Biomaterials for Bone Tissue Engineering Applications
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Module 5
Lecture No 27

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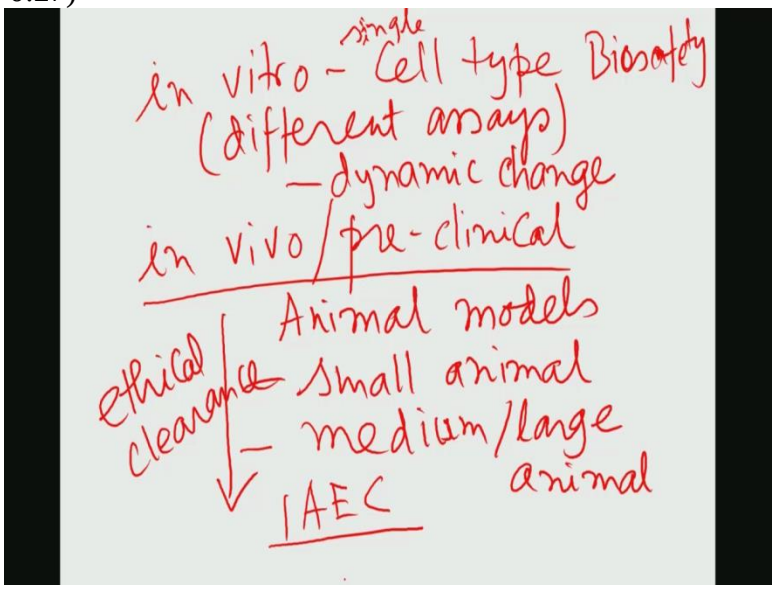

So we will continue the discussions on critical trials. In the last module, I have discussed that what is the basis for clinical trials, what is the relevance of the clinical trials in the overall context of the bio materials development and in the context of biomaterials research. So we will continue from that, and one of the things that we have emphasised in the last module is the need to conduct randomised control trials.

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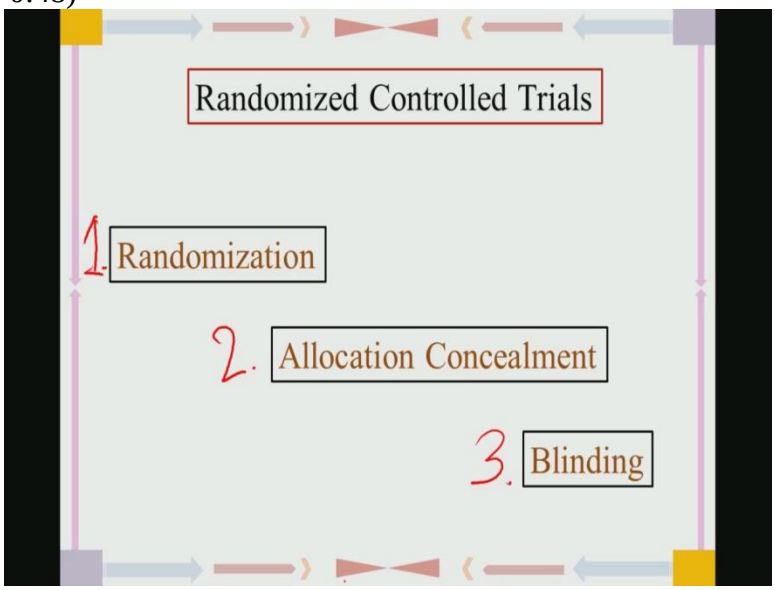

And there are three pillars in the randomised control trials. These are randomisation, allocation, allocation concealment and third one is the blinding. Each of these concepts were also discussed with sufficient details in the last module.

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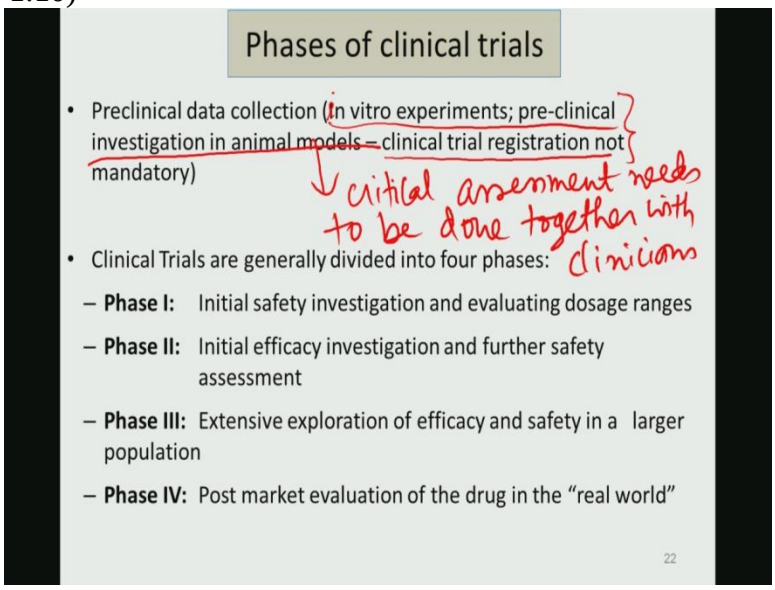

So now coming to that mode in this phases of clinical trials, the first important thing, that I have mentioned in the last module and let me reiterate again, that is first one is the pre-clinical data collection. So pre-clinical data collection that will start with this in vitro, in vitro experiments, pre-clinical investigation in animal models. So pre-clinical investigation animal model means

small animal, large animal . And to conduct this stage or to conduct the analysis at this initial stage clinical trial registration is not mandatory.

However the critical assessment of this of this results, critical assessment of this results needs to be done together with clinicians. Now to substantiate this point further what I want to say is that, that for example for any materials or any implants which are to be used for orthopaedic applications so orthopaedic surgeons needs to be involved at this stage to for him or her to understand that what is the key results of the in vitro cellular level experiments, what is the key results at the tissue compatibility level experiments in the different animal models, so that this clinicians will be convinced about the lack of any potential health risk or the lack of any potential health related risks for this materials and this particular biomedical, this particular biomaterials which are to be now, which are to enter into the clinical trials are biomedically safe.

So that safety assessment needs to be done together with clinicians. Now if it is, if the material under investigation is for cardiovascular applications, then cardiovascular surgeon needs to be involved. The same is true for the neural implant application or neural conduit or nerve conduits, then neurosurgeons need to be involved at this stage. So depending on I repeat, depending on targeted application, of that specific biomaterials clinicians from specific or, or clinicians from the related disciplines must be involved at this particular stage.

Now once you do these things, then it will lead to a the next stage will be, next stage will be to submit the clinical trial projects to funding agencies for financial support as well as to submit it to Institutional Ethical Committees as well as the national level ethical committees.

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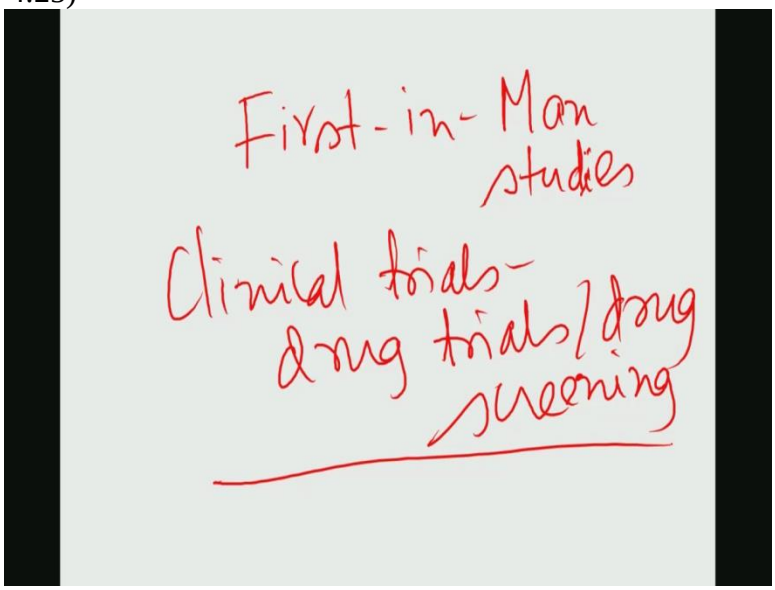

Now these things I have mentioned further and let me again repeat, so typically in the context of the biomaterial it is typically known as First in man study. So clinical trials clinical trials this is kind of one can consider this as a synonym. So clinical trials in the context of biomaterials is known as First in man study and clinical trials the way it has evolved it is more specifically used for drugs screening or drug testing.

So clinical trials are essentially all the protocols, all the phases of the clinical trials are defined with respect to drug trials or drug screening. So for any doctor, the clinical trials the moment you say clinical trial that means that it is essentially meant for drug test or drug screening.

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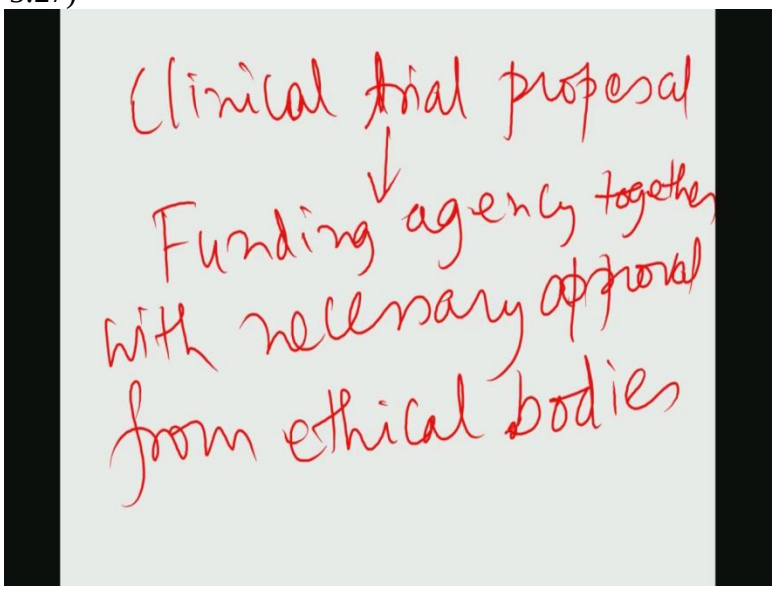

Ok now the other things from I am taking the discussion further or I am trying to extend the discussion further from the last module. So what I said is that, after all these assessments is done, pre-clinical data assessment then clinical trial proposal to be submitted to funding agency together with necessary approval from ethical bodies.

So these ethical bodies if it is to be single central limited clinical trials then it is to be only one hospital where the clinical trial is to be done, if it is multi centric, multiple hospital is there, then ethical committees of individual institutions needs to be sought and then need to be compiled together and then this is to be submitted further for the national level ethical committee and then all the approvals together with this proposal is to be submitted to funding agency for financial support.

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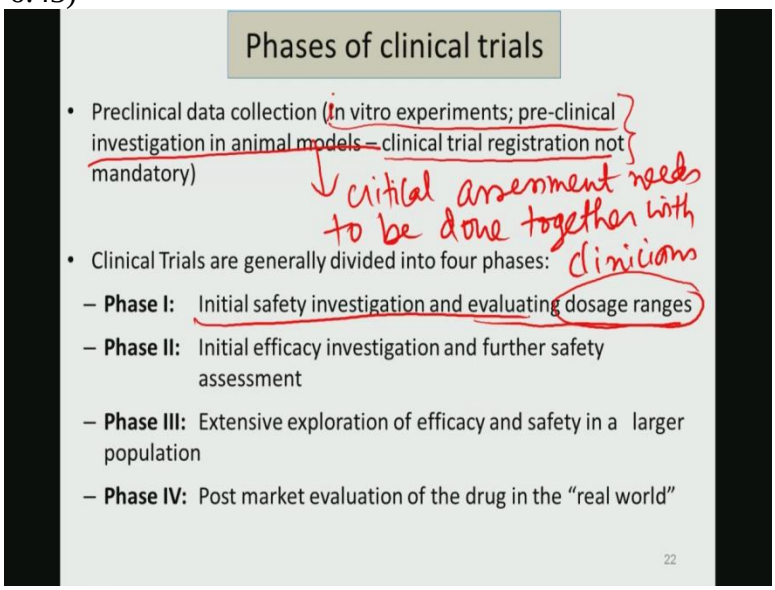

Ok now clinical trials theoretically can be divided into four phases. Phase 1, phase 2, phase 3 and phase 4. Phase 1 is the initial safety investigation and evaluating doses ranges. As I said earlier or just few minutes ago that clinical trials are essentially clinical trials essentially started to screen the drugs. So therefore these phases are also defined in the context of drug trials. So this is, Dosage means if you take any, any single drug A, so what are the dosses this is therapeutically relevant doses that is to be required to start this clinical trials before it is given to a number of human subjects.

That is to be done at the initial stage. So initial safety investigation certainly does not require a large number of human patients or human subjects but certainly very limited number which may give you statistically relevant result. So here comes the importance of the involvement of biostatisticians in the clinical trials. So any clinical trials study needs to be, or any research team which will conduct the clinical trial must involve bio statisticians because statistical relevance or statistical significance of the patient is outcome results need to be analysed with the help of the bio statisticians.

So as I said the number of human subjects to be just appropriate or to be minimal in number but at the same time that minimum number of human subjects should give statistically significant or statistically significant results. So therefore I have emphasised the part here again. Second one,

so now once the phase 1 study is done, then phase 2 study can be initiated or can be planned and phase 2 study involve initial efficacy investigation and further safety assessment.

Now if I recall or if we recall our discussion in the last module I have mentioned very categorically that phase2, phase3, phase 4 essentially depends or, or each time a clinical trial experiments enter into a higher phases let us say phase 1 to phase 2, that essentially mean more number of human subjects are involved or in other words that this efficacy of that particular disease or particular disease treatment is now validated with a larger number of human subject population, so that once it is done completely then people can really believe the result of this particular treatment.

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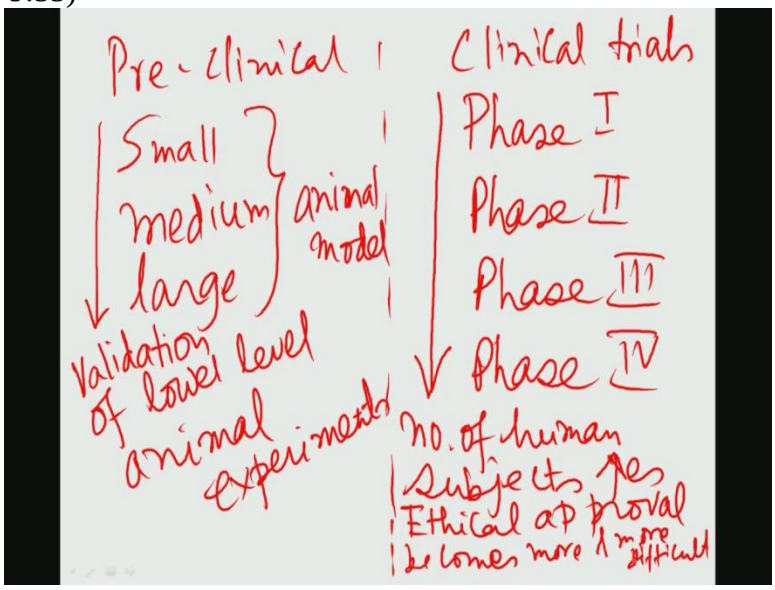

So let me take a blank slide and just explain to this one, little bit with little bit more clarity. So let us say this is your pre-clinical experiment and this is your clinical trial. So pre-clinical experiments if you remember that, I have mentioned that you have to start with small, medium, and large animal models and this small, medium and large essentially you are doing the validation of lower level animal experiments.

And there I have mentioned very clearly that as the size of the animal increases the complexity of the in vivo physiological environment also increases and also the ethical committee approval, animal ethical committee approval will become more and more difficult. For example if you go

to rabbit to dog animal ethical committee approval would be more difficult. If you go from dog to monkey, animal ethical committee, animal ethical committee approval would be even more difficult, because you are now carrying out experiments with primates.

So in case of using the primates of larger animals, animal ethical committee approval would be much more stricter. Similarly now if I, if I may kind of compare that some kind of correlation, like phase1, phase 2, phase 3 and phase 4, clinical trials. So as you enter, or as you travel along these directions from phase 1, to phase 2, phase 3, phase 4, number of human subjects increases and and therefore the ethical approval becomes more and more difficult.

So I repeat my statement, what is aid is that, this, each of this phase, phase 1, phase 2 phase 2, has 3, phase 4, if you enter from phase 1, to phase 2 trials then essentially that means more number of human subjects are now involved in phase 2 trials compared to phase 1 trials and the same is true for phase 3 compared to phase 2 trials. Now if any clinical trial involves only the phase1 trail, the ethical committee is approval is absolutely necessary but it may be little bit less strict or less difficult compared to the case when one is planning to conduct clinical trials up to phase 3.

So first of all, one has to conduct first phase 1 trial completed then they have to take approval for the phase 2 trial based on the satisfactory outcome of phase 1 trials from the patients who participated in the phase 1 trail. Now same is true for if you enter to phase 3 trials or phase 4 trials. So I hope I have kind of made this point relatively clear to you that what is the rational for going from 1 to 2, from one phase to another phase of clinical trials.

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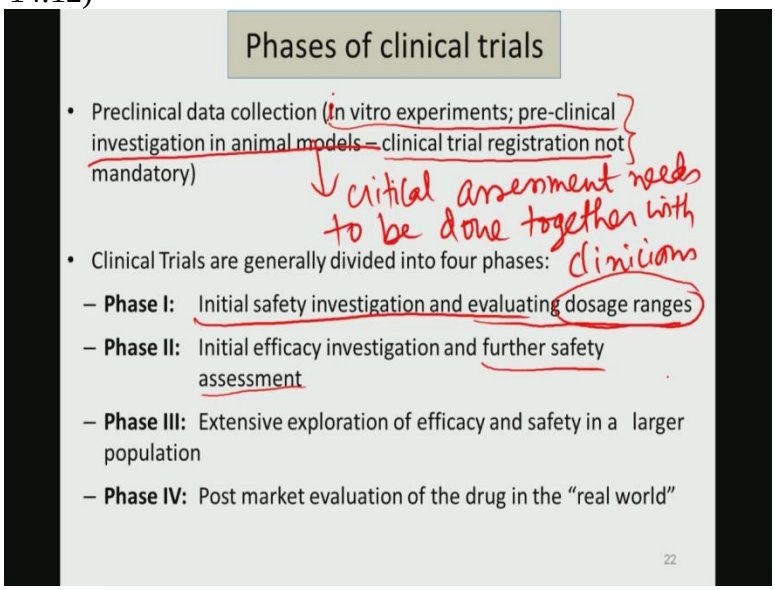

So let me go back to this discussion further. Now I have mentioned that rational from going to one phase, to another phase. So phase 3 essentially means extensive exploration of efficacy and safety in a larger population. So if your phase 1 trial involve let us say 10 patients, phase 2 trials would involve 15 patients, phase 3 trials would involve maybe 100 patients or 150 patients and phase 4, it involves post market evolution of the drug.

Like already drug is marketed in the real world and then how this drugs are kind of used by the by the people in the society and what is there what is their health condition and how certain disease are now treated in a much better manner compared to the earlier one . So all those evaluation needs to be done in phase 4, but normally most of the clinical trials are done up to phase 2 or in some cases it goes to phase 3 trials.

So once the phase 3 trial is done and then clinical efficacy or clinical safety, earlier you have done, just biomedical safety in the pre-clinical stage in the animal models, now you are conducting, by conducting clinical trials, you are essentially assessing, clinical safety or clinical efficacy of that particular drug or of that particular implant to treat certain human diseases. And once that is completed then this implant can be commercialised through some biomedical entrepreneur or certain orthopaedic device companies or other device manufacturing companies.

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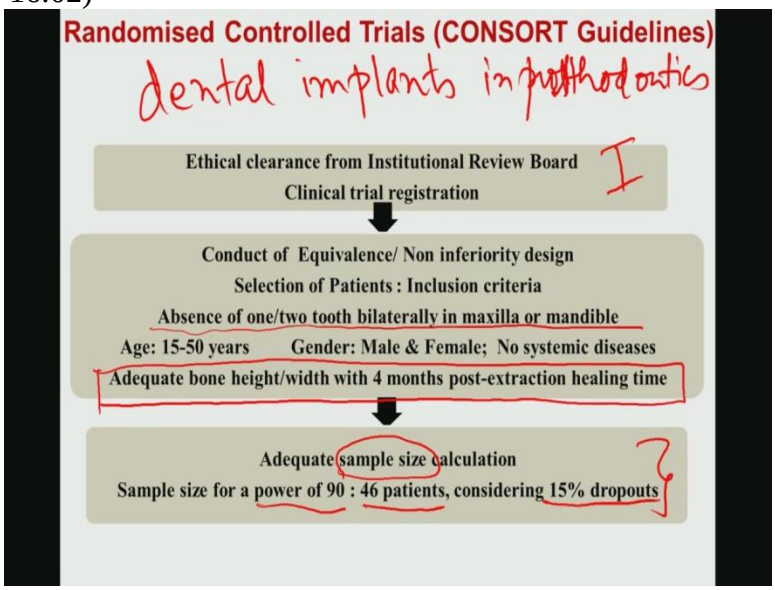

Now before I complete this this discussion on this clinical trials let me give you some examples of that how to design this kind of clinical trial study. So this is with respect to one dental implant for prosthodontics, in posthodontics applications. So as I said that it is a common thing, or it is generally recommended always to conduct the clinical trials following these randomised control trials and according to trhe Consort guidelines which I had mentioned in the last module.

So stage number 1, not phase 1, it is stage 1, phase 1, sorry stage 1 is that ethical clearance from Institutional Review broad and if it is for dental application, when the implant is not or not implanted, when the implant does not go well inside the body, but its stays at the external side of the human like in the tooth. Let us say in the case of tooth replacement or the dental implants, so their strict clearance from the intuitional review board is sought to get the clinical trial registration.

The next one is the conduct of equivalence or non-inferiority design and selection of patients. So their inclusion, exclusion criteria needs to be clearly mentioned like what is the patients age group, whether it is gender, male female and whether the patients will have, should not have any systemic diseases, that needs to be defined. So that means that when this particular age group, so as you can see the age group, that needs to be selected over a good range, not a very narrow range of the patient.

Like 15-50 years is a relatively broad range of age and in this age group the clinicians or the investigator who are participating in the clinical trials do not have any choice of the patients that they would recruit, any patient who wants to voluntarily participate in the clinical trials in this age group in principle should be recruited in the clinical trial study. And as per the gender also there should not be any bias. Now all these biases would be ensured if one follows randomised control trials because if you remember in the randomised control trials the three pillars are there.

One is called randomisation, second one is called allocation concealment, and third one is called Blindness. So once these three concepts are in place or when these three things are followed very critically, then all these other things would be take care. Then in the particularly for prosthodontics treatments one can, one can have additional criteria that the patient, the patient who is recruited in this study, there should be at least 1 or 2 tooth, that should be absent bilaterally in maxilla or mandible and then the, the patient is outcome or the success for the clinical trials needs to be quantified, needs to be defined either quantitatively or qualitatively.

In often, most of the clinical trials people do large, people put lot of effect, people put substantial efforts to qualitatively evaluate the the outcome results rather than quantitatively. But as the field has progressed over the last few decades this particular material for biomedical applications people start using more quantitative tools to estimate the efficacy of the clinical trials or to quantify the efficacy of the clinical trials.

Just to give you this example, after this certain dental implant, is inserted into some patient having the patient following the criteria which I discussed just few minutes ago adequate bone width or bone height and width can be measured using CBCT technique. CBCT is Convergent Beam Computed Tomography technique with four months post extraction healing time. But it means that after the patient receive that implant, there should be a gap of at least 4 months then the patient would visit the doctor again.

Patient would go to the hospital to the same clinician, then the clinician will use this Convergent Beam Computed Tomography technique and quantify that what is the bone width or height around the implants and that quantification will be able to give you, give the clinicians some confidence yes, this particular dental implants which are implanted in this particular patient provide satisfactory results.

The other things that I have mentioned towards the end of this slide is that that adequate sample size calculation, here sample size means it is not a typical material and sample size but it is in the context of the human subjects again. Now sample size for a power of 90. This is the typical language they use, clinicians they use, like 46 patients that needs to be recruited in this single centric clinical trial experiments, clinical trials.

Now considering 15 % drop outs, what is the meaning of 15% drop outs? Like you start with 50 patients and you expect all the 50 patients need to go through all the advice suggestions and need to undergo all the investigation as laid down in the clinical trials. But it may so happen that 15% of the initially recruited patients would decide that they would not undergo all the clinical follow up or all other clinical testing that is required or that is suggested in the clinical trial study design.

So if those drop out cases even if those drop outs, those patients they will drop out from this clinical trial study, it is the moral responsibility for the clinicians to follow up those patients so that once they have received that particular implant, that that does not cause any undesired or any or any undesired effect in the patients as far as the patients' health status is concerned and that should not be clinically significant.

And if those drop out cases also the results are clinically significant that means patients, develop certain side effects because of the implants patient develop certain other complicated heath related effects because of the, because they have undergone that particular the, they have undergone that particular treatment or received that implants because of that particular reason, then those things also needs to be critically considered while analysing the total results of the clinical trial.

So let me summarise therefore that it is important to select the critical number of human subjects so that it provides statistically relevant results. But at the same time, one has the ensure that sufficient number of patients will undergo, who will undergo the clinical trials, will participate all the follow-up study will also participate all the clinical investigations as suggested or recommended by the clinicians or investigators who are conducting this clinical trials and even in case of the drop outs, like the patients who discontinue to participate in the clinical trial study

their health data their health condition needs to be monitored till the time the clinical trials study is over.

Once it is done, once it is ensured all the results together should be analysed so that one can critically conclude that what is the outcome of this particular clinical trial study.

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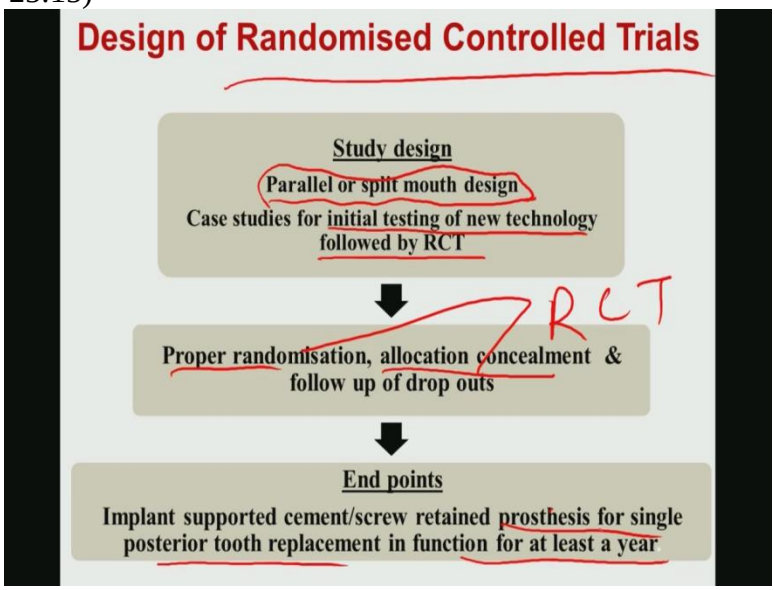

Ok this is that, second last slide and this is this, so this one it has been mentioned the design of randomised clinical trials in the context of the dental implants in prosthodontics applications so study design wise the parallel or split mouth design that is the typical, ah that is typically followed in most of the prosthodontics clinical trials and initial testing of the new technology needs to be done, like for example if you are using titanium 6 percent alumina 4 percent vanadium implants and if you have a commercial implant and then those initial testing needs to be done.

Ok proper randomisation, allocation concealment and follow up of drop outs needs to be taken up or needs to be ensured as I said because proper randomisation and allocation concealment already have two verticals of the randomised control trials. So in the RCT these two are the two verticals. Third one is that end points that is the implant supported cement or screw retained in prosthetics for single posterior tooth replacement in function or for at least a year.

What it means? All the clinical trial study is over up to the 4 months they would do some kind of a quantification of the bone regeneration around implants, but at least it needs to be ensured that the tooth which has been replaced by this dental implant that will remain there in a functional condition for at least one year.

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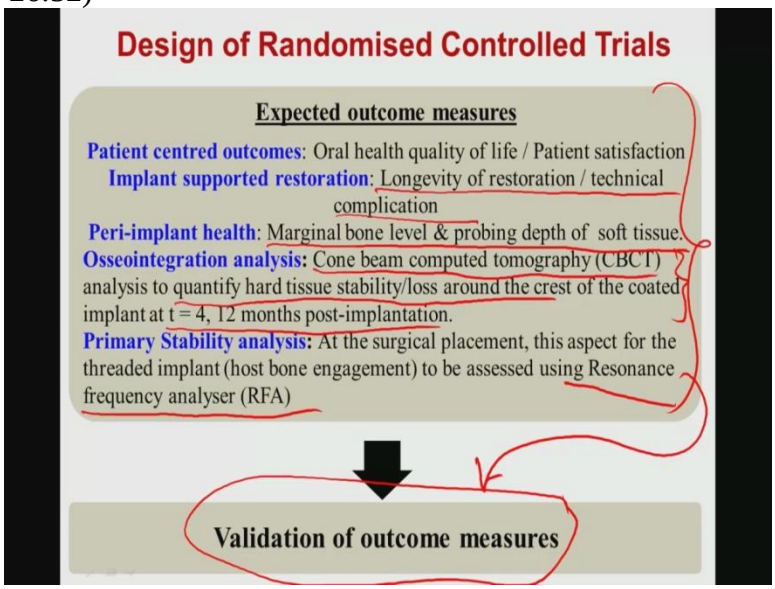

So let me tell you this in this last slide, is that how to ensure that what are the qualitative and quantitative outcome measures. These outcome measures are the kind of results of the now in a typically material science when you develop some materials, one does extra diffraction study to see that what are the phases that is there present. One does microscopy study to see that what is the morphology of this phases, what is the composition of the different phases locally and so on.

And the same time people do some kind of mechanical testing just to see that what is the strength of the material. But those kind of conventional characterisation or conventional testing is not possible in case of these kind of clinical trials. Although this should be done in a scientifically appropriate manner but instead as I have explained in this slide that there are certain patients oriented outcome that needs to be measured.

First one is the oral health quality of life or patient is satisfaction. After they receive these implants in the, after the patients receive this new implants patient satisfaction needs to be first qualitatively recorded whether the patient is complaining about the tooth pain or about some

inflammation or about some uneasiness or they have difficulty in chewing food or certain masticative reactions whether those things are there, that is to be recorded.

And that has to be scored in terms of some qualitative manner. Is it like plus one, plus two that is called (())(28.28) scoring effect and and so on. Second one is that implant supported restoration for the dental restoration like what is the longevity of restoration or technical complications. Third one is the peri-implant health like whether there is a marginal bone level and probing depth of the soft tissue, this can be investigated, and fourth one that I have mentioned which is more quantitative estimation that osseointegration like this implant which is inserted into the mouth how well it is integrated in the osseous system around the, around, the implant.

And here it is the cone beam computed tomography analysis needs to be done to quantify the heart tissue stability at different time level. So this is the different time plant, at the at the, different time frame like 4 months, 12 months, post implantation. That means after the patient receives this implant, so after 4 months, because 4 months is the time that this new bone or new tissue is expected to develop of mature around any orthopaedic implants. So similarly for dental implants also it is true particularly the human patients.

And then 4 months and 12 months they should see that there is no radiolucency and that is there is continuous bone formation around the implants. And last one is the primary stability at the surgical placement. This aspect can be assessed by radiolucency frequency analyser, so this is kind of relatively newer technique and then with all these results in hand that needs to be analysed together to validate the outcome measures. That means what are the patient oriented outcome measures and if it is acceptable to the clinicians then this particular implants can be commercialised in the market. Ok thank you.