Current Regulatory Requirements for Conducting Clinical Trials in India

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Lecture – L9
Schedule Y – Appendices

Hello everyone, welcome we will back to the course Current Regulatory Requirement for Conducting Clinical Trial in India. This is lecture 9; hope you have enjoyed earlier lectures. This is lecture regarding schedule Y and its Appendices.

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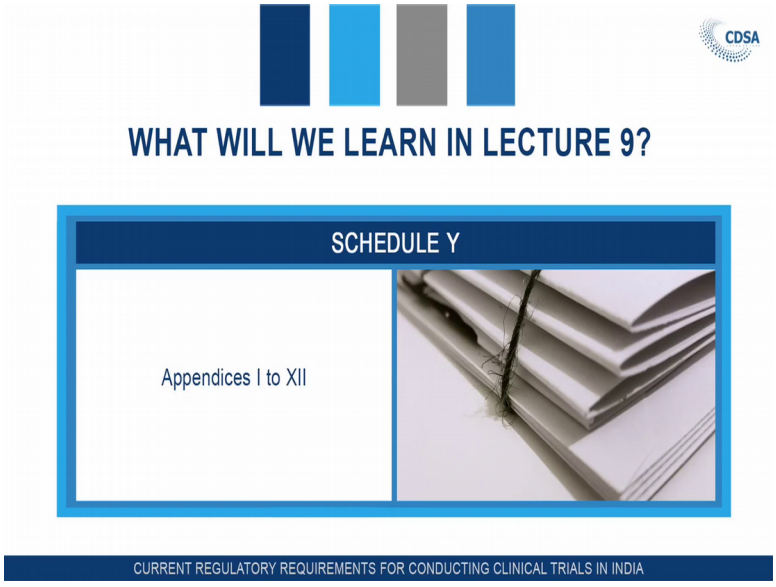

So, what will we learn in lecture 9? Schedule Y we have already seen so, this will also see here, then appendices from appendix I to appendix XII. So, let us start directly to the appendices of schedule Y. Appendix I is data to be submitted along with application to conduct clinical trial for import manufacture of mineral for marketing in the country.

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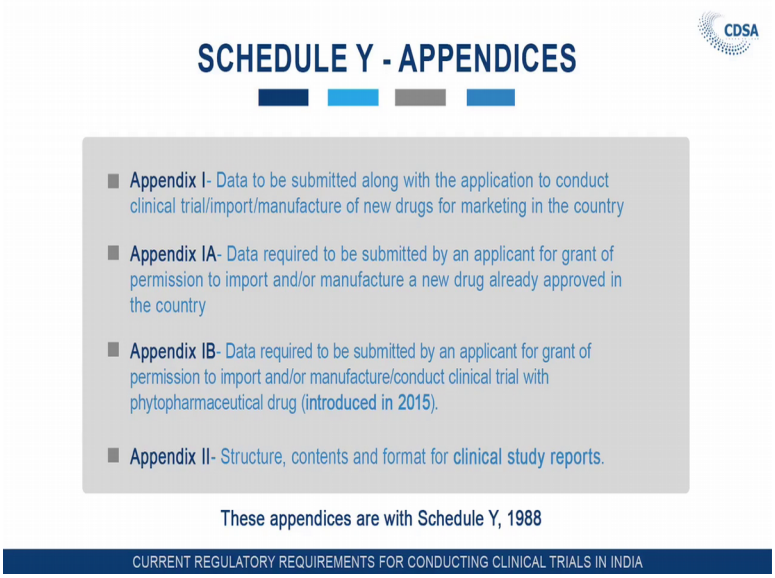

So, all these things which is required to be given while submitting the application for clinical trial, for the new drug to be imported or manufactured is given in this schedule. Then appendix I A data required to be submitted by an applicant for grant of permission to import and or manufacture a new drug already approved in the country. This is for the appendix which is for the drug which is already approved.

Then appendix I B is regarding the data required to be submitted by an applicant for grant of permission to import and or manufacture conduct a clinical trial with phyto pharmaceutical drug. This has been introduced in 2015. Appendix II structure content and format for clinical study reports. So, this is for the clinical study report.

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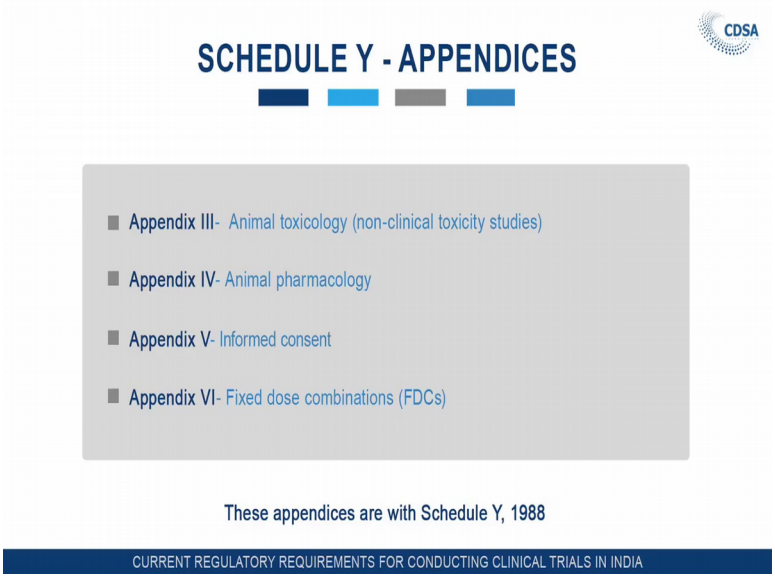

Then appendix III animal pharmacology animal toxicology, appendix IV animal pharmacology, appendix V informed consent, appendix VI regarding fixed dosage combination, then appendix VII is undertaking by the investigator.

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So, these are the appendix from VII to XI that were added after 2005, appendix VIII is related to the ethics committee, appendix IX is stability testing of new drugs. Appendix X is content of the proposed protocol for conducting clinical trial, appendix XI data element for reporting SAE that is Serious Adverse Events occurring in a clinical trial.

And, the last one appendix XII it is related to the compensation in case of death or injury of a clinical trial subject. Rule 122 DAB also added in these 2013 year. So, let us start in detail for the appendix I.

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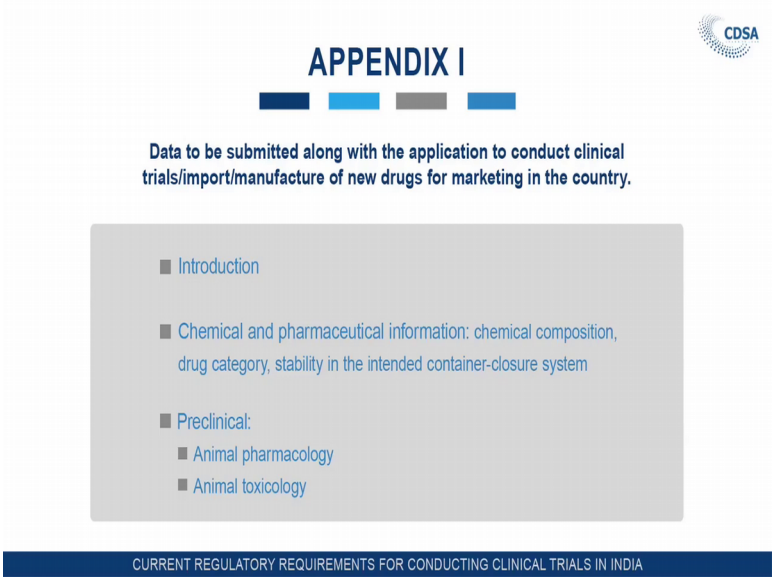

So, as we have seen the appendix I is the data to be submitted along with the application to conduct clinical trial for import manufacture of new drugs for marketing in the country. It means if the drug is new drug and somebody would like to import this new drug then they have to conduct clinical trial. Similarly, if it is for the manufacturing of new drug they have to apply for the clinical trial and after the permission they can import or they can manufacture. So, what are the requirement?

So, applicant must have to submit the following, that is introduction then chemical and pharmaceutical information about the drug like its chemical structure, molecular weight, molecular formula, identification then reconnect. All these regarding chemical and pharmaceutical information, then preclinical consist of animal pharmacology that is related to the safety in animal then animal toxicology related to the toxicity, then clinical that is your phase in human being.

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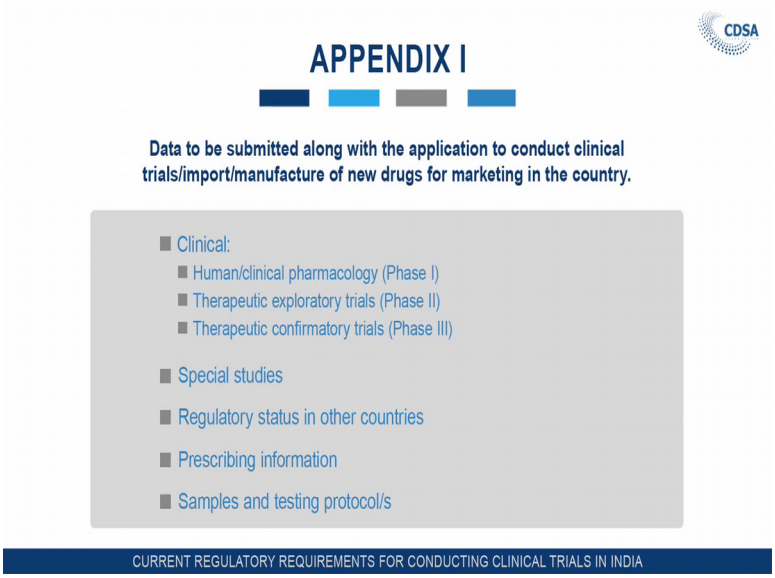

Human clinical pharmacology that is phase I, then therapeutic exploratory trial phase II, therapeutic confirmatory trial phase III. Then special studies if required like resolution studies, by regulatory studies, by equivalent studies, then regulatory status in other countries whether the drug has been approved in regulatory countries or any other countries whether that has been withdrawn or whether it is prohibited in some countries or it is suspended. Then prescribing information regarding the (Refer Time: 05:21) and indication all these information required to submit, samples and testing protocol this is also required to submit.

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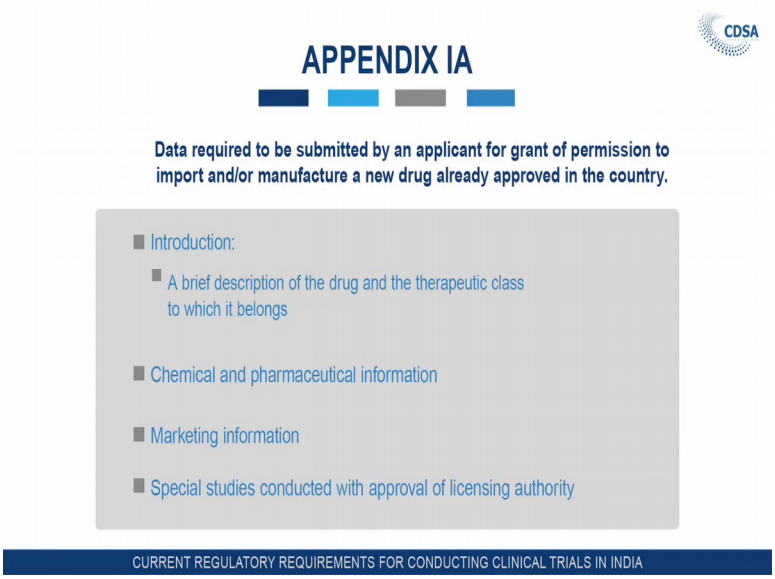

Appendix I A it is data required to submitted by an applicant for grant of permission to import and or manufacture a new drug already approved in the country. It is also same for the import and manufacture of new drug provided that the drug is approved in the country and somebody would like to manufacture this new drug with new dosage form or strength indication. Means is if the drug is already approved and subsequently the applicant has applied same or different then what are the data required to be submitted that is given in the appendix I A.

So, again introduction then brief description of the drug and the therapeutic class to which it belongs. Chemical and pharmaceutical information, then marketing information special studies conducted with the approval of licensing authority. So, in this appendix the preclinical data is not there.

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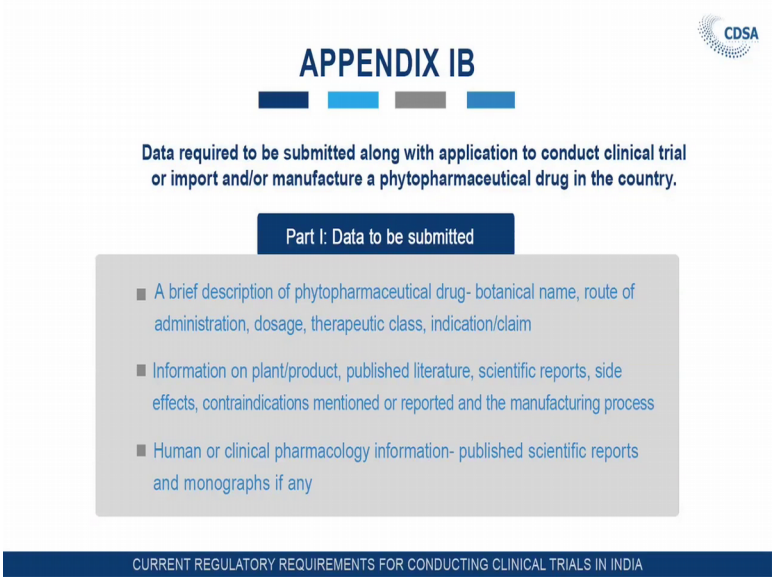

Now, let us see appendix I B these has been added lately in 2015 and this is regarding the phytopharmaceutical drug. Data required to be submitted along with the application to conduct clinical trial or import and or manufacture of phyto-pharmaceutical drug. Actually these appendix I B it has been divided in two part: part I consist of data to be submitted by the applicant wherein a brief description of phytopharmaceutical drug like its botanical name, route of administration, dosage, therapeutic class, indication claim. Then information on the plant, product, published literature if you have any available,

scientific report then its a side effect, contraindication method of whether any reported manufacturing process all these to be submitted.

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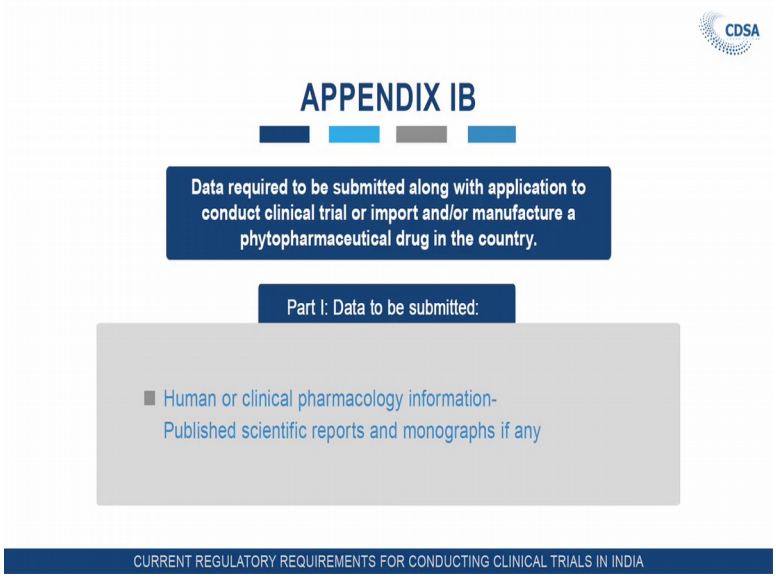

Then human or clinical pharmacological information published scientific reports monograph if any available.

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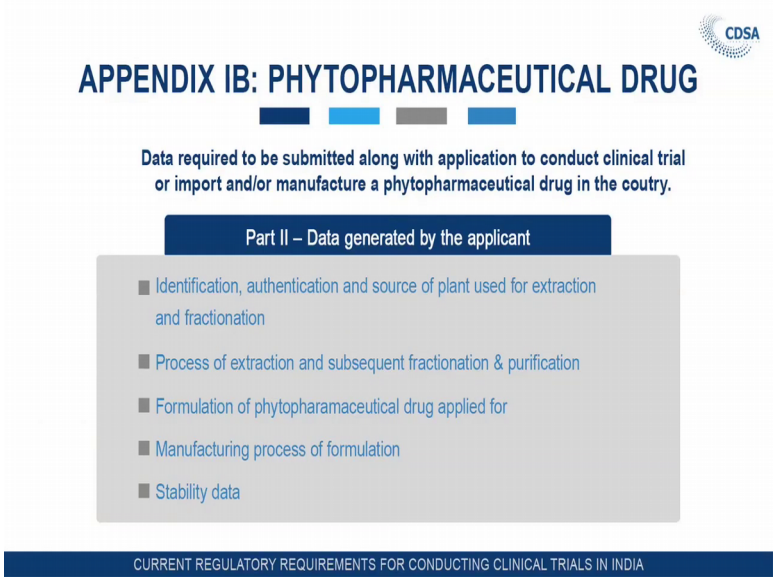

Then part II consist of data generated by the applicant, in these also identification of the plant then authentication and source of plant used for extraction and fractionation. Process of extraction and subsequent fractionation and purification, formulation of phyto

pharmaceutical drug applied for, then its manufacturing process of the formula then stability data.

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Then safety and pharmacological information, human studies as we have seen in the ah new drug then confirmatory clinical trial, then regulatory status whether it is uploading any other countries or not, then marketing information post marketing surveillance report if any.

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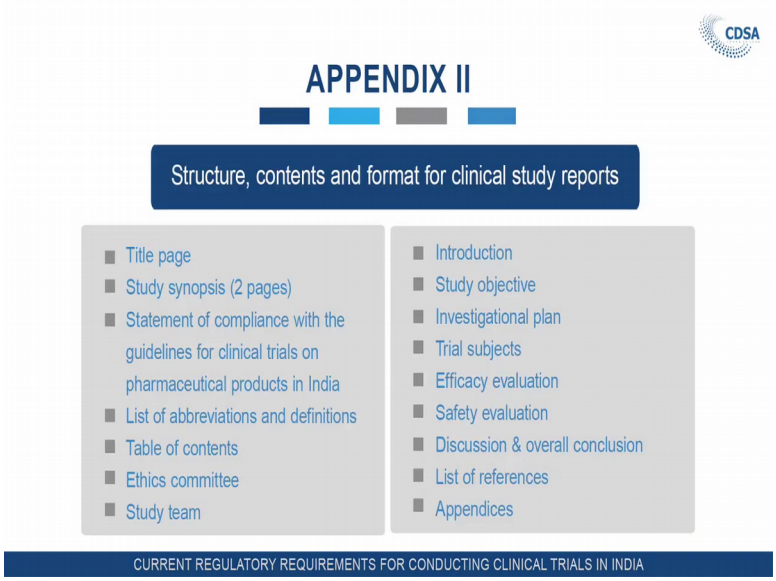

Now, coming to the next slide that is appendix II it is a structure content and format for clinical study report. So, after completion of the study the report has to be submitted to the licensing authority for its verification and the content and format is given in this appendix II. So, according to this appendix II what should be the content? So, first the title page should be there then study synopsis should be there consist of 1 to 2 pages briefing about the all the studies. Then statement of compliance with the guidelines for clinical trial on pharmaceutical product in India, then whatever the abbreviation for example, BA, BE, Bio Laboratory, Bio Equivalence, CT Clinical Trial.

Whatever the abbreviations used the meaning of that abbreviation and definitions. Table of contents in any list of table of content regarding statistical evaluation and other that also has to be given. Ethics committee; the committee which has reviewed and accorded approval, the name of the ethics committee and detail about the ethics committee; then study team those who are involved in the conduct of the clinical trial detail about them, then introduction study objective. So, primary objective, secondary objective with what purpose the study has been conducted that has to be given.

Then investigational plan trial subject, the number of subject used and their details has to be given, then the procedure applied for the efficacy evaluation, safety evaluation discussion and overall conclusion. So, after completion of the study the discussion conducted by the study team and what is their influence or conclusion that also has to be given. Then list of references which are used during the study and the appendices that has to be given.

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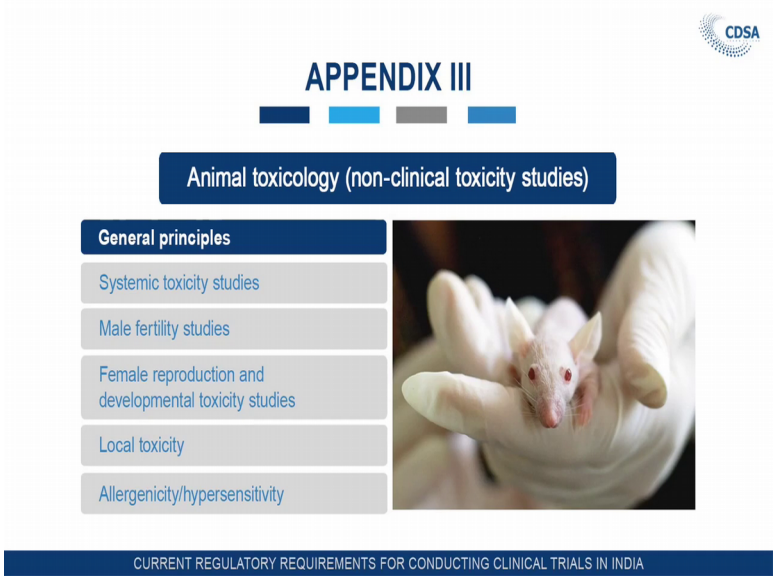

Appendix III is animal toxicology that is a preclinical study nonclinical toxicity studies. So, in this studies the general principles that is systemic toxicity studies, male fertility study, female reproduction and developmental toxicity study, local toxicity, allergenicity hypersensitivity.

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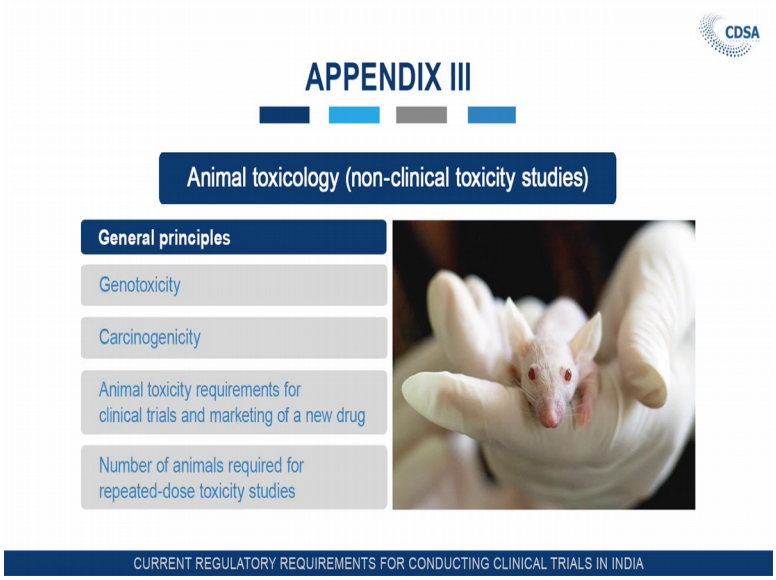

Then genotoxicity, carcinogenicity, animal toxicity requirement for clinical trial and marketing of new drug, number of animals required for repeated dose toxicity study. All

this is given here the number of animal the number of animal species so that is also mention here.

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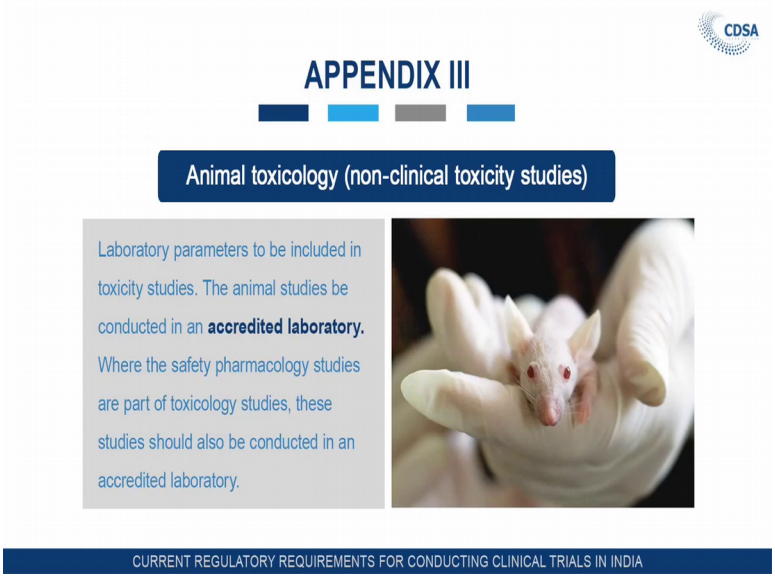

Then laboratory parameters to be included in toxicity studies; so, which are the parameter now while conducting preclinical study to be considered that have been also given. The animal studies to be conducted in an accredited laboratory, the animal study we have seen in the history that from the 2005 the GLP made mandatory and again the lab should be accredited. Where the safety pharmacology studies are part of toxicology studying, the study should also be conducted in an accredited laboratory.

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Appendix IV is a animal pharmacology. So, this is regarding the safety of the dog; in the general principle is given the specific pharmacological actions, then general pharmacological actions, follow up and supplemental safety pharmacology study. Condition under which safety pharmacology studies are not necessary, timing of safety pharmacology studies in relation to clinical development. Then whether the GLP was there or not application of GLP, the animal studies conducted in accredited laboratory we have seen it; where the safety pharmacology studies are part of toxicology studies the study should also be conducted in an accredited lab.

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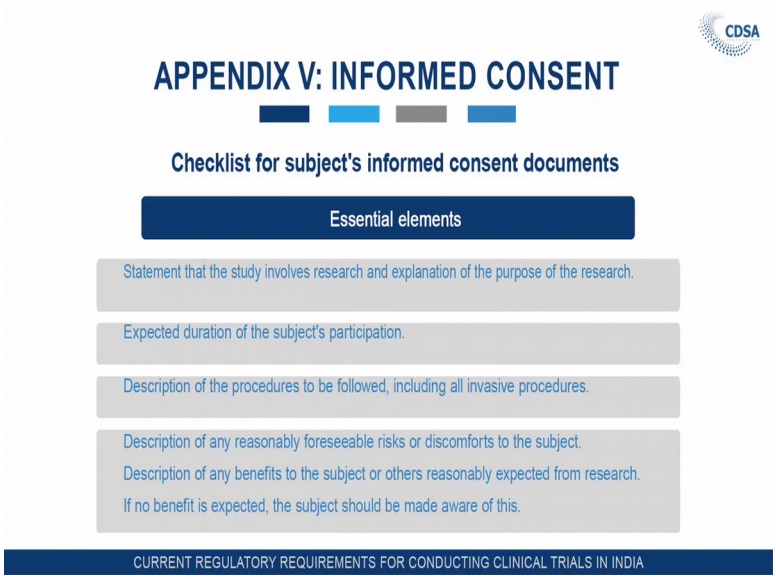

Appendix V is regarding the informed consents, actually this inform consent is also called as informed consent documents. So, first is the patient information sheet, the data to be provided to the patients or subject and next is the information confirmation sheet or consent sheet where the subject has to sign. So, inform consent let us see the checklist for study subjects inform consent document. So, here are the essential elements are given the first statement that the study in research and explanation of the purpose of the research. So, the first and very important thing, that they have to disclose that the study is only for the research purpose and not for any other purpose.

Then expected duration of the subjects participation whatever the time is required for the study for example, 1 week, 1 month that has to be disclosed. Then description of the procedure to be followed including all invasive procedures whatever the description of the procedure what they are going to do whether it is a parental injections or tablet, they are going to give the blood sampling procedure they have to mention. Description of any reasonable foreseeable risk or discomfort to the subject; if any risk is there then that has to be described there. Description of any benefit to the subject or other reasonably expected from research, if no benefit is expected subject should be made aware of this. So, whatever the benefit whatever the risk that has to be disclosed.

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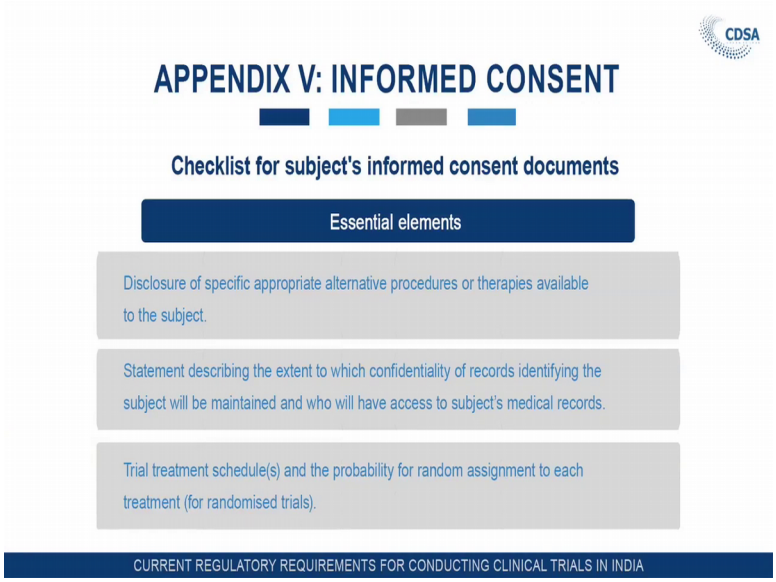

Disclosure of specific appropriate alternative procedure or therapies available to the subject; if this therapy fail then what are the other alternative measures that also has to be

disclosure. Statement describing the extent to which confidentiality of record identifying the subjects will be maintained and who will have assist to the subject medical record. Then trial treatment schedule and probability for random assignment to each statement; if the trial is a randomized trial, then compensation and treatment available to the subject in the event of trial related injury. So, the patient has to be make aware that you will get the compensation in case of any injury or dead during the clinical trial.

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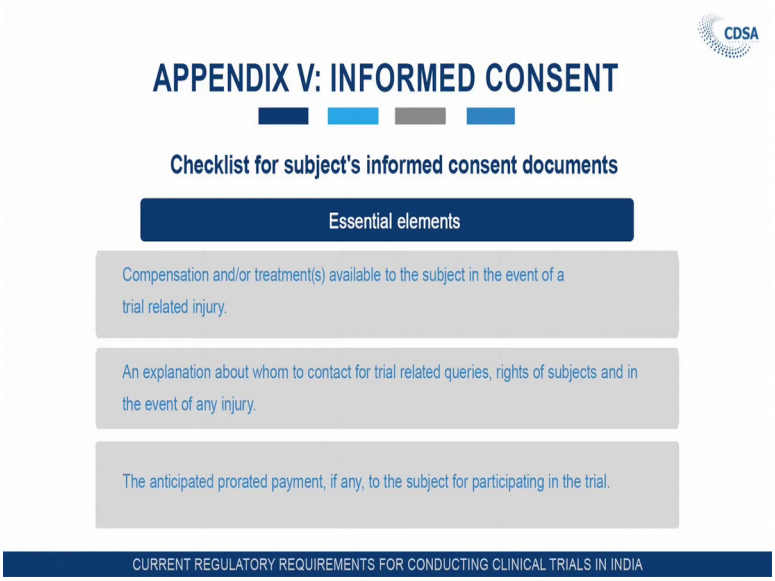

And explanation about whom to contact for the trial related queries right of subject and in the event of any injury. So, in case of injury or SAE to whom he has to contact the telephone number, email fax number everything they have to mention. The anticipated prorated payment, if any to the subject for participating in the trial.

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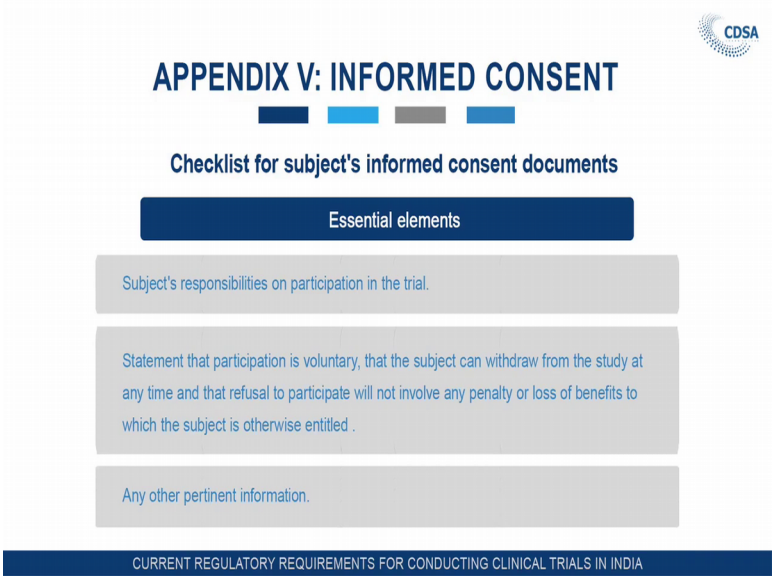

Subject's responsibility on participation in the trial; so, what are the responsibilities of that subject that has also mention. Statement that participation is voluntary that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefit to which in the subject is otherwise entitled.

So, the subjects they should have to make clear that the participation is fully voluntary there is no binding and they can we draw at any point in the study. Any other permission or any other pertinent information required to be given to the subject that has to be mentioned.

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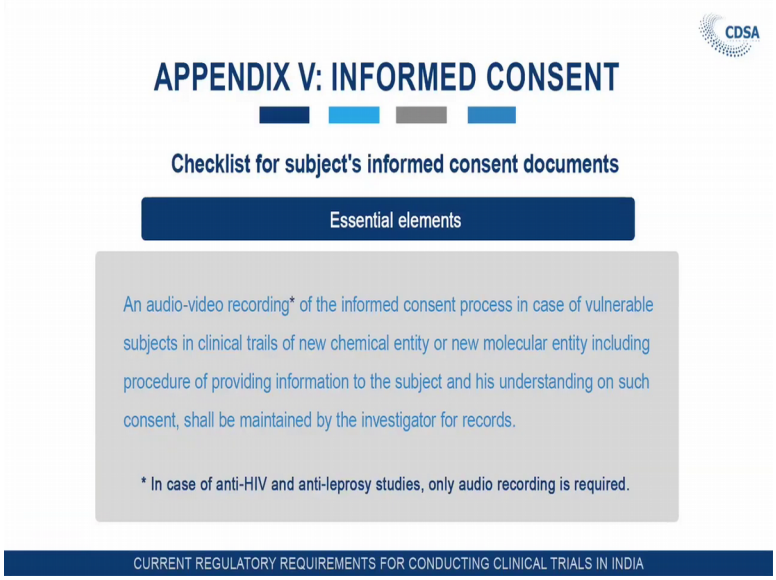

Then AV recording of the informed consent procedure in case of vulnerable subject in clinical trial for new chemical entity; so, that also has to be mentioned that they are going to have the AV recording. In case of clinical trial of anti-HIV and anti-leprosy only audio recording is required. So, these are some essential elements enlisted here.

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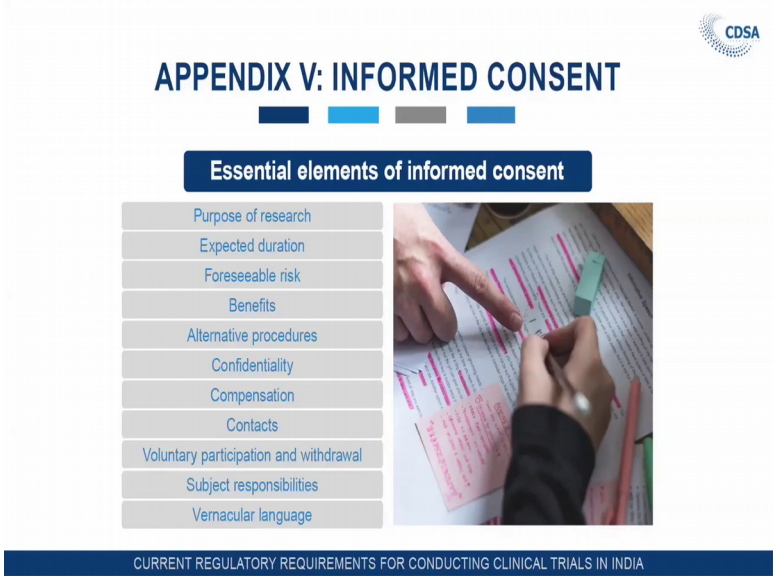

The purpose of research then expected duration, foreseeable risk, benefit, alternative procedure, confidentiality, compensation, then to whom to contact; then voluntary participation, subject responsibility and the ICF to be in vernacular language.

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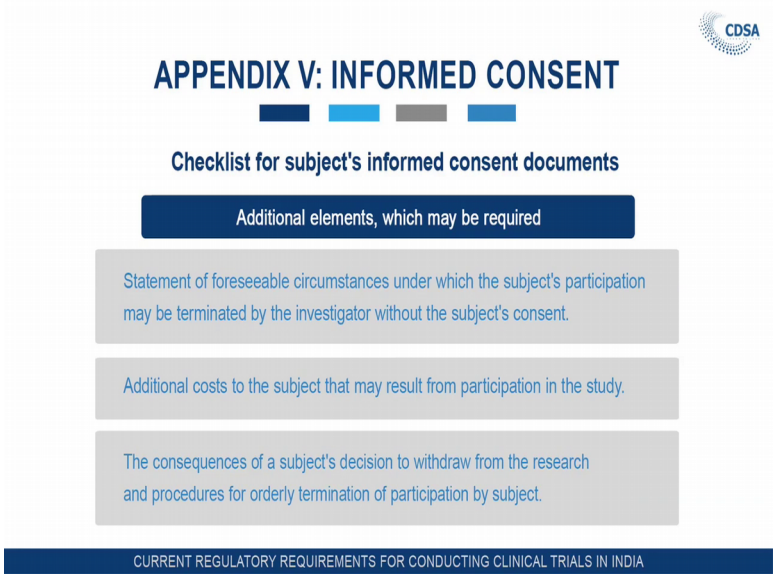

Additional element which may be required; so, statement of foreseeable circumstances under which the subjects participation maybe terminated by investigator without the subjects consent. The next is the additional cost of the subject that may result from participation in the study, the consequences of a subject's decision to withdraw from the research and procedure for orderly termination of participation by subject.

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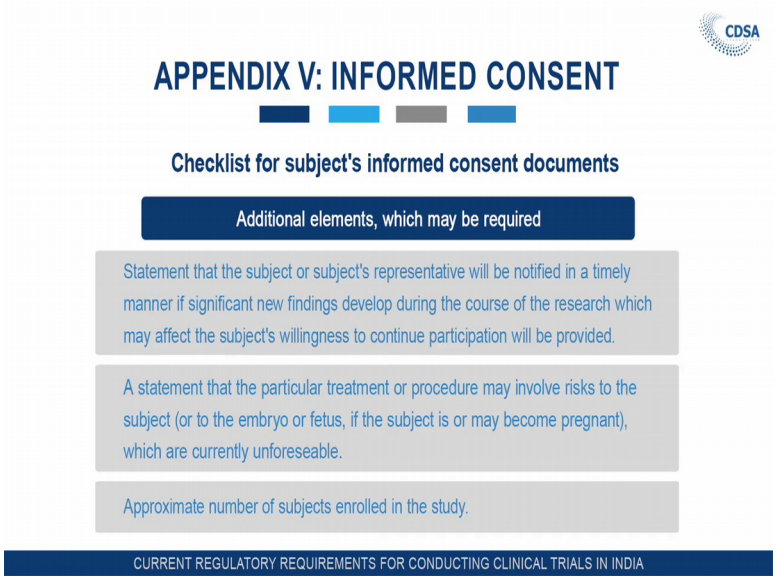

The statement that the subject or is representative will be notified in a timely manner, if significant new findings developed during the course of the research which may affect

the subject willingness to continue participation will be provided. It means if any risk is there or the sponsor or any other (Refer Time: 18:10) they came to know that there is some SAE occure somewhere else then that also has to be informed during the clinical trials. The statement that the particular treatment or procedure may involve risk to the subject; so, the treatment if it is involving the risk that also has to be mentioned, its approximate number of subject enrolled in the study.

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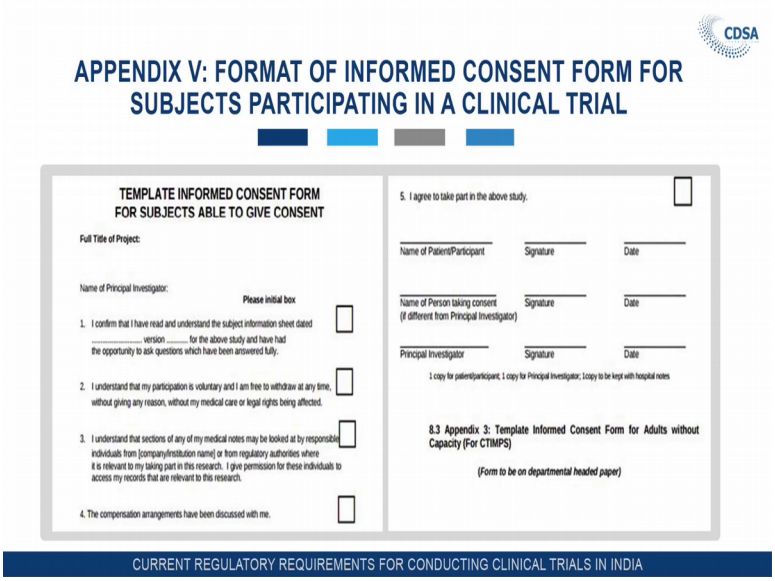

So, this is the format of informed consent form for subject participating in a clinical trial. So, this is a template provided where in the subject has to tick mark that he has read and understood the all the conditions, then he is participating voluntary and for that he is giving this sign in. And, he has to tick mark in the box and he has to give the initials for every elements given here and below you can see the name of participant or then he has to write his name, signature along with the date when he has enrolled. So, all the details he has to fill and give to the PI.

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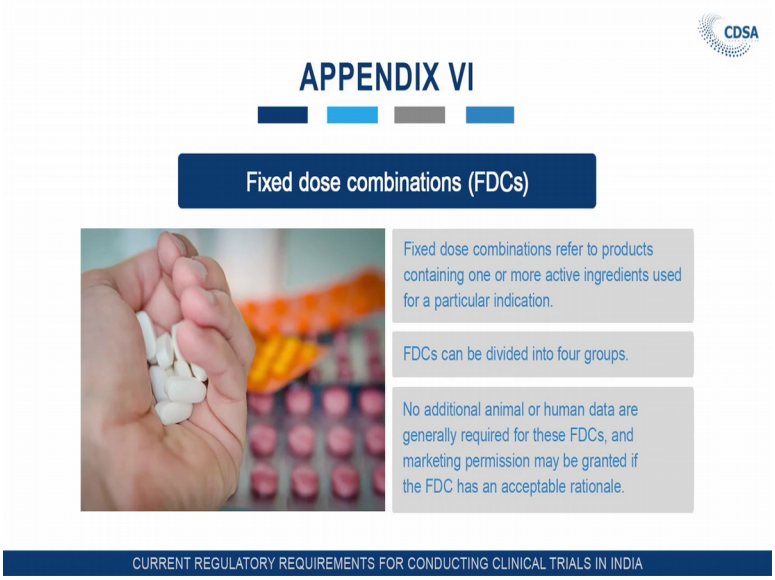

Appendix VI is related to the fixed dose combination. So, what is the fixed dose combination we have already seen; here also it is given the fixed dose combination. It refers to product containing one or more active ingredient used for particular indication. This FDC actually it has been divided into four groups that is when the new individually approved to product or more than two product first time it is combined then it is a FDC in new FDC.

Then if the ratio has been changed the strength has been changed, if the dosage form has been changed indication then also it is considered as a fixed dose combination. As these are already approved in the country no additional animal or human data generally required for this FDCs and marketing permission may be granted FDC has an acceptable rationale.

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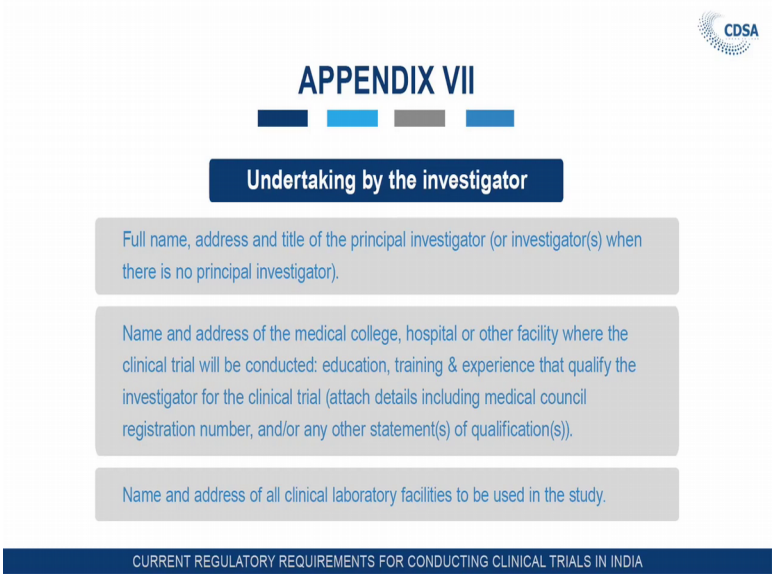

Appendix VII head is the most important that is undertaking by the investigator. So, while giving the undertaking by the investigator these are the content the investigator should fill. Full name, address and the title of the PI that is Principal Investigator, if the (Refer Time: 20:38) are more than sometime investigator are also there.

So, if the investigators are there then there is also required to do; name and address of the medical college hospital or other facility where the clinical trial will be conducted. So, wherever these trials are conducting the details about the address of this hospitals or site has to be given. Then education training experience of the PI investigators involved and the other members that details also has to be given. Name and address of all clinical laboratory facilities to be used in the study, what are the laboratories they are using for testing and analysis of the sample the details of this laboratory has to be given.

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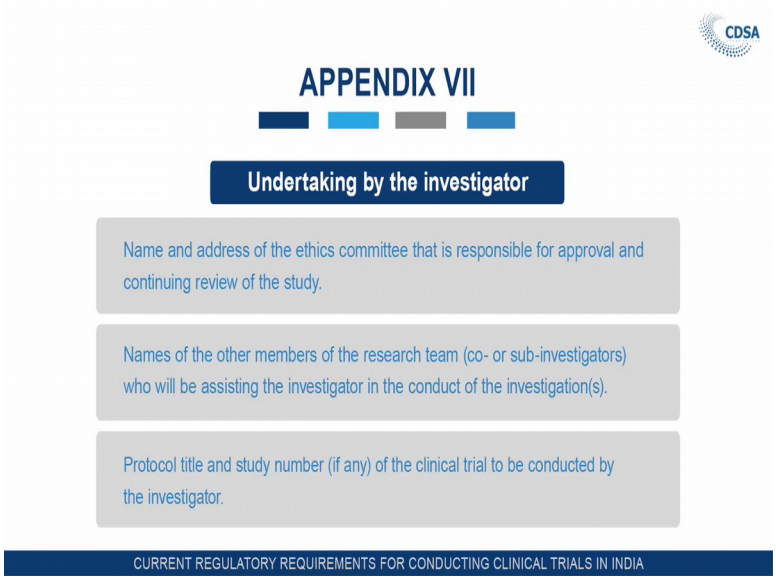

Name and address of the ethics committee; so, the ethics committee which is responsible for giving the approval detail about that ethics committee whether it is institutional, independents its address, composition quorum all the things regarding ethics committee has to be mentioned. The name of the other members of the research team as already mentioned. Protocol title and study number; so, under the undertaking by investigator again here required to give the protocol title and study number that which study is going to monitor or conduct.

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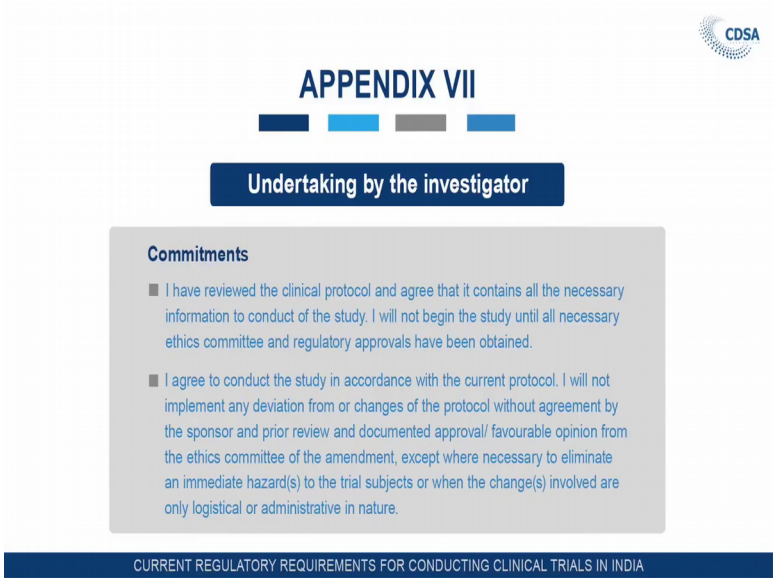

Then some commitments will given that he has reviewed the clinical protocol and he has agreed that it contains all the necessary information to conduct of the study. And, he will not begin the study prior to the approval of ethics committee and the regulatory authority, this commitment has to be signed by the principal investigator and other investigators.

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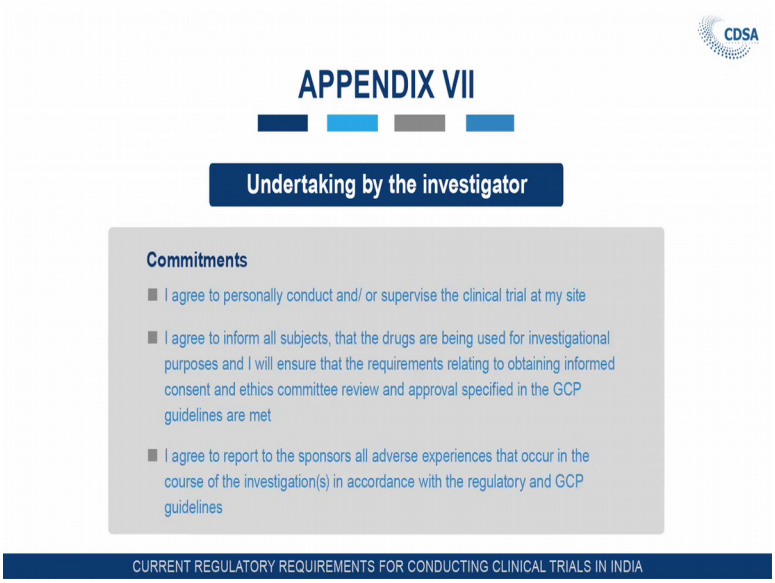

I agree to conduct the study in accordance with the current protocol. I will not implement any deviation from or changes of the protocol without agreement by the sponsor. So, he has to give in the written that he will follow the approved protocol and if any changes are there then he will take the permission from the ethics committee and from the licensing authority.

Then he has to agree to personally conduct and supervise the clinical trial at his site, before that I agree to inform all subject that drugs are being used for investigational purpose. And, I will ensure that the requirement relating to obtaining inform consent and its committee review and approval specified in GCP guidelines are made, that he will follow all the GCP guidelines. And, the research is for the research the trial is for the research purpose that also has to mention. I agree to report to the sponsor all adverse experience that occur in the course of the investigation in accordance with the regulatory and GCP guidelines. This is regarding the adverse experience.

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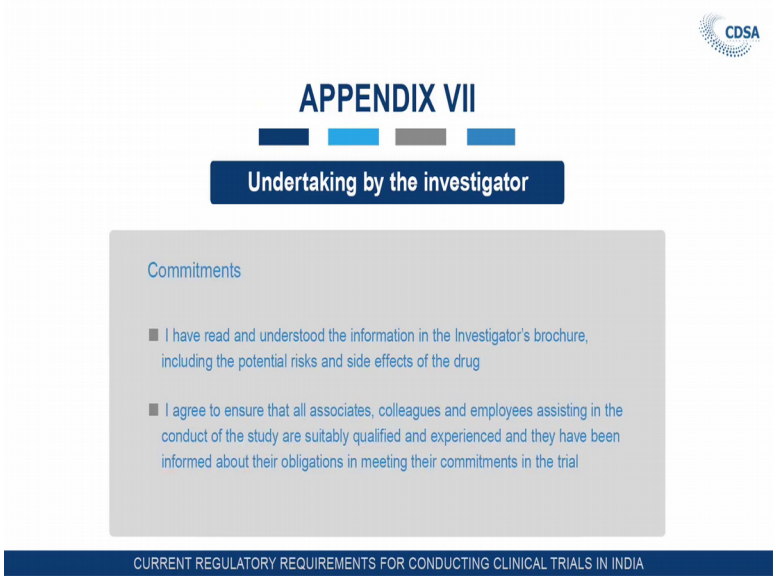

I have read and understood the information in the investigator brochure including the potential risk and side effect of the drug. So, he has to first read all the investigating investigators brochure and if he agree then had to give the agreement. I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are suitably qualified, experience and they have been informed about their obligations in meeting; this agreement also has to be signed.

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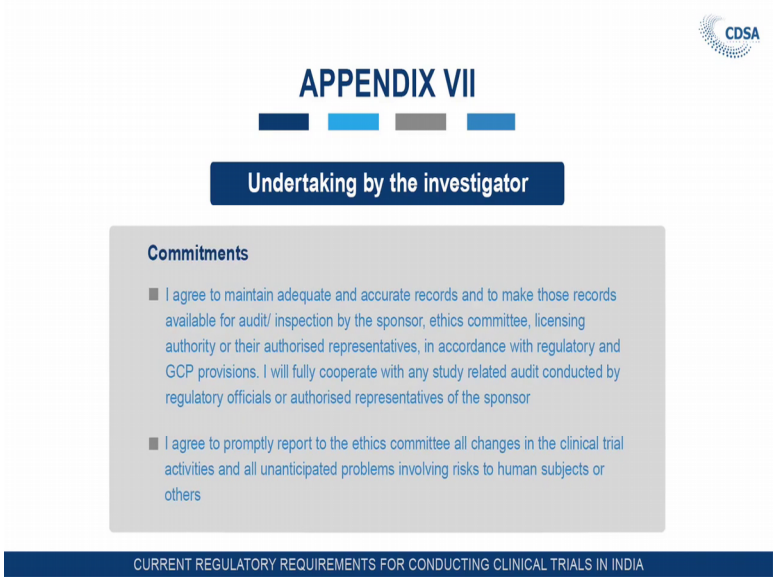

Then I agree to maintain adequate and accurate record and to make those record available for the audits. So, the PI and the investigator it is their responsibility to maintain all the data and it has to be made available during the audit. Then I agree to promptly report to the ethics committee all changes in clinical trial activities. So, any changes in the clinical trial activities he has to immediately inform to the inform ethics committee.

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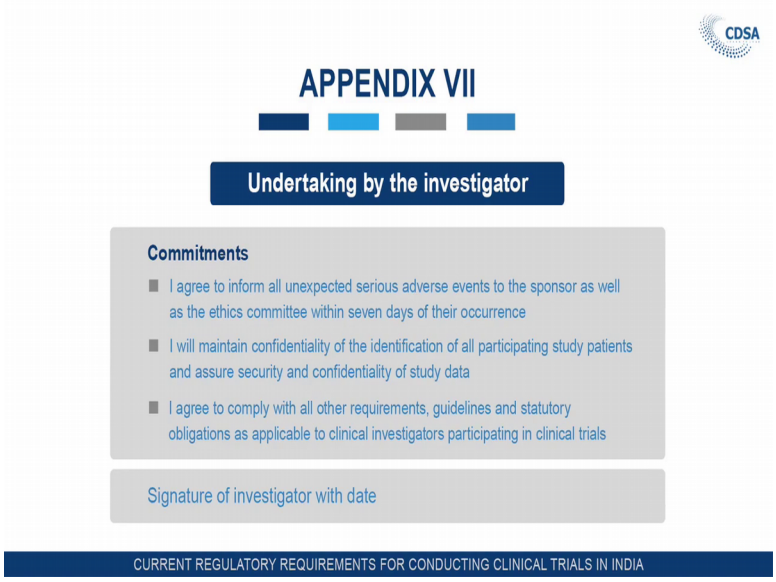

I agree to inform all unexpected SAE to the sponsor as well as ethics committee within 7 days of their occurrence. I will maintain confidentiality of the identification of all participating study patient and assure security and confidentiality of study data; study data and patients information has to be made it confidentially. Then I agree to comply with all other requirement, guideline and statutory obligation as applicable to clinical investigator participating in clinical trial. Signature of investigator with date; so, all this commitment he has to sign within date.

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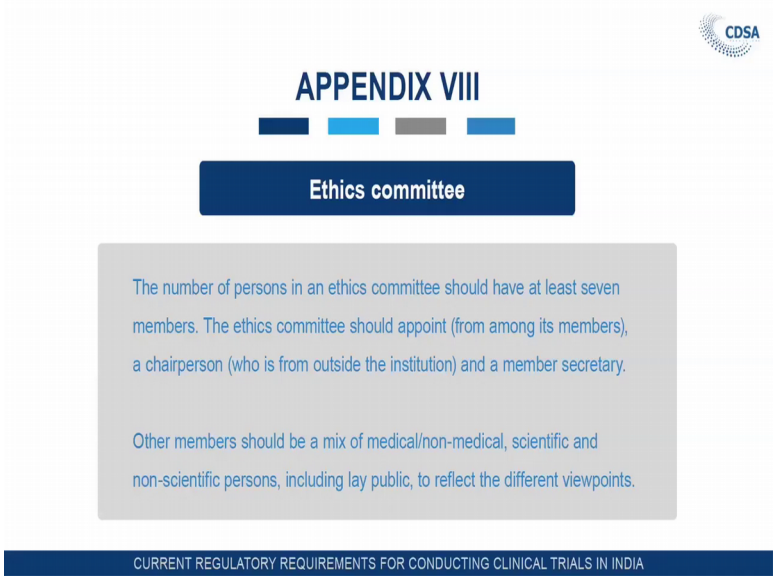

Coming to the next appendix that is appendix VIII, it is related to the ethics committee. So, we have seen this in detail in our previous lecture. So, we will not go in detail only will have the brief that at least 7 member should be there.

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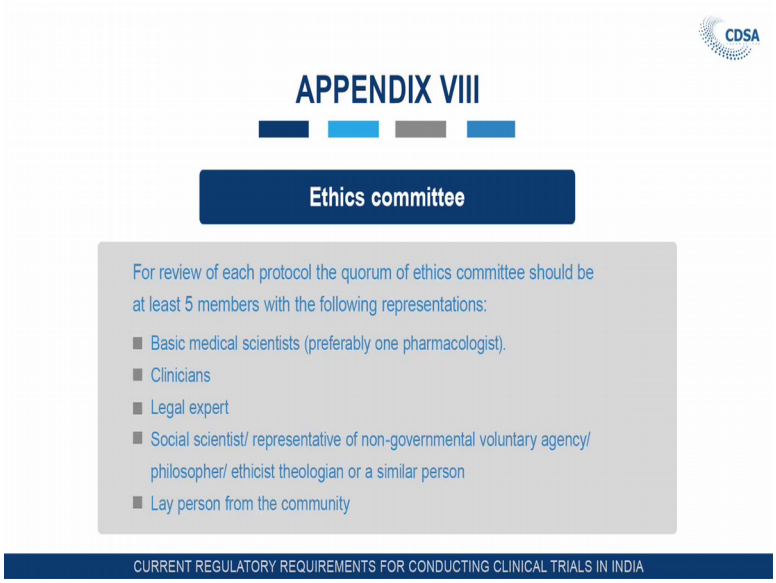

Then for the quorum required the 5 members and this members are like this basic medical scientist, clinicians, legal expert and other we have already seen it in detail.

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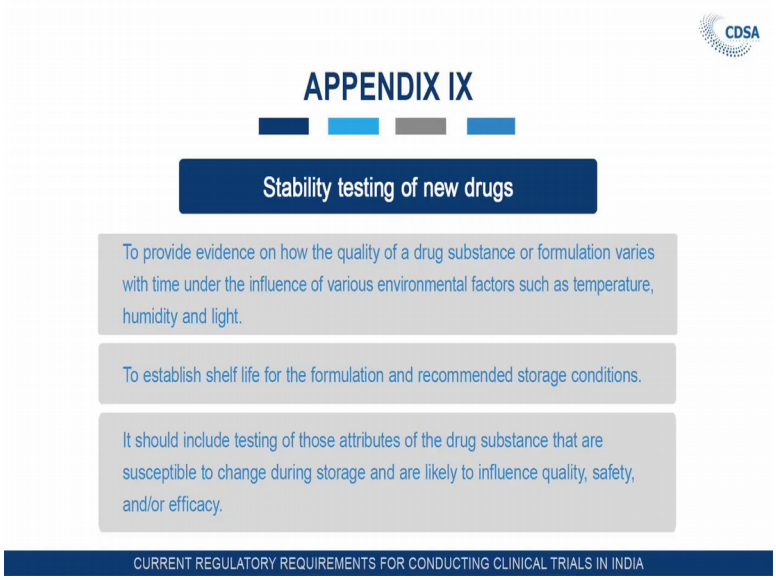

Appendix IX is related to the stability testing of new drug whether the drug is stable or not that has to be proven and the documented proof has to be given. To provide evidence on how the quality of drug substances or formulation varies with time under the influence of various environmental factors such as temperature, humidity and light this stability studies are required. To establish shelf life for the formulation and recommended storage condition; stability studies are also required to establish the shelf life for the formulation and recommended dosage form. It should include testing of the attribute of the drug substance that are susceptible to change during storage and likely to increase quality safety and efficacy.

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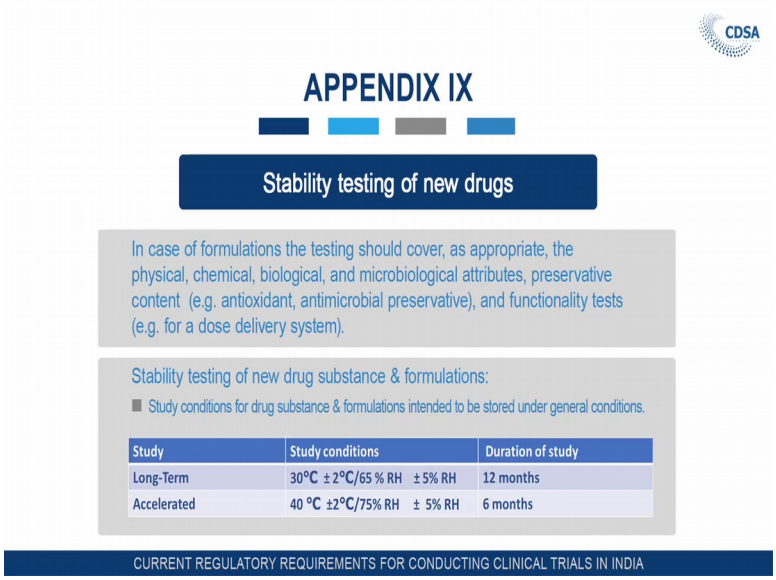

In case of formulation the testing should cover as appropriate, the physical, chemical, biological and microbiological attribute preservative all this has to be mentioned and here it is given. Then the stability testing of new drug substance and formulation, study condition for drug substance and formulation intended to be store under general condition. So, these are the storage conditions and the stability study conditions, stability testing of for the new drug. So, for the general storage condition that is room temperature or 25 degree Celsius; the stability study has to be carried out for the long term and accelerated.

For the long term or also called real time the study condition 30 degree Celsius plus or minus 2 degree Celsius with the relative humidity 65 percent plus or minus 5 percent. The study has to be conducted for the duration of 12 months, for accelerated is 40 degree Celsius plus or minus 2 degree Celsius with the relative humidity 75 percent plus or minus 5 percent for the 6 months. If at any time during 6 months testing under the accelerated storage condition such changes occur that cause the product to fail in complying with the prescribed standard. Aadditional testing under intermediate storage condition should be conducted and evaluated against significant changes criteria.

If the products are required to be stored in refrigerator condition then this following type of the study conditions are and the duration is required. For the long time it is 5 degree Celsius plus or minus 3 degree Celsius, study required to be conducted for 12 months.

And, for the accelerated it is 25 degree Celsius plus or minus 2 degree Celsius with relative humidity 60 percent and duration is 6 months. Now, let us see the product to be store in the freezer, the study condition for a drug substance formulation intended to be stored in freezer.

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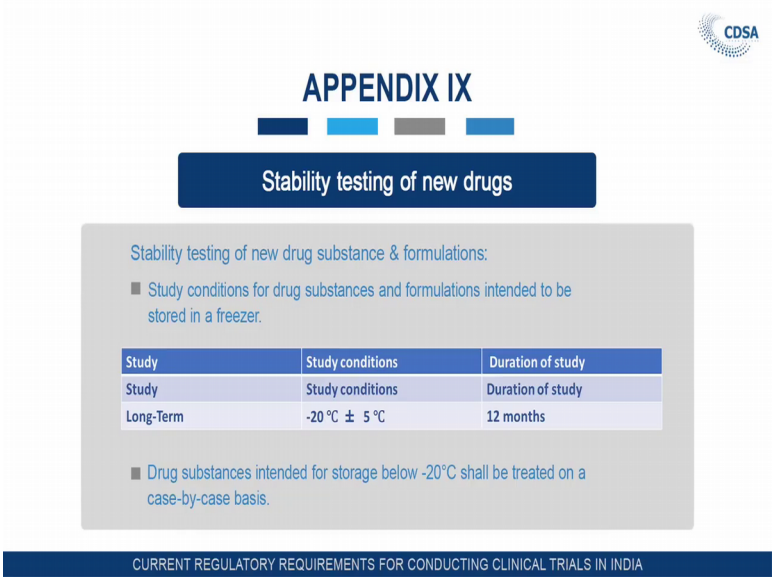

So, these are the conditions, in this case only long term study has to be conducted minus 20 degree Celsius plus or minus 5 degree Celsius for 12 months. Drug substances intended for storage below minus 20 degree Celsius shall be treated on case by case basis.

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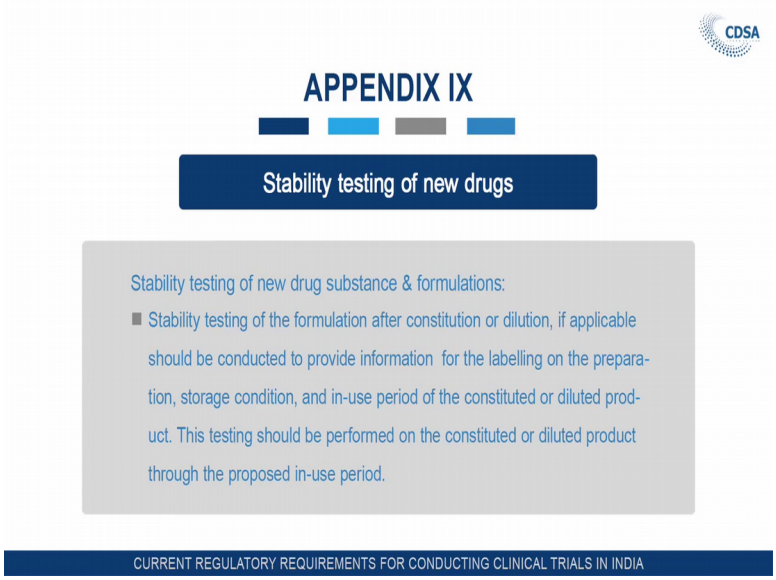

Stability testing of the formulation after constitution of dilution, if applicable should be conducted to provide information for the labelling on the preparation. If the preparation is life preparation and dilution is required then the after dilution how much is the stability shall find that also has to be mentioned. This testing should be performed on the constituted or diluted product through the proposed in hospital.

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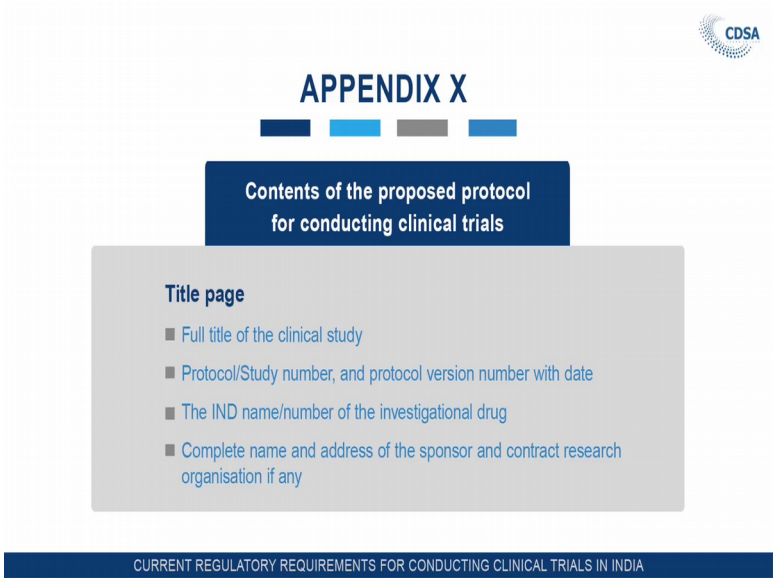

Coming to the next slide that is appendix X, it is regarding content of the proposed protocol for conducting clinical trial. So, while applying the form 44 we have seen, that

form 44 is required there for the application of new drug, for manufacture or for import purpose for the clinical trials or marketing in the India. So, these are the contents; first in the title page has been given, full title of the clinical study has to be given.

So, that from the title itself one can understand what type of study is there. Protocol study number and protocol version number with date, if it is the original protocol and protocol number, if it has been revised in the version number or region protocol number. The IND name if in case of the investigational new drug then whatever the name they have given code number that has to be mentioned. Number of the investigational drug, complete name and address of the sponsor and the CRO so, who is the sponsor and where from you getting done the clinical trial that is the CRO that also required to.

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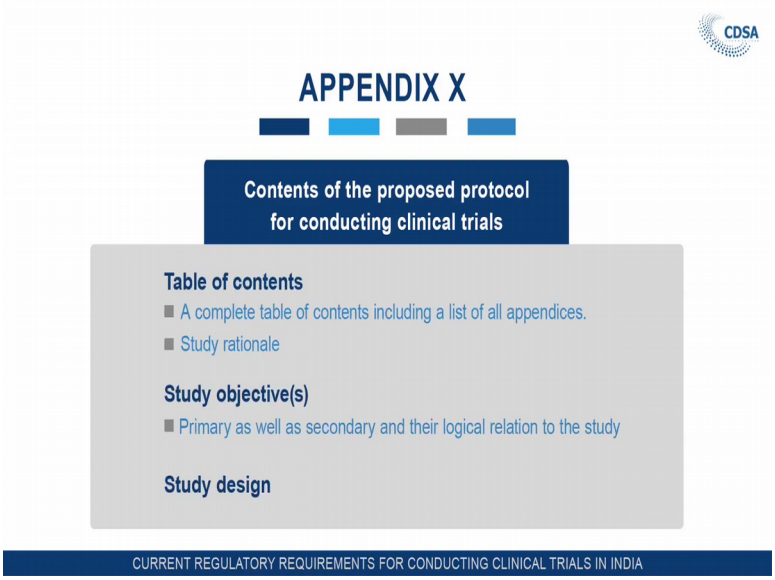

Number of investigators involved in the study. So, details about the number of investigator and their name address everything has to be given.

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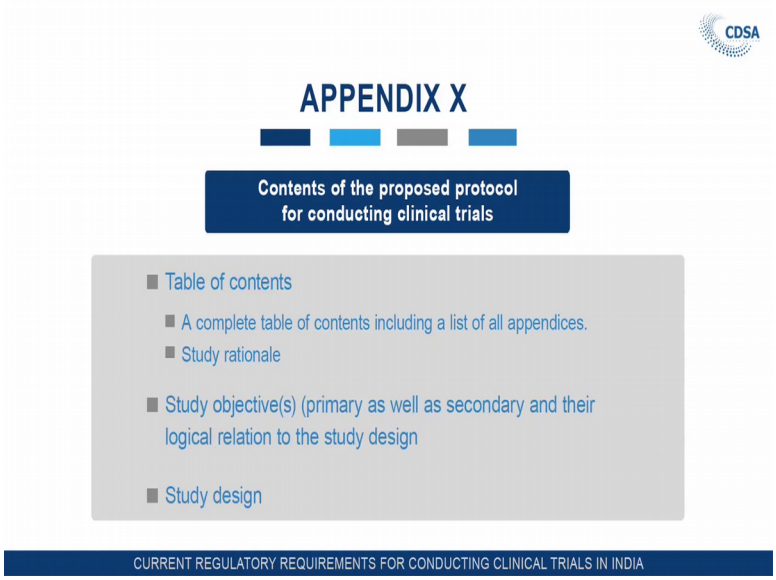

Table of content a complete table of content including list of all appendices, if the appendices are attached than list of all the appendices the table has to be given. Study rationale then study objective all the objective of the study that is primary, secondary whether it is for safety purpose, whether it is for efficacy purpose or to see the adverse reaction that study object has to be given. Then study design like a double blinded study or open label, study randomization is there or not, cross all these sequence treatment period this should be given in the study design.

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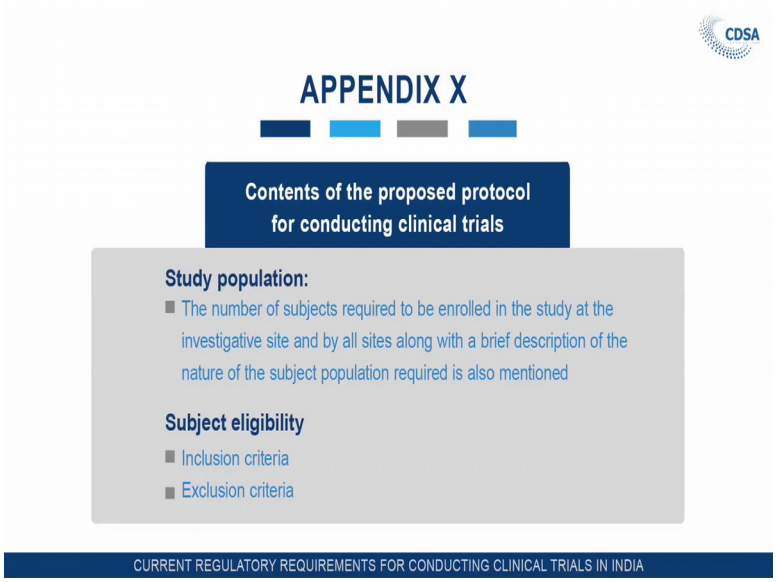

Then study population the number of subject required to be enrolling in the study at the investigative site and by all sites along with brief description of nature of subject population required in required to mention. Subject eligibility that is inclusion criteria and exclusion criteria those subjects which are to be included, what should be the criteria for their inclusion and what should be the criteria for the inclusion exclusion that is also has to be given.

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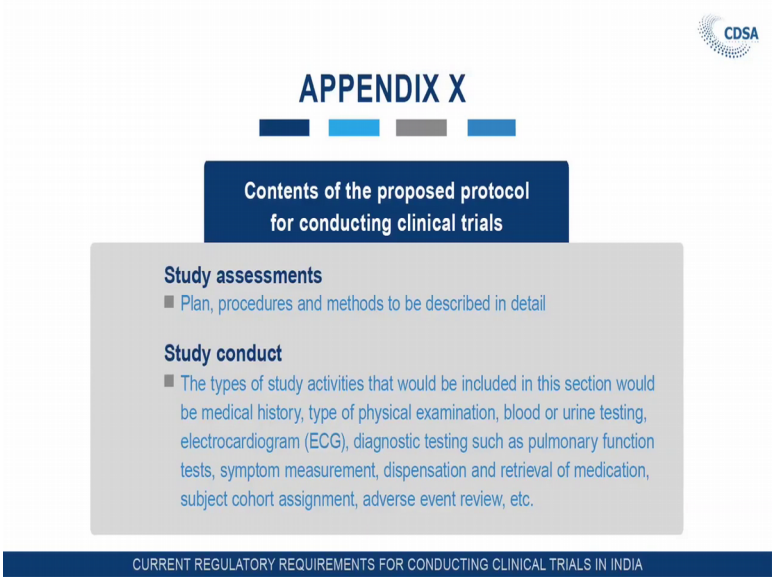

Study assessment plan procedure and methods to described in detail. Study conducting the type of study activities that would be included in this section would be medical history, type of physical examination, blood or urine testing. Then ECG diagnostic testing such as pulmonary function test, symptoms measurement dispensation and retrieval of medication, subject cohort assignment, AE review etcetera has to be given.

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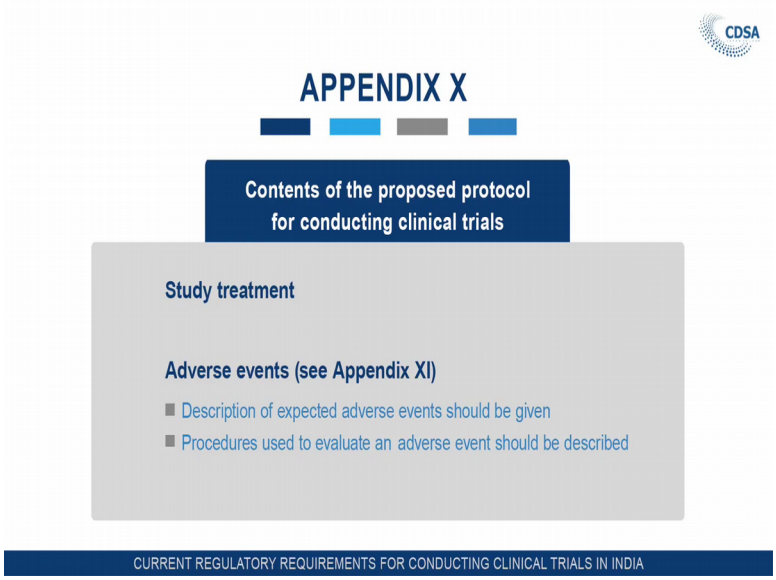

Then what are the study treatment that also required to give, then adverse event description of expected adverse event should be given. So, whatever the available knowledge for the adverse event that also has to be mentioned. Procedure used to evaluate an adverse event should be described whatever the procedure; the CRO is following as per the protocol that has to be mentioned. Ethical consideration so, the summary of the ethical consideration required to be give.

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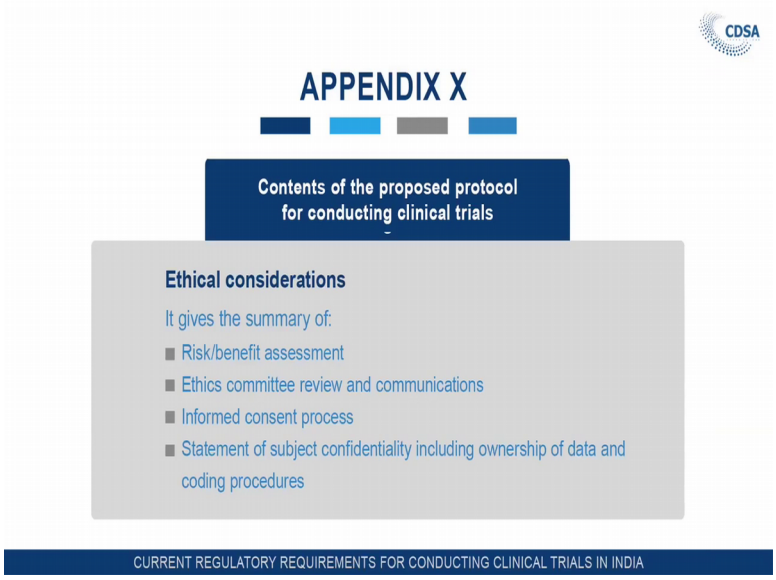

Like risk benefit assessment how they have calculated, then it is committee review and communication then informed consent processes how they are the SOP for that. In a statement of subject confidentiality including ownership of data and coding procedure that they will maintain the confidentiality, what is the procedure to maintain the confidentiality that also has to be given.

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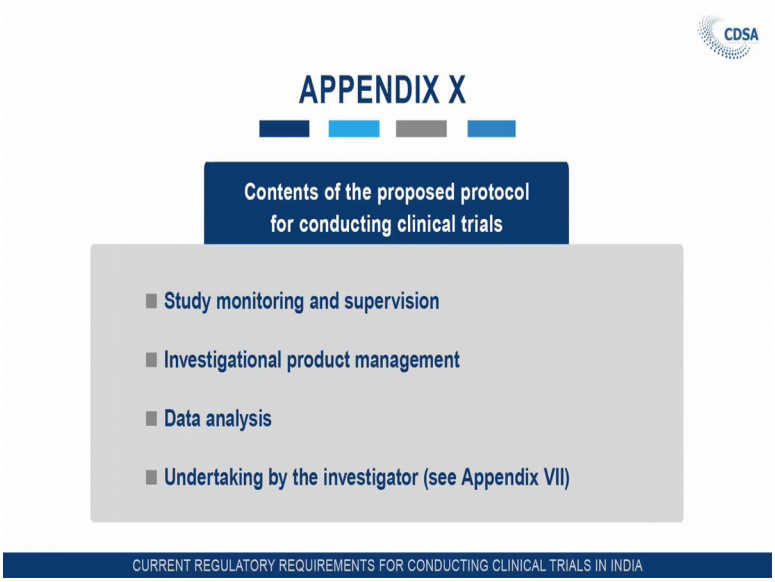

Study monitoring and supervision; so, how they are going to monitor the study, who will be the responsible, how they are going to supervise the study the detailed procedure, then investigational product management. So, what are the products they are going to use in the study. So, how they are going to store that product, what is the stability of that product, who is responsible to dispense that product. So, whatever the management is there they have to give; then data analysis undertaking by the investigator we have seen in appendix VII. So, undertaking by the investigator whatever whosever investigator involve, they have to give the sign and the undertaking.

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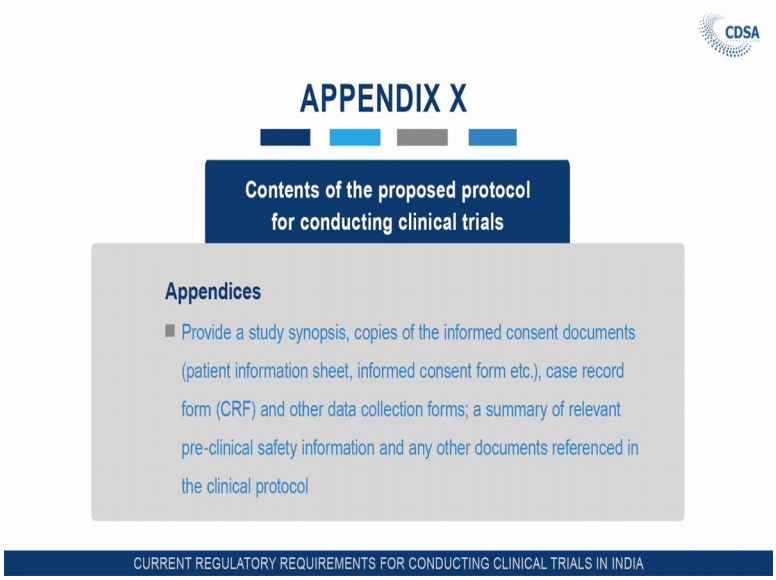

Then appendices provide a study synopsis, copies of the informed consent document, informed consent document as I have said into part patient information sheet, the information to be converted to the patient and informed consent form that, if you agree then you to sign. CRF and other data case record form and other data collection form; summary of relevant pre-clinical safety information any other document reference in the clinical protocol. So, here it is briefly given the content of this appendix X that is title page table of comments and other things.

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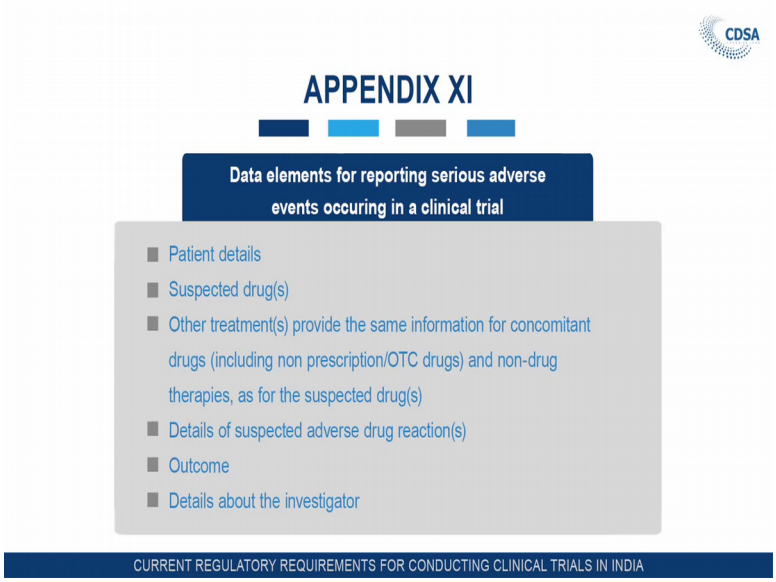

Appendix XI is the data element for reporting SAE occurring in clinical trial. So, this is regarding the patient details, suspected drugs other treatment to provide the same information for concomitant drug including non-prescription drug, then details of suspected AE, outcome details about the investigator.

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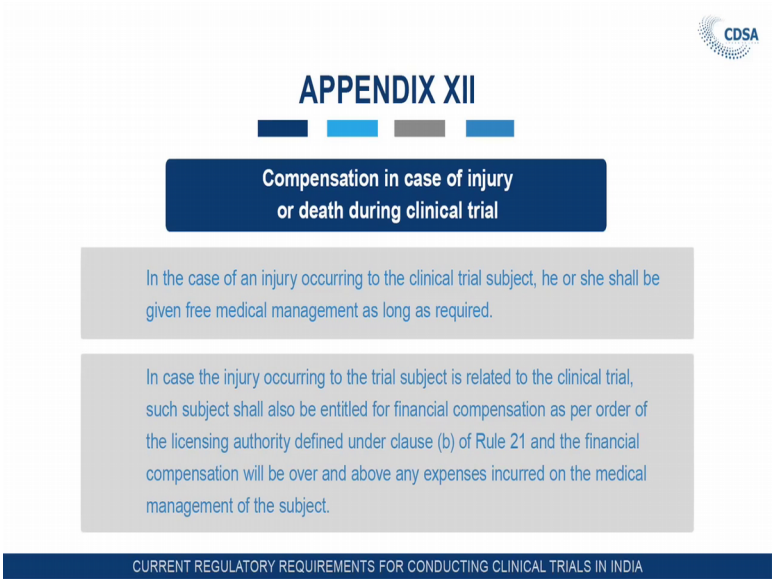

The next is appendix XII; compensation in case of injury or death during clinical trial. So, this is your related to the compensation in case of the clinical trial. In the case of an injury occurring to the clinical trials subject he or she shall be given free medical management as long as required. In case injury occurring to the trial subject is related to the clinical trial so, subjection also be entitled for financial compensation as per the order of the licensing authority, that is a drug controller general of India; we also called the CLA will be over and above any expense incurred on the medical management of the subject.

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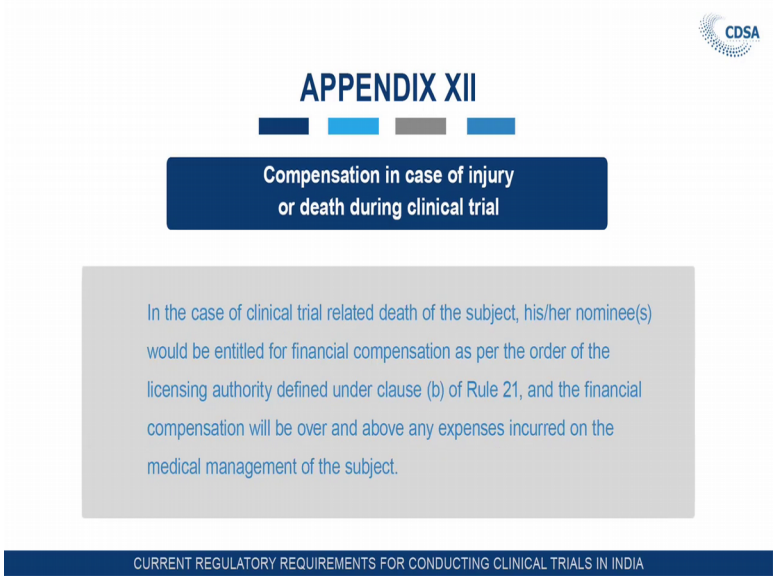

In the case of clinical trial related death of the subject his or her nominee would be entitled for financial compensation as per the order of the licensing authority defined under clause b of rule 21, and the financial compensation will be over and above any expense incurred in the medical management of the subject.

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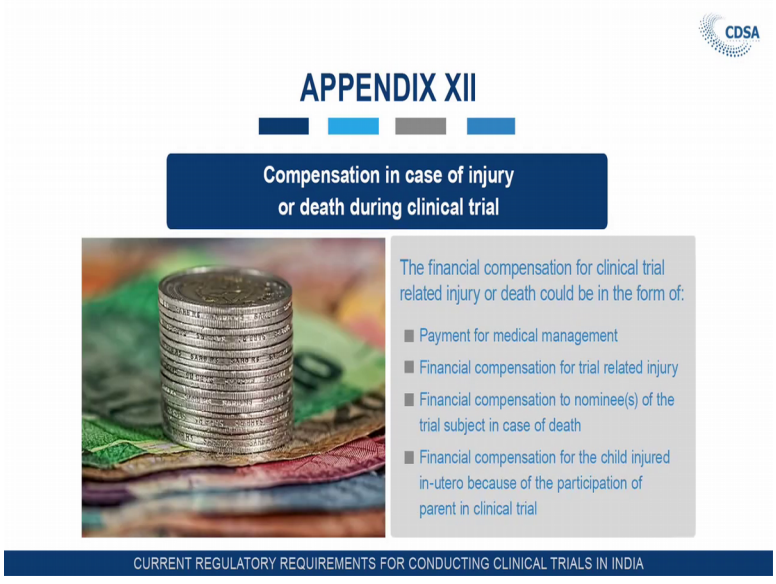

The financial compensation for clinical trial related injury or death could be in the form of payment for medical management, then financial compensation for trial related injury. Financial compensation to nominees of the trial subject in case of death, financial

compensation for the child injured in-utero because of the participation of parent in clinical trial.

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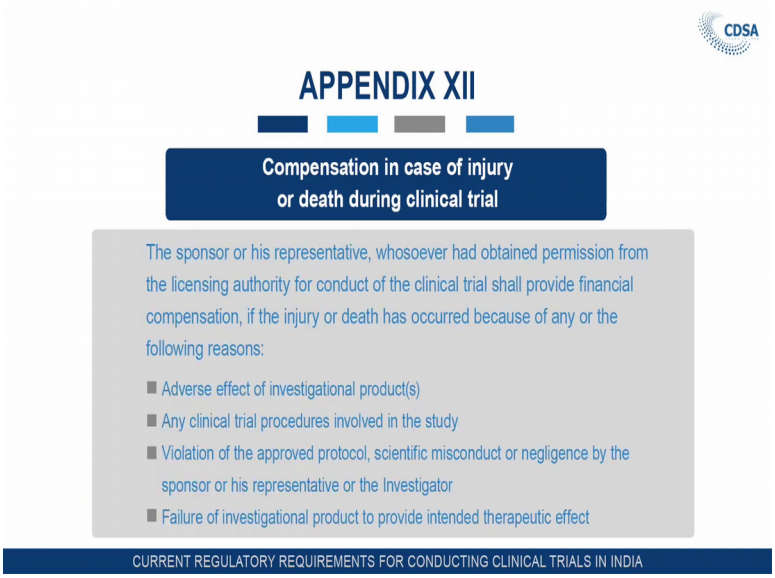

The sponsor or his representative whosoever had obtained permission from the licensing authority for conduct of the clinical trial shall provide financial compensation, if the injury or death has occurred because of any of the following reasons. The reasons are given here below. Adverse effect of investigational product, any clinical trial procedure involved in the study, then if there is a violation of the approved protocol, if the protocol has been approved and the PI has not followed the condition stipulated there in, scientific misconduct of the protocol or any negligency by the sponsor of his representative or the investigator, failure of investigational product to provide intended therapeutic effect.

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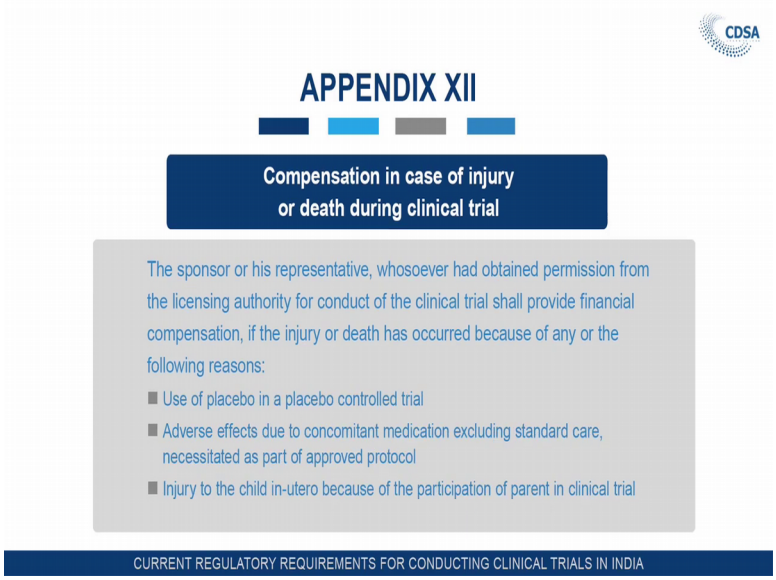

Use of placebo in placebo controlled trial, if any adverse effect due to the concomitant medication if any other medication has been used and due to which the adverse effect or SAE occur, but this is excluding standard care necessitated as part of approved protocol. Injury to the child in-utero because of the participation of parent in clinical trial, procedure for payment of financial compensation has to be given. So, these are all the appendices is given in the schedule Y we have seen.

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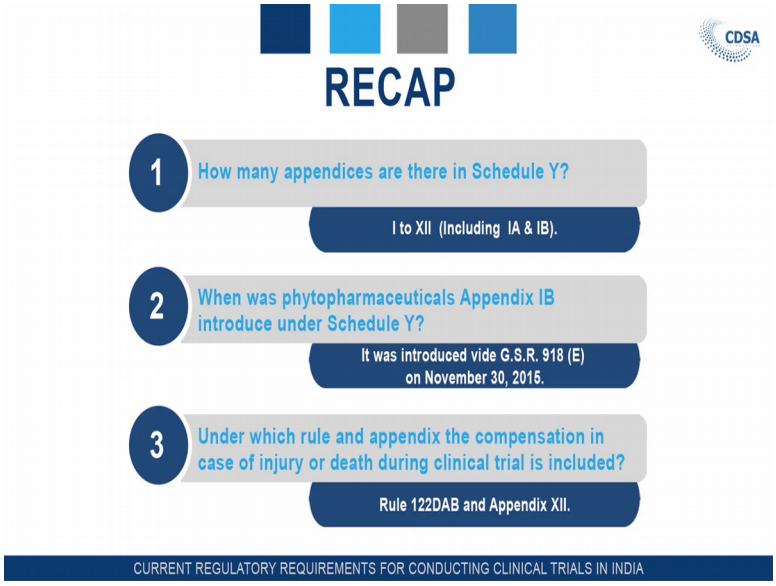

Now, let us have quick challenge for you by giving the question as usual. So, have the first question, how many appendices are there in schedule Y? So, there are XII appendices including appendix I A and I B. Then next question, when was phytopharmaceutical drug appendix I B introduced under schedule Y? So, it was introduced vide GSR 918 on 30th November 2015. Next question under which rule and appendix the compensation in case of injury or death during clinical trial is included? So, this is rule 122 DAB and appendix 12 related to the compensation.

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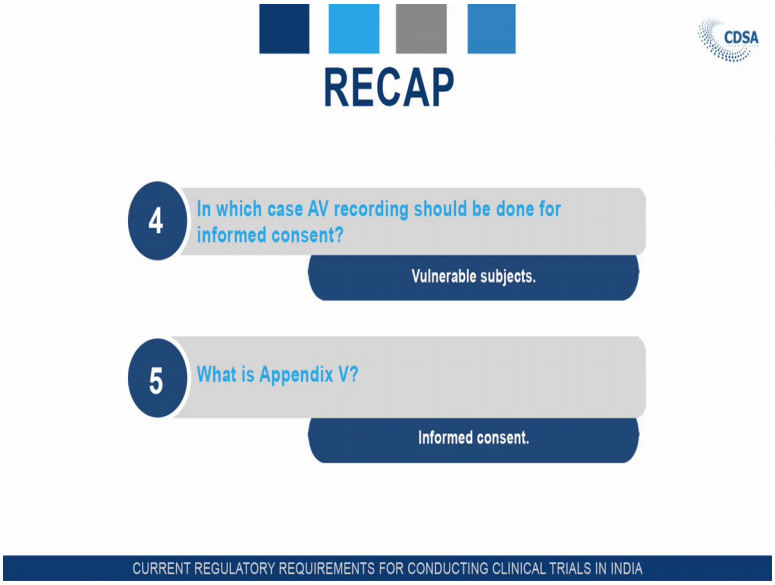

In which case AV recording should be done for informed consent? So, the answer for this is vulnerable subjects, AV recording is required. The last question what is appendix V? This is very important appendix. So, the appendix V is related to the informed consent document.

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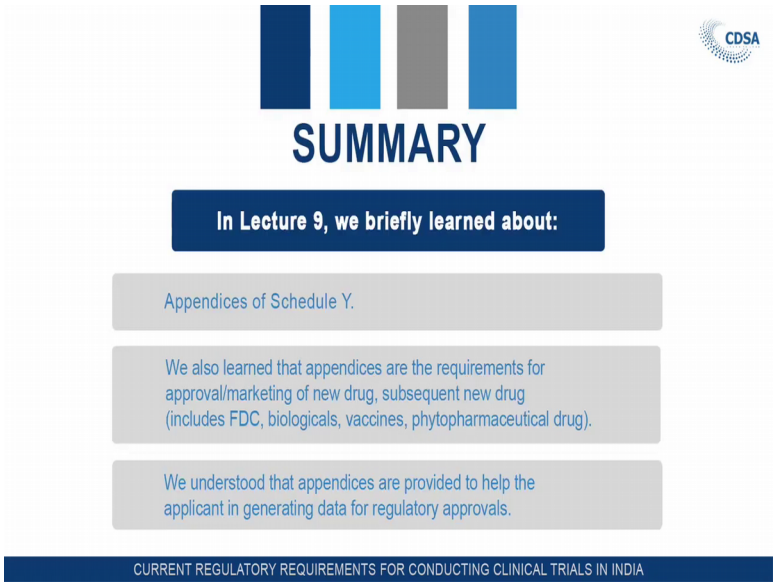

Let us summarize and briefly the lecture 9. So, in this lecture 9 we have seen all the appendices that is appendix I to appendix XII including I A and I B. We have also learned that the appendices are the requirement for approval of marketing new drug, subsequent new drug, then FDC, biological, vaccine, phyto-pharmaceutical drug. We understood that appendices are to help applicant to generate data for regulatory approval. So, this is all about the lecture 9 and schedule Y and its appendices. So, we will see again in our next lecture till then bye bye and.

Thank you.