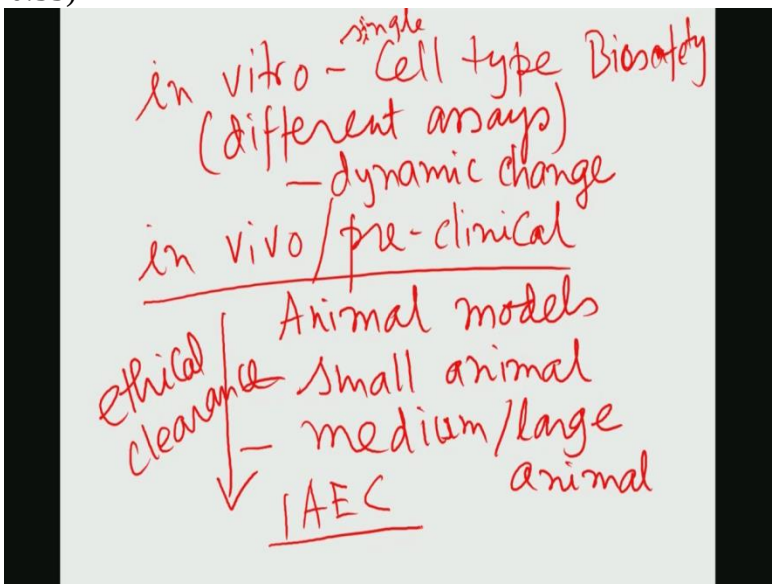

So I will first try to refresh your mind, that what we have learned So far. So we have learned so far, that in vitro studies that we have done very, we have learned to a greater extent, to the same extend or maybe little bit lower extent we have also we have also discussed the in vivo biocompatibility study. And in vivo is typically known as the pre-clinical study.

Now in vitro study depending on the cell type you need to have different assays, and different assays were also discussed which can be used to quantify the cell functionality cell viability on different material substrate. Now as you go from, or as you translate in vitro results in the in vivo context or pre-clinical studies, you need to do experiments in the different animal models.

So in last couple of modules I have discussed the need for the in vivo study ah. Essentially in vivo study will have direct relevance or will have more appropriate relevance for the human environment. So in vivo study is very important in the context of biomedical research and it is

called pre-clinical because it is the one step before the clinical trials where human patients are involved to establish the efficacy of any biomaterial device or to establish the efficacy of any implants.

So coming to the difference or if we, if we can recall the difference between in vitro and in vivo. In the in vivo case we have only one single cell type or unless or otherwise their co culture technique is used so this is the single cell type and also the tissue remodeling aspect, the influence of hormones and influence of dynamic change in the physiological environment so this dynamic change in physiological environment, all this aspects cannot be studied in the in vitro studies.

For that you need to conduct the in vivo experiments where a material will be exposed to the dynamic change in the physiological environment and what I have emphasized while discussing the in vivo studies. Normally you have to start with the small animal models and small animal models are very good for toxicity study. Then you have to go to medium or large scale. And another thing I have also emphasized during this, during the discussion on the in vivo experiments or in vivo study is that the small animal experiment, the result of the small animal experiments are to be validated at the medium or large animal model.

So, and this Ethical Committee clearance is becoming more and more tougher as you go from the small animal model to the medium or large animal model. In the normal in vitro you need to take the approval for the bio safety, so there is the Institutional Biosafety Committee. So you need to take the approval from the Institution Biosafety committee just to just to ensure that the way you conduct the in vitro cell culture experiments are actually as per the are actually following the ethical guidelines so that you are not doing large scale manipulation to the cells as such .

And this ethical committee or stem cells committee is approval is required in case you are using the stem cells in your research like you are trying to understand that how stem cells will be differential when they are being grown in a biomaterial substrate. So in all those kind of cases, you need to take the institutional approval.

But coming to the in vivo study, even if you use small animal medium and large animal irrespective of whatever the animal model experiments that you want to use, institutional

approval or institutional IAEC that is called Institutional Animal Ethical Committee, approval is a must. And in all these animal approval Institutional Animal Ethical Committee approval you have to mention that how well you will be taking care of that animal health during the implantation experiments and further.

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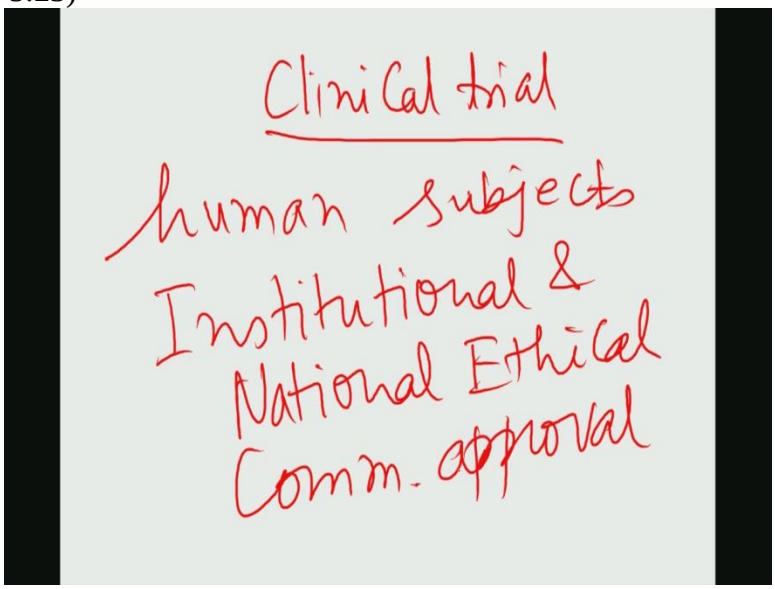

Now when you go to the clinical trial experiments then human subjects are required. So clinical trial experiments, so essentially, the small animal model and large animal model, so the human patients who will take part in this clinical trial, they are, they are referred in the published literature as well as in many books and so on as human subjects. So that human subjects are involved in the clinical trials and it is not only Institutional Animal Ethical Committee, so both Institutional and National Ethical Committee is approval are required. Both Institutional and National Ethical Committee is approval is required for conducting prior to conducting the clinical trials.

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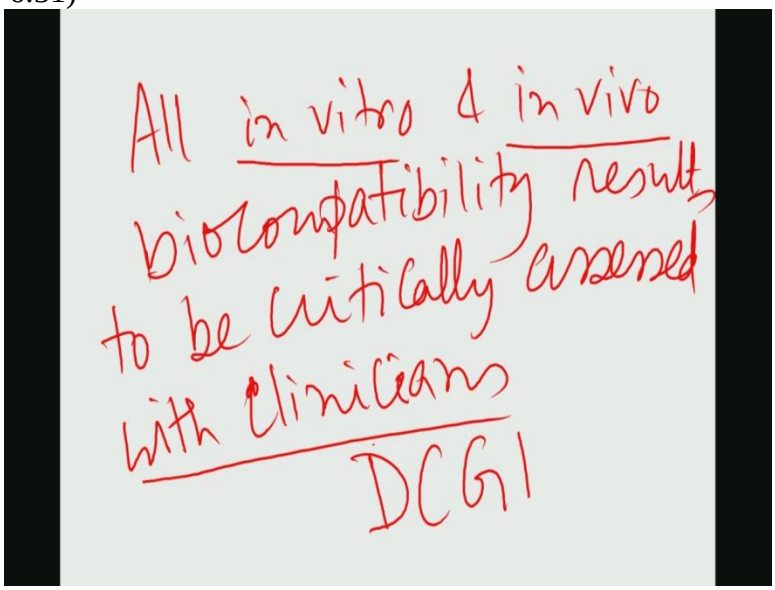

The other thing is important, just before the start of the clinical trials all the in vitro and in vivo biocompatibility results to be critically assessed with clinicians. So all this all the in Vitro and in particular in vivo results, biocompatibility results are to be critically assessed and National Ethical Committee is approval is required. In India this approval is typically sought by DCGI that is Drug Control General of India. That is that ICMR also gives this the approval for the clinical trials.

So we have, one has to propose that the need for conducting clinical trials and one has to also propose that how the results of the clinical trials will advance the scientific understanding on these particular set of new biomaterials or new implants so that these materials final can see the light of the day, in terms of their commercial scale production or commercialisation. So this aspect is really important and so that initial clinical trial plans need to be done in in collaboration with clinicians. Or in other words, clinicians are to be involved in all these clinical trial proposals.

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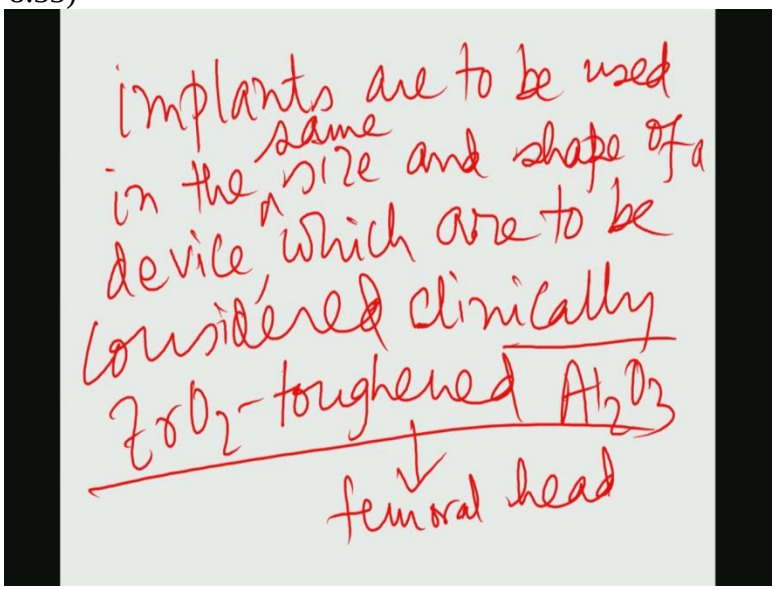

Third important thing that in this clinical trial study is that you have to understand that what is the, how many patients are to be recruited in the clinical trials and these materials whatever implants are to be used in the size and shape of device in the so implants have to be used in the same size and in the same size and shape of the device which are to be considered clinically. For example let is say you have for example you have developed a zirconia toughened alumina based composite for femoral head or acetabular socket as device.

So you have to shape this zirconia toughened alumina. We cannot simply keep this zirconia toughened alumina a simple cylindrical piece or rectangular piece and put it in some human patients. It has to be first fabricated in the shape of the femoral head or acetabular socket and then you have to put it inside the human subject or human volunteer patents, human volunteers as part of the clinical trials.

Or in other words although you are in vivo, in vivo or pre-clinical study is conducted on simple geometrical shaped biomaterial implants, clinical trials must be conducted on the same in vivo tested materials but in the final shape and size of the device which would be ultimately implanted in the human patents. So that point needs to be very clear. So clinical trials is very important and very critical and very sensitive so therefore all the serious approaches need to be taken (duri) as required for the final commercialization of the biomedical device.

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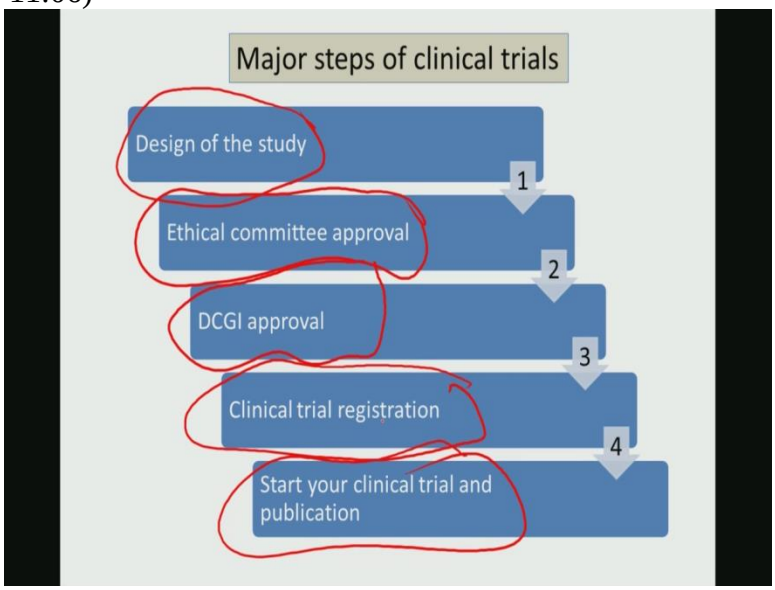

So having said all these things, so the major steps clinical trials. Essentially clinical trials are scientific experiments involving human subjects, to establish the efficacy of certain biomedical treatment using some drugs or some biomedical devices or implants. So first one is the design of the study. Second, so as I said the design of the study is to be, is to be finalised with the help of the clinicians. Second one, is the Ethical Committee is approval as I said, in India Drug Controller General of India approves this kinds of clinical trials.

Then clinical trial is registered and then you can start your clinical trial and finally publish the results of the clinical trials. So these are the steps. So therefore as you can see from this brief description of the major steps in the clinical trials it is quite a challenging task and it requires very strict approval process at different stages.

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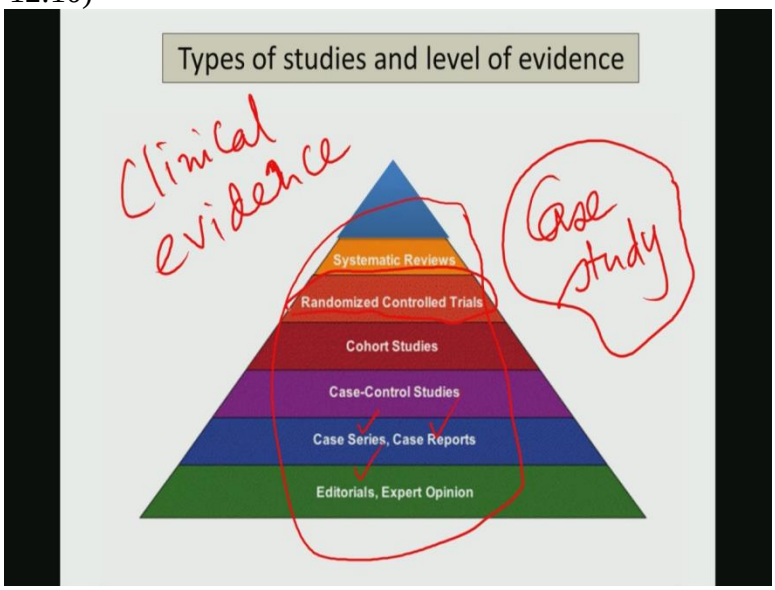

So the types of studies and levels of evidence. So clinical trials, one of the things that is very important is the clinical evidence. Many clinicians when they do, you know their higher studies or post graduate studies or masters and so on, normally their projects mostly involve or their research projects mostly involve at the post graduate level, mostly is the evidence based research. Like they do certain treatments and then they see what changes in the patient is health status, what changes those kind of treatment bring to the patient is health conditions, then they get the evidences, they record those evidences, then they may analyze those evidences and then they put they try to explain it from clinical perspective.

Now it may not be necessarily, it may not be necessary for clinicians doing post graduate research to conduct lot of scientific or significant scientific experiments, significant scientific analysis what a typically masters of Ph.D. Students at many of the academic institutions they typically conduct at the masters or Ph.D. level. So having said this, the clinical evidence is important in any kind of study, and particularly for the clinical trials when it involves clinicians because the clinicians believe in the clinical evidence.

I mean but as an academic researcher one has to conduct scientific experiments, scientific analysis to prove certain points or to establish certain points. However in the domain of the clinics or at the clinical settings it is mostly driven by the evidence based research. So they see something they believe something, and then they record the evidences and they try to infer based

on those evidences that how this particular treatment can give patient satisfaction whether this particular treatment is, can provide satisfactory patients outcome.

So these are the kind of things that they normally no in the clinical settings. So therefore I just wanted to make you understand that this clinical trials the whole concept of clinical trials are to be thought in more from the clinical translational perspective rather than more from pure scientific understanding more from pure scientific research the way we conduct in typical academic settings, because academic settings and clinical settings are quite two different kind of concepts or two different kind of approach that we use while conducting clinical trials.

So there are several kinds of mode of studies, but one of the things that people do and this is kind of a triangular kind of an approach that we have seen. So people read different editorials or expert opinion clinical opinion then they set case studies or case reports. So many times if you speak to any, if you, if you talk to any clinicians in general in a hospital they refer each time they conduct any operation, they say, that we had a case study, that means that the evidence that they collect from one operation on one single patients they consider this is one single individual case study.

So like that if you conduct the similar treatment or experiments on 15 patients, you have 15 case studies for you to analyse the evidences that you can collect from 15 case studies. Then similarly that clinical trials as we will explain later, there is something called control trials and randomised control trials which is most widely used in the typical clinical trials.

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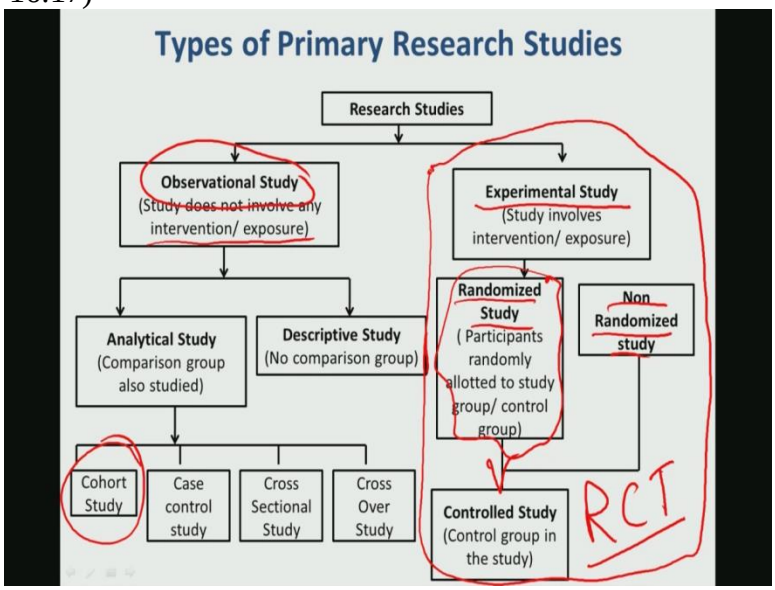

So in the, as I said in the clinical settings, research studies are to be, can be classified in two modes, one is observational study, you do something and you simply observe the patient is behaviour. That does not involve any intervention or exposure. Intervention means the clinician does not need to intervene the treatment that the patient is currently undergoing. Their job is to just observe the patient is behaviour or the patient is you know different organ functions and so on.

Second one is the experimental study. Experimental study means for example in the case of drug trials you give some drug A, with certain dose X, but you just see that whether the dose X is quite high level dose or it can cause some side effect or it is causing more side effect. Then you reduce the dose from X to X by 2, but then it requires intervention by clinicians or just changing the mode of the treatment or changing the treatment procedure itself and then, then collect the evidences.

In the experimental study, being a scientific researcher you should be very much excited about, that one is called randomised study and one is, second one is called non randomised study . Randomised study means, all the participants, like human subjects they are randomly studied without any preference of any particular patient. So this randomised study actually is very good in a sense that you do not have any bias for any specific patient.

Like you cannot choose all the male patients or all the female patients, it can be male, it can be female. You cannot choose that all the patients should be the below the age 30. No, it can be random, it can be from age 15 to age 55, or age 25 to age 55. In this large wind of the age, any patient who volunteers to take part in this clinical trials they are most welcome and you smut consider that. So essentially to remove the bias, because that is very important in the case of clinical trials, you need to conduct this randomised control study.

So that, I say that RCT what I just mentioned one slide back that stands for randomised control trial. Randomised means you do not have any control on the age of the patients, on the sex of the patients, on the previous history of the patients but it controlled means then you have to see that how many number of patients, what is their different ages and all.

Observational study can be more analytical study or descriptive study and so on and they are one of the studies sometimes people do is the cohort study. But our discussion will be mostly concentrated on this part of the slide that is it is experimental study, it is randomised study, and then how one can do, RCT, that is randomised control study.

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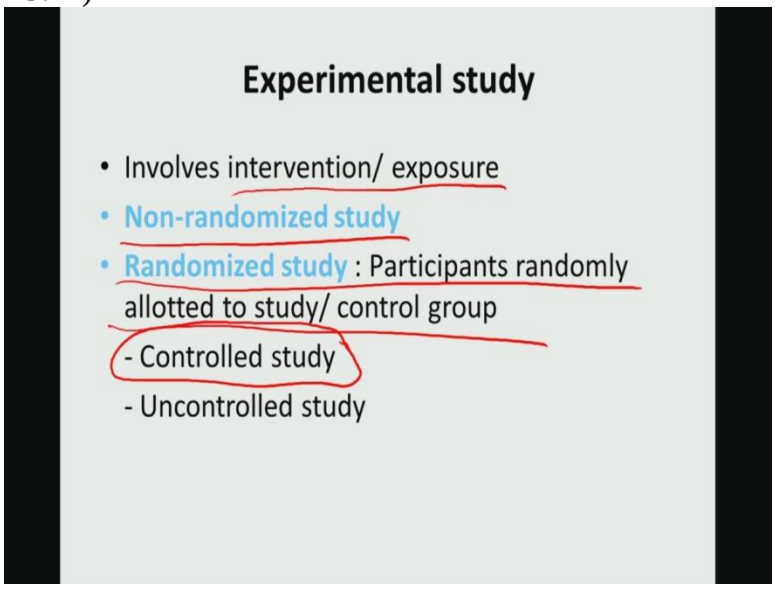

So as I said in the last slide that experimental study essentially involves intervention or exposure and it is not randomised and in case of randomised study as I said participants randomly allotted

to study cohort group and it can be controlled or uncontrolled. But I will circle to put your attention on control study.

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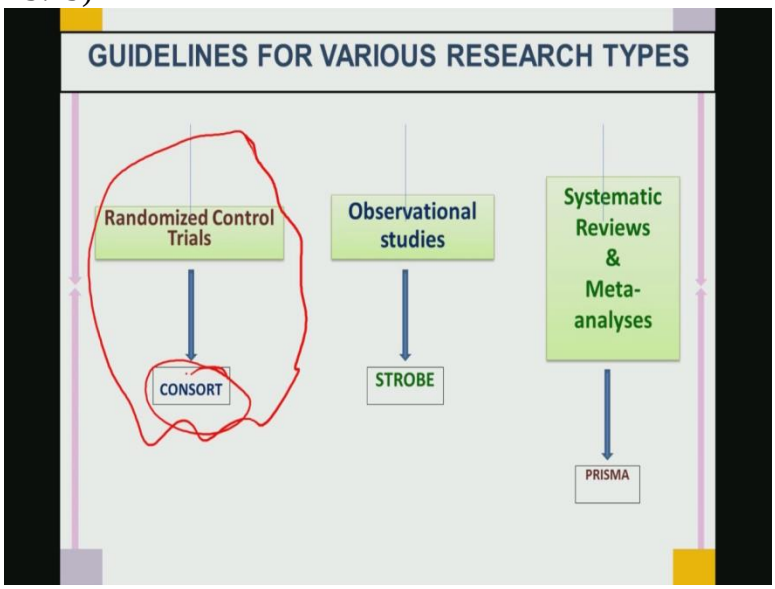

So there are different guidelines that need to be performed. Since we are mostly interested in the randomised control study so this consort guideline is more important.

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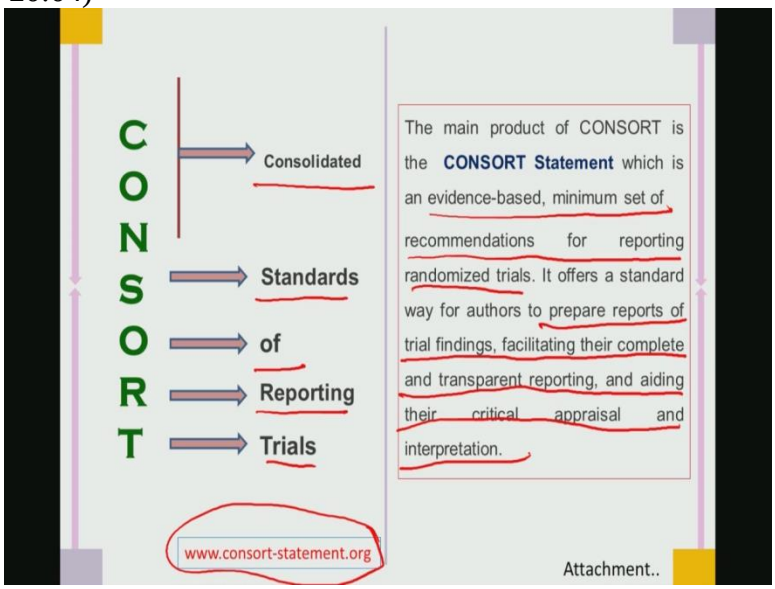

Now we should see what is consort guideline. Consort stands for consolidated standards of reporting trials. That means these there are certain guidelines which are already mentioned in this

particular website that is www.consort-statement.org. So this consort statement is essentially evidence based minimum set of recommendations of reporting randomised trials. It offers a standard way for authors to prepare report of trial findings, facilitating their complete and transparent reporting and aiding their critical appraisal and interpretations.

So that means here this, all this interpretation that should be clinically meaningful interpretations. So essentially you have to keep the clinical aspect in mind and accordingly you have to prepare the clinical trial reports.

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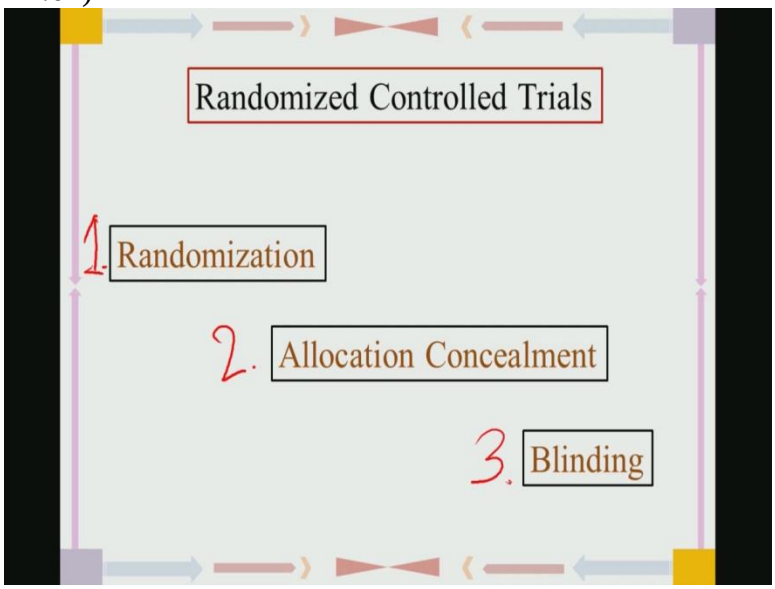

So the three appealers of clinical trials, randomised clinical trials are number 1, is randomisation, number 2 is allocation concealment, number 36 is blinding. So these three concepts, I will try to take up one by one and I will try to discuss in the next 3-4 slides that what is the meaning of randomisation, meaning of allocation concealment and third one is blinding. As I said that these three constitute three pillars of randomised control trials.

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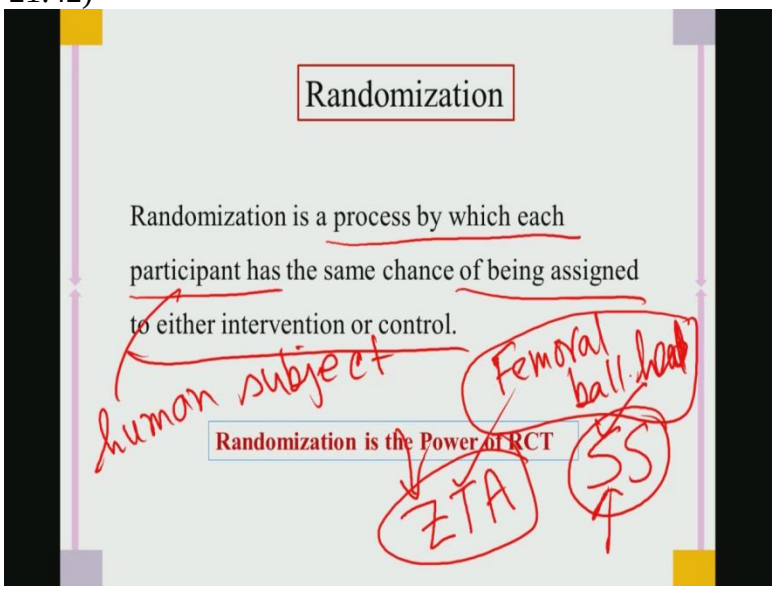

What is randomisation? It is a process by which each participants means, here participants means that is a human subject or people say human volunteer. So here you, you you use the term human subject or each participant who voluntarily take part in this clinical trial. So randomisation means this is the process by which each participant has the same chance of being assigned to either intervention or control.

What is the meaning of this clinical trials? Let us say you are, you are using some fumoral ball head ok that we are some people, some institution or some research groups would like to conduct clinical trials on the femoral head, so and then there is one type of femoral head which is very research grade like Zirconia toughened alumina another type of clinical head is stainless steel clinical head or cobalt chrome moly clinical head, fumoral head. So one side it is ceramic and one side it is a metal.

So a human participant or human subject or human patient would not be knowing whether he or she is getting ZTA or SS. They would not be, so each patient would have equal probability to receive either ZTA or Metallic femoral head.

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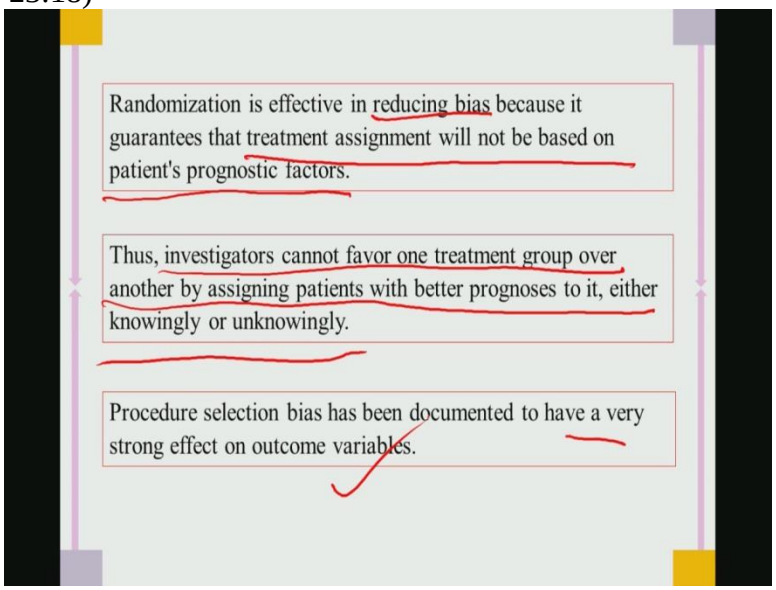

So randomisation is effectively reducing bias as I said before, because it guarantees the treatment assignment will not be based on patient is prognostic factors. So this is very important and investigators also cannot favour one treatment group over another by assigning patients with better prognosis to it either knowingly or unknowingly and procedure selection bias has been documented to have a very strong effect on outcome variables.

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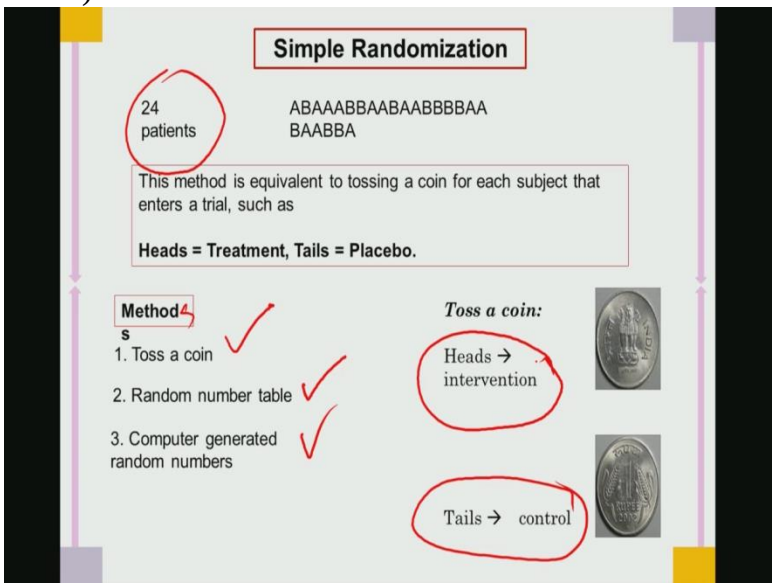

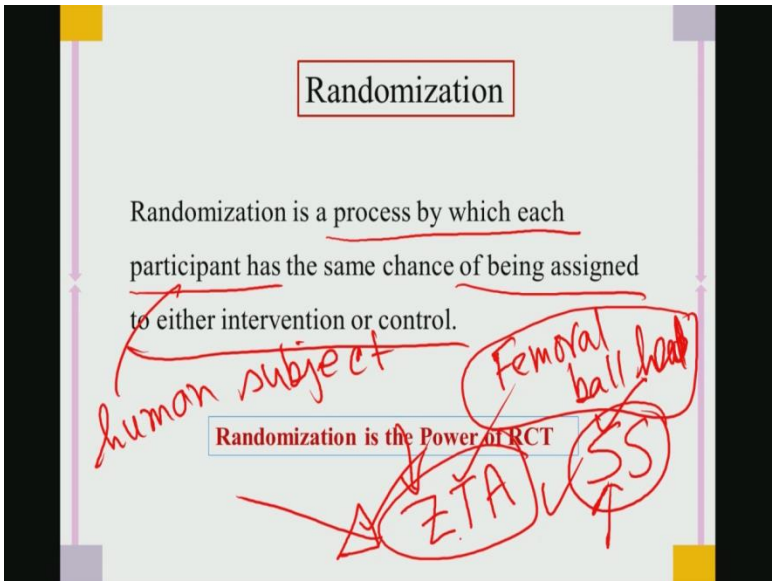

So sample randomisation for example like 24 patients are there in a simple clinical study and these 24 patients they have like assigned like AB, AA, BB or something like that. So it is, basically when you toss a coin it have equal probability either it will be head or it will be tail. So head is like treatment, tail is like placebo. So you, you essentially here, it has been, methods has been mentioned, you toss a coin, randum number table and computer generated random numbers. So trail, tails is your control or placebo and heads is the intervention.

So the control things if you go back to the same thing. so let us say, you, this is your experimental great femoral head, zirconia toughened alumina which you have just, fabricated in the laboratory scale, but commercially and clinically stainless steel fumoral head has been used for ages. Now doctors are trying to do clinical trials so researchers conducting clinical trials to see whether zirconia toughened alumina can potentially replace stainless steel based fumoral head.

So therefore if you put head and tail, so if head is ZTA and tail can be stainless steel. So the patient does not have any change of choosing whether they will get zirconia toughenedalumina fumoral head or that they will receive stainless steel or metallic fumoral head. So therefore that biases can be removed clearly by this randomisation process.

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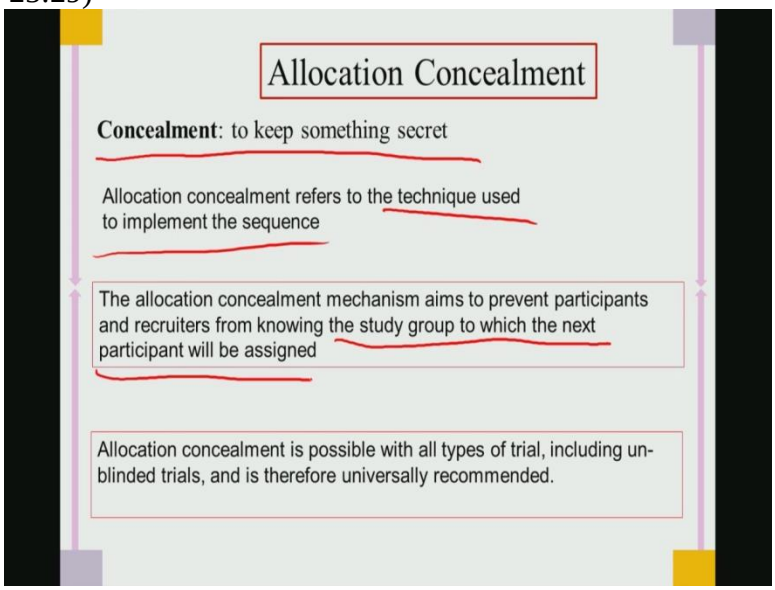

Second one is the allocation concealment. Concealment to keep something secret, so like a patient is now allocated either ceramic head or metallic head, right. Now patient would not be knowing what is the femoral head composition that he is getting or he or she is getting, that means patient will be knowing only that they are getting one potentially clinically acceptable fumoral head, so allocation concealment refers to the technique used to implement the sequence and allocation concealment mechanisms aims to prevent participants and recruiters from knowing the group to which the next participant will be assigned.

For example there is 24 patients as is said in 1 or 2 slides back. So if the patient A is getting one type of head, Patient A will not be knowing what patient B will receive, because all these femoral head in the (cont) in reference to femoral head description so there will be no clarity what each of the patients will be receiving.

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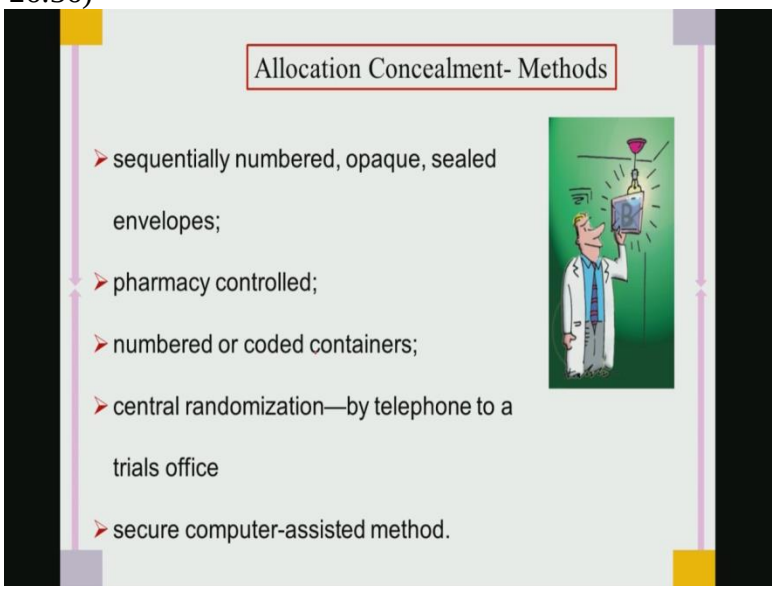

So subsequentially numbered opaque, sealed envelopes like in in in case of drugs that has been mentioned, it is pharmacy control number or coded and all.

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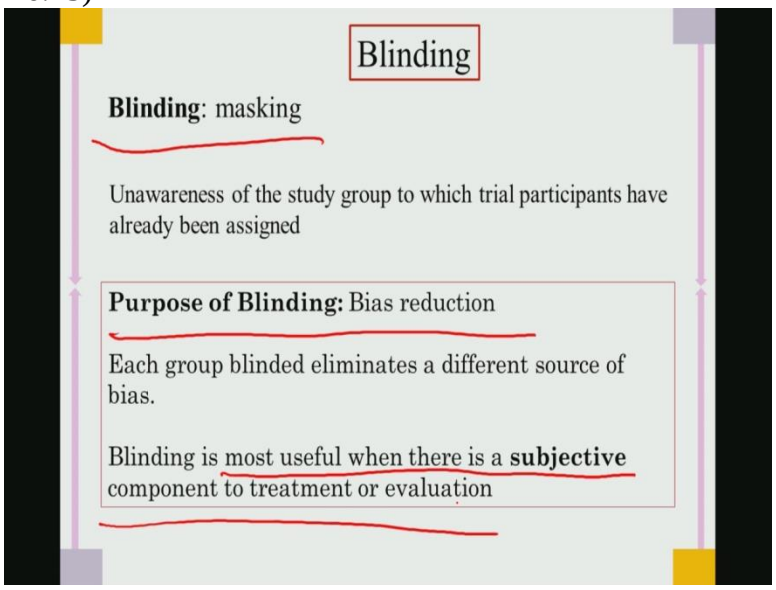

Now third one is blinding. Blinding means it is essentially masking. Unawareness of the study group to which trial participants are already been assigned. So purpose of blinding is again bias reduction. Each group blinded, eliminates a different source of bias, and blinding is most powerful when there is a subjective component of treatment or evaluation.

What it means is that that a group of patients will be receiving again I go back to my original example of this femoral head. So a group of patients will be receiving one type of ceramic head another type of group of patients will be receiving another type of femoral head. So each group they will not be knowing what kind of fumoral head that they have received. So this is that kind of examples that I thought will be interesting.

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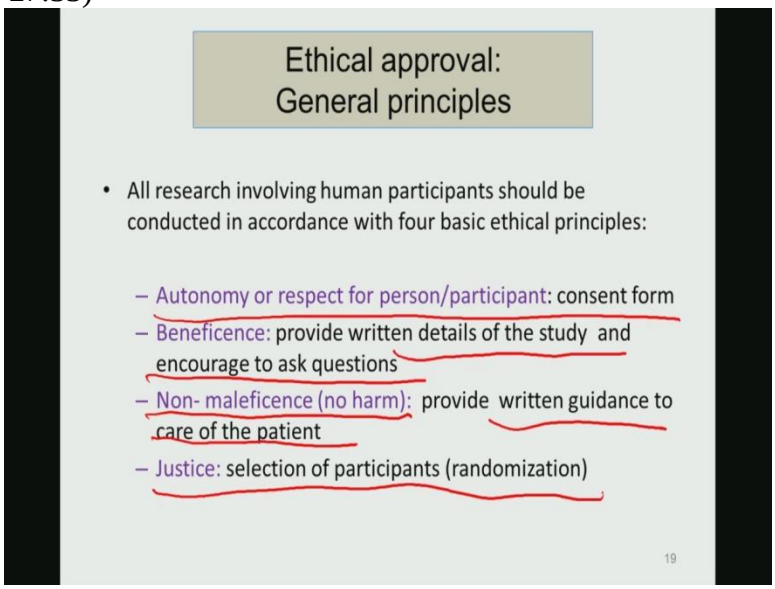

And then as I said that ethical approval is a must and all research involving human patients will be conducted in according to the, in accordance with the four basic ethical principles. Number A, is the autonomy or respect for person or participant that means one has to fill the consent form, each human subject, each human volunteer taking part in the clinical trials must fill up the consent form. That means they are willing to participate and they are willing to participate in a very honest manner to take part in this clinical study.

Beneficence like provide written details of the study and encourage to ask questions. Like each human patients, patient is encouraged to ask as many questions to the investigator as possible. Third one, that there is no harm, non-maleficence. So they provide written (gar) guidance to the care of the patients. The patient care is important, and which is equally important when you conduct the pre-clinicaltrials in the in vivo experiments. And 4th one justice, selection of participation like randomisation process is to be ensured.

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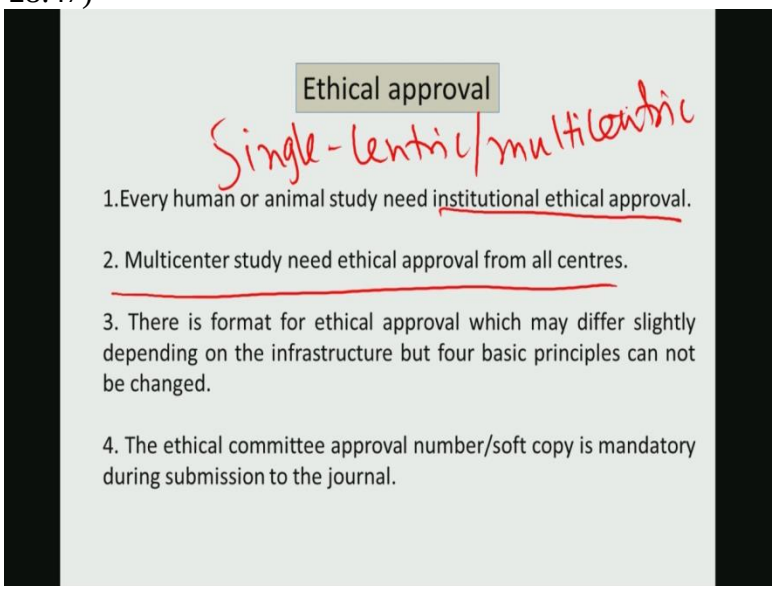

The other things that I mentioned here that every human or animal study need institutional ethical approval as well as (eth) in the multi-centre approvals, so there is something called single centric approval and there is something called multi centric approval. So single centric approval means for example you take any hospital A, you want to conduct the clinical trials on the limited number of patients on single hospital then you call single centric.

Multi centric means you need to conduct the the clinical trial experiments on a large number of patient population but not restricting to one single hospital but again in 3-4 different hospitals perhaps in different parts of the country, same country. So therefore this is multi centric study and that is, that again approval from all the participating hospitals which will participate in the study. There is format for ethical approval which differs slightly depending to the infrastructure and ethical committee approval number and soft copy is mandatory during submission to the journal.

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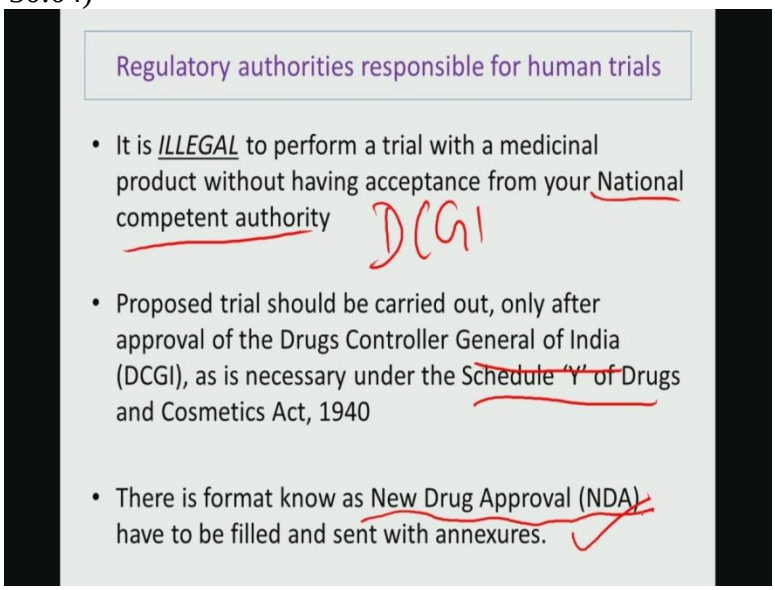

So the other things, that is, because in the (cli) in the clinical trial one of the thing that legality comes into picture in a big way, because you are using human subjects in your experiments or in your scientific study. So it is illegal to perform a trial with a medicinal product without having acceptance from a national competent authority.

This national competent authority I have mentioned it before that is called DCGI that is Drug Control General of India that is really important, and proposed trials should be carried out only and necessary under schedule Y of the drug and cosmetics act and also there is a new drug approval . So what happens in the context of biomaterials?

This, since biomaterial implants, clinical trials are something which has becoming, or which is becoming popular. So essentially people follow whatever drug related trials, that that ethical committees' approval is there, similar ethical approval is also followed in case of the biomaterials. So I think I will stop here and I will try to complete on these clinical trials with some more discussions so that you understand the fundamentals and other concepts in these clinical trials.