Current Regulatory Requirements for Conducting Clinical Trials in India for IND/New Drug Version 2.0

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Lecture – 18
Post Marketing Assessment & Clinical Trial Compensation

[FL] Welcome to the course Current Regulatory Requirements for Conducting Clinical Trials in India for Investigational New Drug and New Drug. This is the version 2. Today, I will take you through lecture 18, which is the Post Marketing Assessment and Clinical Trial Compensation.

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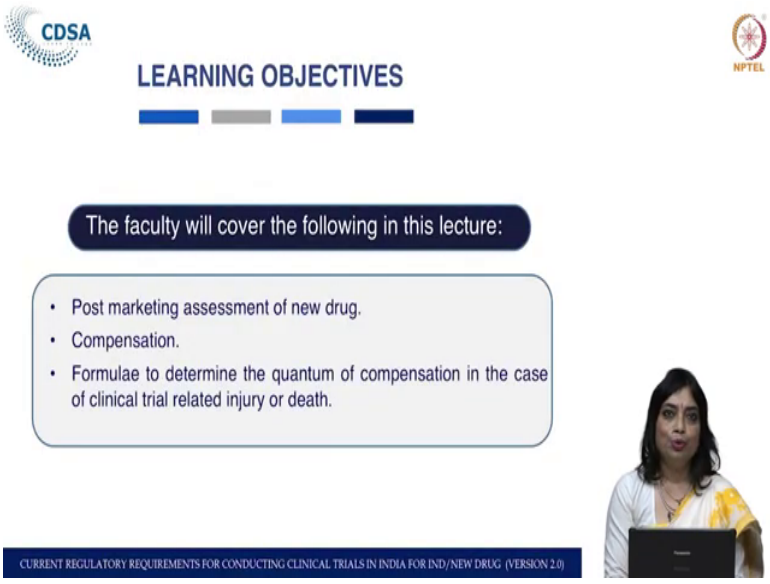

So, one of the part of this lecture 18 is the post market assessment which is related once the drug is manufactured and marketed for sale and distribution in India or it is imported for sale

and distribution in India, that is also related to the new drug. And, also for any drugs manufactured and marketed or imported and marketed in India. And, the other part is the clinical trial compensation, which is related to the clinical trial before the drug is approved for marketing in India.

So, the lecture has two different parts. So, what is the learning objectives? What we are going to learn? The post market assessment of new drug how it is conducted, what are the different requirements or what we do in post market assessment of new drug and there is a compensation mechanism for a clinical trial in the country and the formula to determine this compensation.

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We start with the post market assessment. So, as already has been told many times for other parts of this course. So, you may be knowing that the new drug and the clinical trial rules they

have various chapters, various rules under these chapters as well as the various schedules. So, there are 13 chapters in this new drugs and clinical trial rules and under these 13 chapters there are 107 rules; which describe the different requirements for the our requirements for applications requirements, for conditions to be fulfilled, the different forms formats which are what are to be filled.

These are all the requirements of the clinical trials and the requirements for the ethics committee for the different parts of any new drug and clinical trials related issues are covered under these 107 rules, in these 13 chapters. And, also there is a there is 8 schedules, which have the various requirements for the specific requirements under each of these rules. So, now, we come to the post market assessment which is the fifth scheduled in this new drug and clinical trial rules.

So, what is this post market assessment of new drug? So, we have approved the new drugs the new drugs, has passed the clinical trial has proved its safety and efficacy and now it has been marketed. So, when it is marketed? There is a requirement of post market assessment. It is not finished that when it we have if it has gone through the clinical trial means the drug is ready for marketing, it does not mean the drug has proved completely; it is safety and efficacy there are many other issues.

But, what are these issues? What are the things? What are the concerns? Because when we approve a new drug for clinical when we approve the new drug through a clinical trial it is through a controlled clinical setting where the clinical trial is conducted in a limited number of patients. Many times these are only studied under randomized clinical trials and there are many cases like the high risk patients and patients with concomitant illnesses that require the use of the other drugs.

Then there are different age group of patients like the geriatric patients, the pediatrics, the lactating women, the pregnant women and the patients with some diseases like the kidney further the disease special diseases like renal diseases or other co-morbidities such type of patients are not included initially in a clinical trial. So, these patients are excluded in the

normal clinical trial, where the clinical trial of the new drug is conducted only in limited number of patients with a specific inclusion and exclusion criteria.

So, that is what is required now and these patients these patients as they are include as they are excluded in this clinical trial. And, further now when the drugs are approved for marketing for sale and distribution in the country then comes the actual patient population. And, also when there is a clinical trial these patients whom these clinical trials are conducted the limited number of patients, they are closely monitored for evidence of adverse events.

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What happens in actual clinical practice? The monitoring is less intensive broader range of patients, which are treated with the age groups co-morbidities there may be some genetic abnormality abnormalities; like there may be defect a bit defective in the enzymatic system, there may be different other genetic diseases. So, these patient groups come in the actual real

clinical which is a real world situation, we call we may call it a real world situation. And, then there are events which are too rare to occur in a clinical trials may be observed.

Therefore, subsequent to approval of a new drug, the drug which has to be closely monitored and the post marketing assessment has to be done to establish the benefit risk profile. The drug is released or approved for marketing in the country, when the benefit outweighs risk, but it is to establish further the benefit risk profile of this drug.

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So, in this post are marketing system, what is the what are the different things which had to be done? A person who is intending to import or manufacture in a new drug for sale or distribution, they have to have a pharmacovigilance system in place for collecting processing and forwarding the adverse drug reaction report to the central licensing authority emerging

from the use of this drug imported or manufactured or marketed by the applicant in the country.

So, who is the Central Licensing Authority? That is the central drug standard control organization, who approves drugs for import or manufacturing any new drug for imported manufacturing in the country. And, the pharmacovigilance system as already defined in the new drug and the clinical trial rules, it says that it is the science, it is defined the new drugs and the clinical trial rules also define the pharmacovigilance system in the country and which means the science and the activities for detection, assessment, understanding and prevention of drug related problems or adverse effects of drugs.

So, in case the drugs the drugs are permitted for marketing in the country so, every firm every such license holder has to have a pharmacovigilance system in place.

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The pharmacovigilance system what is said in this in this under this post marketing assessment? That the pharmacovigilance system shall be managed by qualified and trained personnel and the qualification for such person shall be like they are called the officer in-charge for collection and processing of data and they shall be a medical officer or a pharmacist who is trained in collection and analysis of adverse drug reaction reports.

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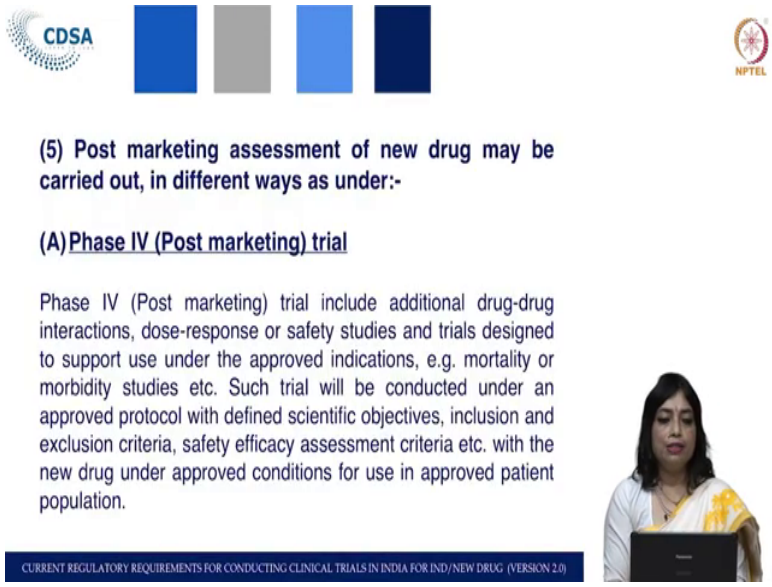

How this post market assessment of the new drug is now carried out? The post market assessment for the new drug is carried out, by three different methods we can say which is given under this post market assessment. The one may be the post marketing trial and this is we called is at a Phase IV clinical trial. So, it is a clinical trial after marketing of the drug. So, it will include all the requirements of a clinical trial. So, it has to have a defined scientific objective, there has to be a clinical trial protocol, there has to be inclusion and exclusion

criteria and the drug has to be given to the patients under the in the approved indications and to the patients for whom it is indicated.

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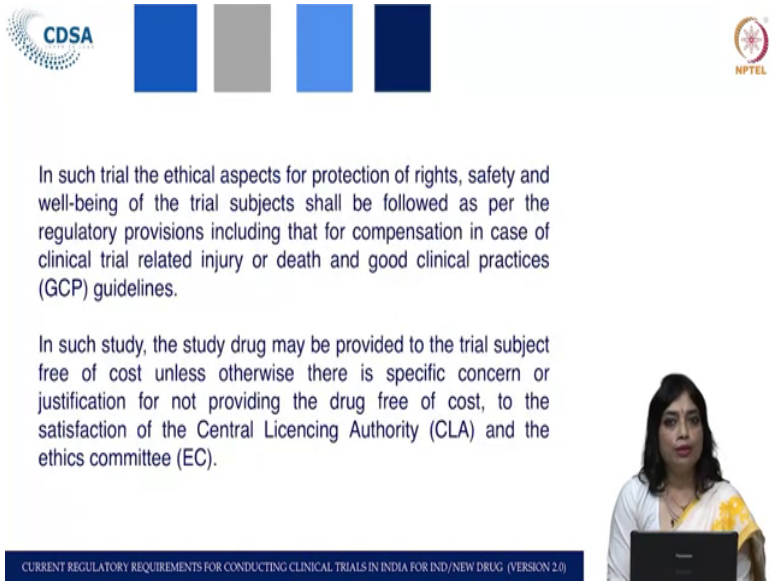

So, the drug given for the specific group of patients for whom the drug is approved under the approved indications. And also in such cases all the regulations and requirements of clinical trials are applicable which includes the compensation in case of a clinical trial related injury or death and also all the principles of good clinical practices.

In such study the subject may be provided, the subject should be provided the drug free of cost. And in case there is a cost incurred on the subject, then there has to be a reasons, which has to be given by the applicant to the licensing authority to support that why the cost of the drug has been taken from the patient, otherwise the drug should be provided to the patient free of cost.

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Also the other part of the post marketing so, this is one. There can be a phase IV clinical trial as it is said and also there can be a post marketing surveillance study or observational or non-interventional study. So, what is this non-interventional study? By the what we can just say that it means that the drug is given to the patient in the real life situations in the real world real world situations or the real life situations; that it is given to the patient in the under the prescription in the by the prescriber and also when the patient with the specific indication.

So, such studies are conducted with the drugs under the approved conditions of its use. And that has to be it is also expected that there has to be a protocol with the scientific objective, inclusion and exclusion criteria of the subject would be decided as per as recommended as per the prescribing information or the package insert. And that would be a such that such type of study would be a part of the treatment of the patient in the wisdom of the prescriber included

in the protocol. So, the regulatory provisions and guidelines are not applicable in case of such studies. So, this is to establish further the safety of the drug.

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And, also the other requirement we come to this part c of the fifth schedule which calls talks about the post marketing surveillance through periodic safety update reports. So, this particular requirements of post marketing surveillance through periodic safety update reports, is already given under the conditions of permissions for a marketing or import of new drugs or investigationals new drugs in the in the country.

This is under the chapter 10, under rule 25, the 4 and the 5 these are the two conditions, which says that as post marketing surveillance the applicant has to the manufacturer or the importer has to submit periodic safety update reports and also under the specified conditions. As well as also in case of any adverse events any adverse drug reaction or any serious unexpected

adverse drug reactions reported for the new drug which is approved for import or marketing. It has to be it has to be analyzed causality analysis has to be done and this is to be reported to the licensing authority.

So, these are the two conditions which are being given as a conditions of permissions for import or manufacturing of new drug in the country. In this periodic safety update reports, the what is there in this periodic safety update reports? Let us see the applicant shall furnish periodic safety update reports to report all the relevant new information about the drugs from the appropriate sources and it should relate to the patient exposure.

They have to summarize all the marketing authorization status of these drug in different other countries and if there is any significant variations with respect to the safety of the drug. And, it has to be also indicated with the changes shall be made to the product information in order to optimize the use of the product.

So, what is the content of this periodic safety update report?

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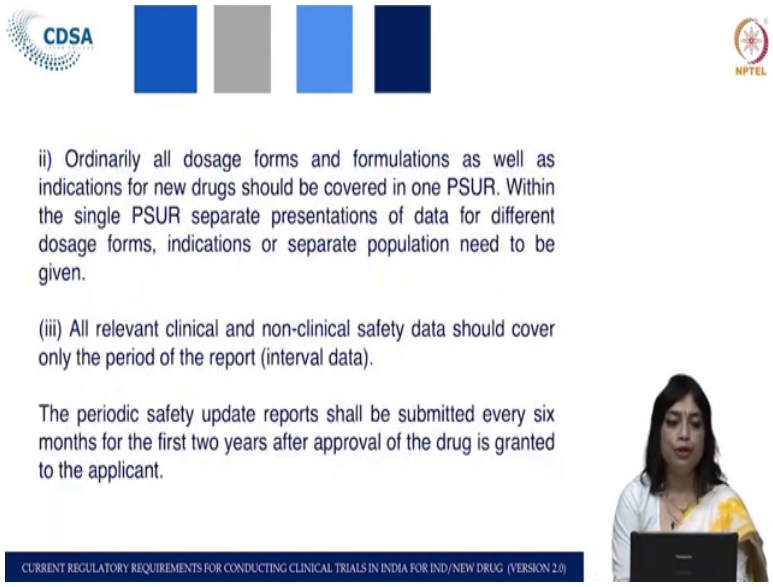

It should also include ordinarily all dosage forms, all formulations of a particular drug as well as all indications, all dosage forms, all formulations, all strings everything which is switches for a particular drug can be included as a part of one PSUR and, but only that the data for one particular dosage forms. So, when we say dosage form, it means either a tablet or a capsule or an injectables. So, these are the different dosage forms this has to be made in a.

The data for each presentations has to be given separately, but within the same PSUR and as also the if it is indications all and also the separate populations need to be given. So, everything can be covered under one PSUR; within the single PSUR separate presentations of data for different dosage forms indications or separate populations whether it is child reign, whether it is geriatric patients this has to be given. All the relevant clinical and non-clinical

safety data for the period of this submission of the periodic safety update reports has to be given.

So, what is the what is the interval for the submission of the periodic safety update reports once the drug is permitted for marketing in the country? So, it is six months for first every six months for first two years and then it is annual for the next. So, the total period of submission of any periodic safety update report for any drug, which is manufactured or imported new drug manufacturer imported in India is four years. So, a drug continues to be as a new drug in the country for four years.

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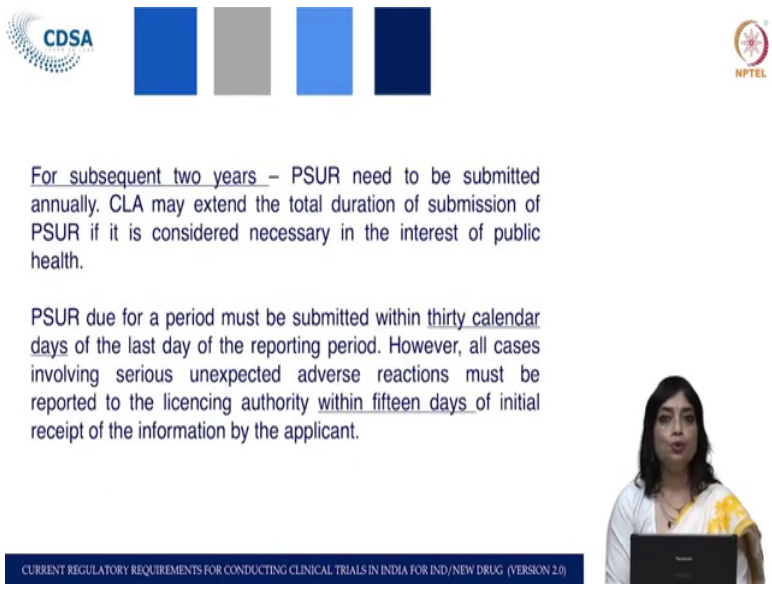

For subsequent two years as it is said it is to be a it is to be annually and also the PSUR due for a period must be submitted within thirty calendar days of the last day of the reporting period. However, all cases involving serious and expected adverse events if it happens during

this period of reporting it has to be reported within fifteen days from the receipt of this information in all cases.

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And, in case the marketing of the drug is delayed for some reasons, then in that case the date from where the marketing of the drug is study started the PUSR has to be submitted from that time onwards. So, if the marketing permission has been given and the marketing of the drug is delayed by six months so, it is after six months that your period of submission will also start from their and your four years also will be counted from that time onwards.

New studies specifically planned or conducted to examine further safety issues also has to be covered in the PSUR, but all cases it is said that it has to be within this specific period of reporting. So, if you have the six months period what is the time period of your reporting? So, your any information related to this particular interval has to be submitted.

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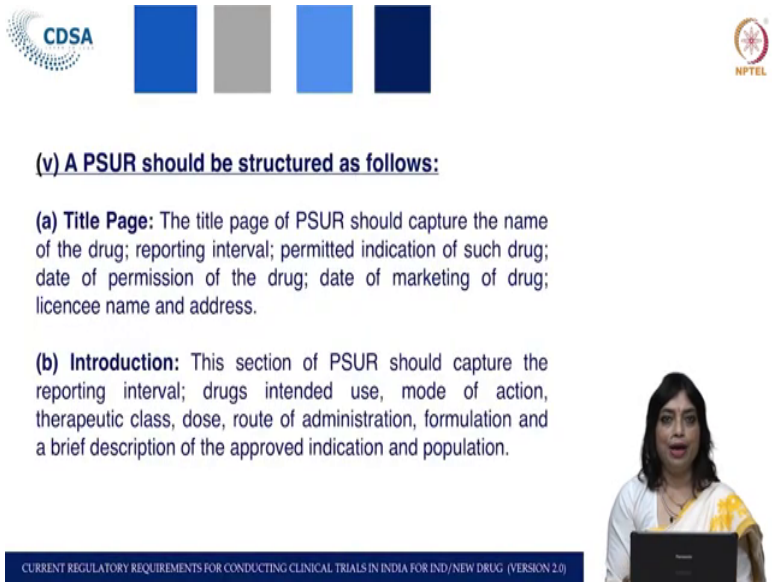

So, structure of the periodic safety update report it should be structured as follows. So, it has to be have a title page and introduction, so, the information under the title page all are very important. So, any incomplete information relates to in this submission, actually gives you know the there is a problem when you analyze such data when there is an even the date of marketing of the drug, date of approval of the drug everything has to be covered. Even if says the title page also has the same content and also the introduction, it should be filled completely and completely and due care should be taken when filling up PSUR, an incomplete PSUR is an incomplete submission to the regulatory authorities.

So, this title page of PSUR should capture the name of the drug, reporting interval, the permitted indication of such drug, date of permission of the drug, date of marketing of the drug, licensee name and address. Also in case of the intro introduction also the reporting

interval, drugs intended use, mode of action, therapeutic class, route of administration formulation and a brief description of the approved indication and population.

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The current worldwide marketing status is to be in informed in this narrative. There is a brief narrative where the all the details of the countries, where the drug is currently approved. And in case there has been the date of approval, the date of marketing and if in case there are any safety issues or if the drug is withdrawn in such countries for some reasons this is to be informed.

And, in case any action has been taken by anybody which is involved in this drug like, the sponsor or the market the country or the ethics committee or the data monitoring board whosoever or any other regulatory issues in any country has are has allows in this reporting interval also has to be covered in this PSUR.

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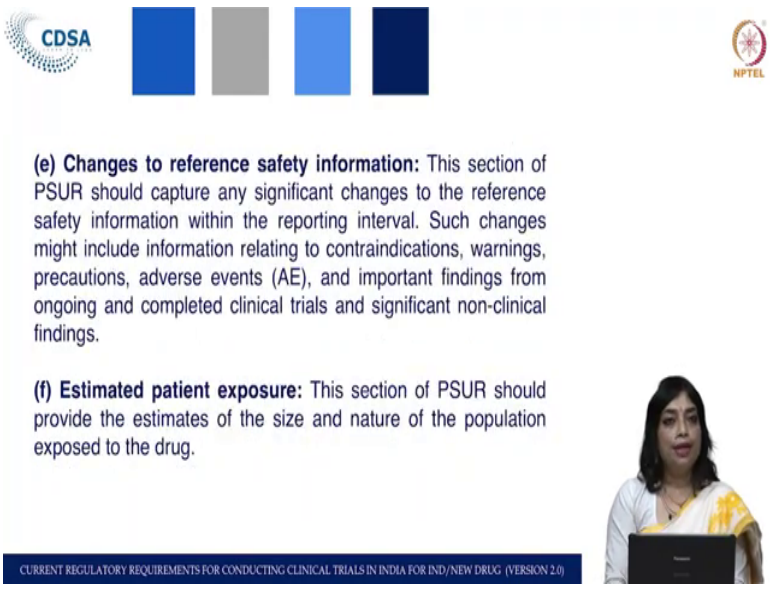

There is if there has been any changes in the reference safety information, due to various other interventions or due to some other studies which has come up in this by the results of the studies which has come up during this period or any countries who have raised any issues for some safety reasons, every information should be covered. So, that can relate to changes in the contraindications, warnings, precautions, adverse events and important findings from ongoing and completed clinical trials and also any significant non-clinical findings. So, if some non-clinical studies have also been planned in this interval, then any findings from that non clinical studies also should come up in this information.

The estimated patient exposure this section of the PSUR should provide the size and the nature of the population exposed to the drug.

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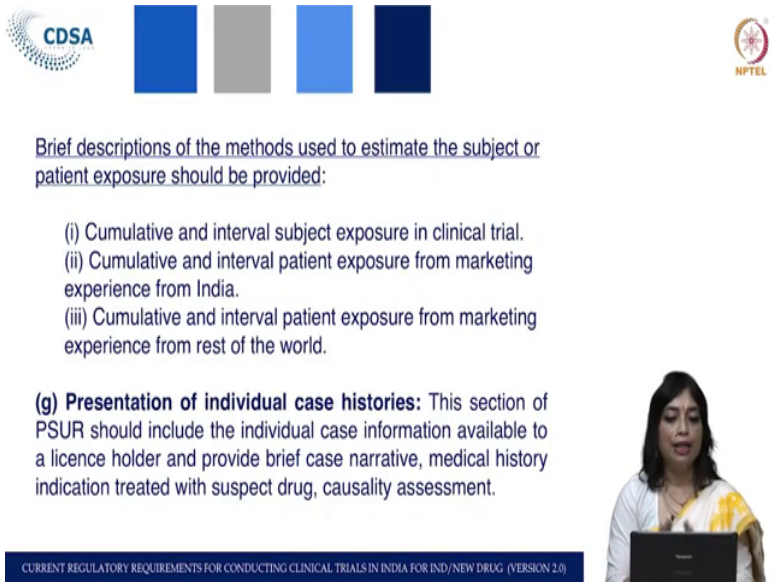

When you do this estimated patient exposure, the there should be a brief description how this patient exposure has been calculated and there has to be the cumulative. So, you I do not know how many patients were there in the clinical trial and during the and the interval subject exposure, if there has been a particular group of clinical trial patients during this interval.

So, you have cumulative and interval subject exposure in the clinical trial; cumulative and interval patient exposure from the marketing experience in India; and cumulative an interval patient exposure covering this particular interval of the reporting from the marketing experience from other part of the globe if it is marketed in other part of the globe. Also there has to be presentation of individual case histories, when there is a adverse events reported it has been it has been analyzed, it has the causality assessment has been done and that has to come as a brief case narrative along with the causality assessment.

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There has to be following information prescribing information; individual cases received from India; individual cases received from the world; cumulative and interval summary tabulations. So, had there has to be a tabulations of the serious adverse events from the clinical investigations as well as the serious adverse events or from the post marketing data sources. If there are studies conducted in this period, then it should it should come as a part of this section under the studies of the PSUR; which should capture the brief summary of the clinically important emerging efficacy or effectiveness and safety findings.

So, if you use the word effectiveness we mean and so, you know you may be knowing by this time what is the difference between the word efficacy and what is the difference and what is the meaning of the word effectiveness. So, when we say efficacy, it is in the clinical the efficacy of the drug is always assist in a control clinical trial settings. And when we say

effectiveness it means in the real life situation when the drug is used in a large number of patient population.

So, you have to have all the information's if it is if it is also done during this interval period. There may be some sponsored clinical trials done and who is whose report has come up during this interval period or there may be published safety studies results which have also become available during this reporting period. So, all this will have an impact on the safety information of the new drug.

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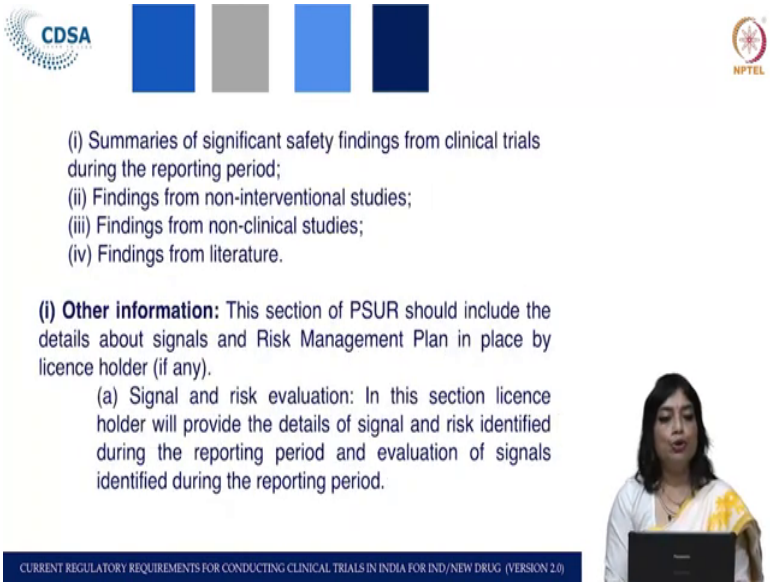

So, you summarize significant safety findings from clinical trials during the reporting period, findings from non interventional studies if it is there, findings from the non-clinical studies and also findings from the literature. There may be other information, the section of the PSUR should include the details about the signals and risk management plan. So, you make a least

risk management plan assessing all the safety information for the new drug, And this basis of this risk management and the risk management plan comes out of your if there is any signal detection.

So, you have a signal and risk evaluation section in the which the license holder will provide the details of the signal if at all you have a specific adverse reactions reported and you capture it as that a this is related to the drug. So, you capture it as a signal. So, it in a very simple sentence or in a simple word, I can just explain there are different methods of doing assessing or detecting the signal. The simplest way that when there is an adverse events reported and there are number of patients populations where the same adverse events have been reported. Then there is a specific way to analyze these adverse events and capture it as a signal that this is the adverse events which is related to the use of this drug.

So, that is called signal detection and accordingly you do your risk evaluation.

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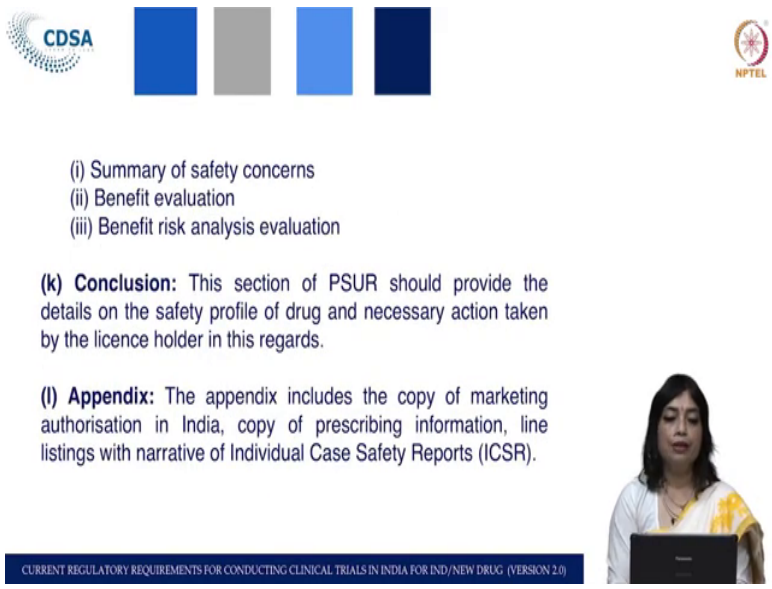

So, you will have the summary of the safety concerns, benefit evaluation and the benefit risk analysis evaluation. Finally, the conclusion the section of this section of the PSUR should provide the details on the safety profile of the drug and necessary action taken by the license holder. So, what are the actions which have been taken whether you have suggested for some changes in the labels, changes in the safety information, changes in the different indications like, indications whether there has been some specific recommendations of use for the prescriber. So, all this kind of things will come up in the conclusion.

And, finally, the appendix will include some of the regulatory documents like copy of marketing authorization in India, copy of prescribing information, line listings with the narrative of the individual case safety reports.

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Clinical trial compensation and as I told before the clinical trial compensation is related to the drug new drug or investigational new drug, when it is under clinical trials; that means, it is under a controlled clinical trial settings, a clinical trial is being conducted; the various requirements which are to be fulfilled by the applicant. The rules I would like to just say while going through this clinical trial compensation, already this has been said many times in this lecture, what is clinical trial.

When we say clinical trial which is in relation to a new drug or an investigational new drug means any systematic study of this new drug or investigational, new drug in human subjects to generate data for discovering or verifying the clinical or pharmacological including pharmacokinetics and pharmacodynamics. That means, the response of the human body to the drug and the response of the drug to the human body. You can say in simple words as well as

adverse effects with the objective of determining the safety efficacy or tolerance of such new drug or investigational new drug in the patients.

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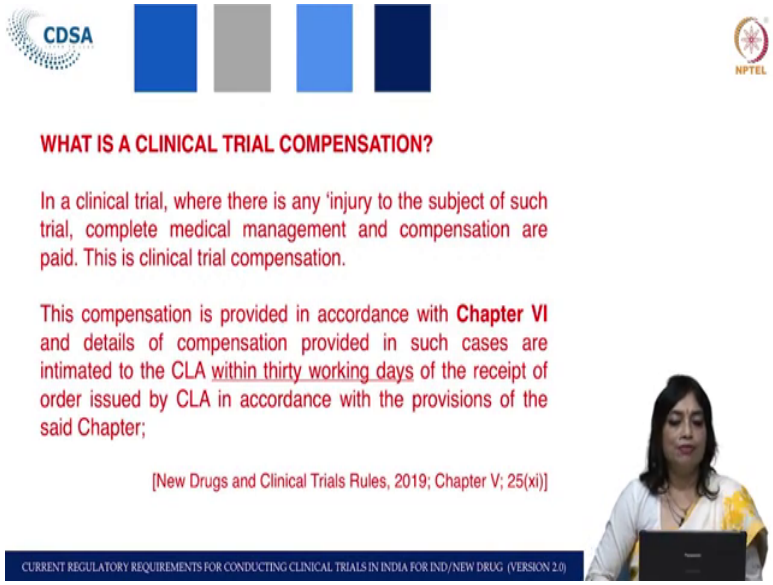

Just coming to this clinical trial compensation, the conditions of permissions for conduct of clinical child which is covered under chapter V rule under rule 25 it is said under this there are 2 para on this or we can call them as a clause, clause 11 and clause 12.

So, it is said in this condition of permission for conduct of clinical trial that in case of injury during the clinical trial to the subject of such trial complete medical management and compensation shall be provided in accordance with the chapter VI. And details of the compensation provided in such cases shall be intimated to the central licensing authority within thirty working days of the receipt of the order issued by the central licensing authority.

And, in the same way it is said that in case of clinical trial related death or permanent disability of any subject of clinical trial during the trial compensation shall be provided in accordance with the chapter VI to the legal years. And that details of the compensation also has to be intimated to the central licensing authority within thirty working days of receipt of the order issued by the central licensing authority. So, these are the conditions of permissions of clinical trial which is given in chapter V rule 25.

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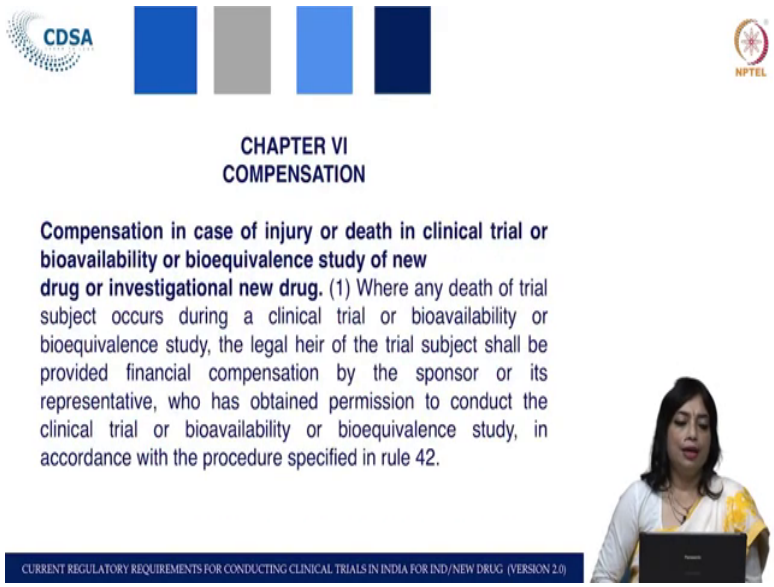

In this compensation requirement, which is given as a condition of permission what is written that it is to be done as per the chapter VI. So, coming to this chapter VI there are rules 39, rule 40, 41, 42 and 43; these are the rules which describe the different requirements of compensation the compensation in case of clinical trial related injury or a permanent disability or related or death. And, in case the injury may not be a permanent disability and also what would be the ways what is expected from the clinical trial applicant for such cases. And also

the undertaking which each applicant of a clinical trial has to be give has to give while submitting an applications for the clinical trial.

So, let us first go through rule 39, which says about the compensation in case of injury or death in clinical trial. When there is a death or of a trial subject occurs during this clinical trial, then it is said that compensation has to be given complete financial compensation has to be provided by the sponsor or the representative. So, what is the representatives? So, when case in case there is a foreign sponsor, there has to be a representative Indian representative or the sponsor can appoint some other organization as it is representative to make an application to the central drug control for a clinical trial.

So, whosoever has obtained this permission of the clinical trial, they are liable to pay this compensation to the legal year of the patients who has died during the clinical trial.

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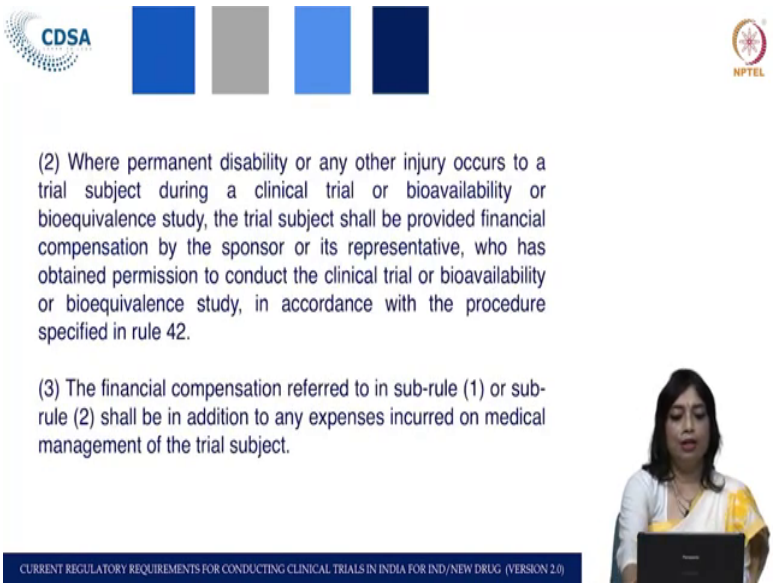

The procedure is specified in rule 42. Now when there is a permanent disability or any other injury which is occurring which is not death, but it is an serious adverse events, but it is not death in that case also the trial subject has to be provided financial compensation by the sponsor or its representative. And this financial compensation which has to be provided in case of a permanent disability or other injury; it has to be addition to the expenses which has incurred for the medical management.

So, it is the various medical treatment, which is being given to the subject when there is an reported clinical trial injury.

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In the event of an injury which is not being permanent in nature when there is not a permanent nature, but it is, but still it is connected or it has been found to be related to the clinical trial; in that case the nature of the quantum of the compensation shall commensurate with the loss of

wages of the subject as provided in the Seventh Schedule. So, then it is connected to the wage loss. In this connection, I would like to mention that this compensation rule is a very unique and very specific in case of the regulations of the clinical trial and very specific to India.

Nowhere in the world that any other rules, which govern the clinical trial includes this compensation rule or no other countries have this compensation rules provided as a task to the regulatory authorities. Here in this compensation rule which is which is the which is the part of this new drug clinical trial rules there are various rules and responsibilities of various the sponsor, the investigator, the ethics committee, the independent expert committee, which is to be constituted by government of India for examining the compensation as well as the central licensing authority.

Everybody has specific rules which is very clearly specified in this new drug and clinical trial rules. Whereas, throughout the world in the other regulatory provisions in the other regulatory in other regulations in the world such compensations are the or the authority of compensation, the onus of the compensation or calculation of the compensation is not given to the regulatory agency. The regulatory agency does not perform this function, other than the regulatory provisions which is given in this law in the new drugs and the clinical trial rules in case of the Indian regulations.

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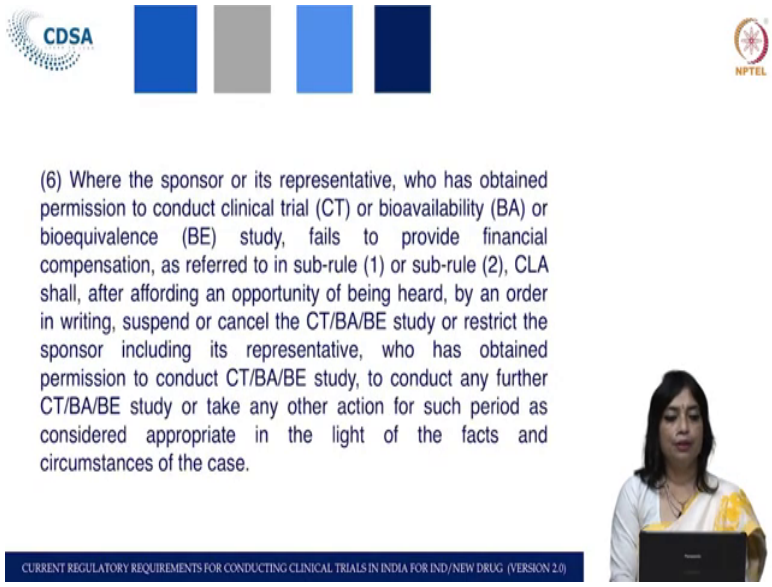

What is said further? That the sponsor or the representative has to give an undertaking with the applications for the clinical trials to provide compensation in case of a clinical trial related injury or death. And, in case the sponsor or its representative fails to provide the compensation, then after giving an opportunity of being heard the licensing authority can suspend or cancel the permission of the clinical trial given to this sponsor. As well as it can be also like this the sponsor can be debarred for a certain period or any other appropriate action can be taken by the licensing authority.

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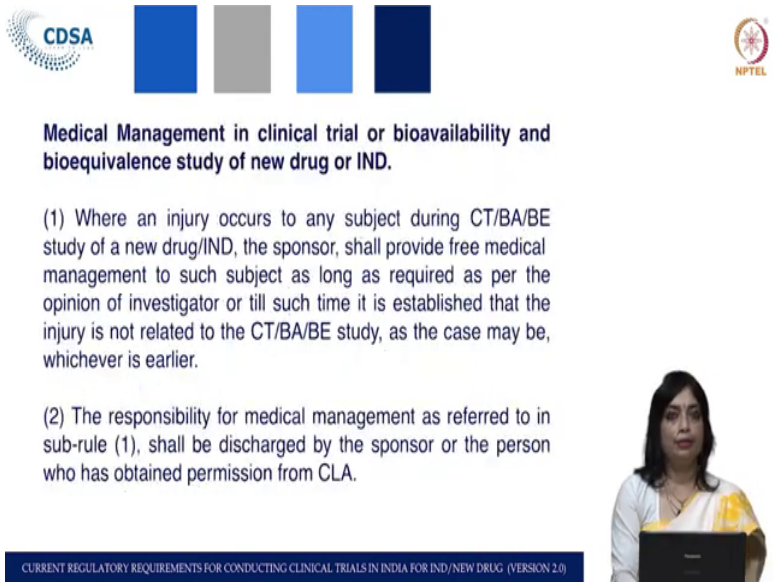

So, what is written under rule 40? In coming to this rule 40, it talks about the medical management. So, when there is an injury occurred to a clinical trial subject it is said that free medical management has to be given to the subject as long as or as per the opinion of the investigator or till such time it is not established that the injury is not related to the clinical trial. So, free medical management has to be given as per the decision of the investigator and till such time it has been not taken or it has not been decided by a causality assessment, that the trial that injury is not related to the trial or related to the drug.

The responsibility of the medical management is also discharge has to be discharged by the sponsor or his representative who has made this clinical trial application and, has obtained the clinical trial application. And in the same way in case they are they fail to provide the medical management, after being given an opportunity to hurt, the permission for the clinical trial can

be cancelled, suspended or it can be the sponsor can be debarred or vary as some specific action can be taken as deemed fit by the regulatory authority.

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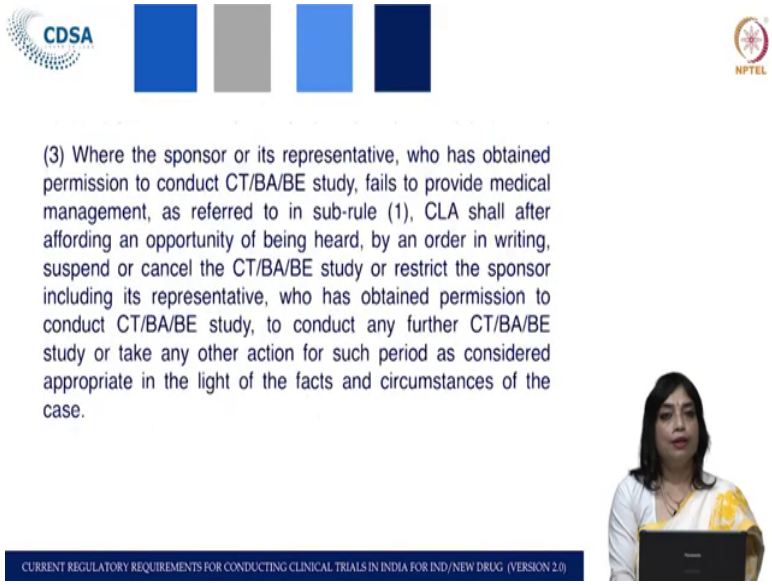

Coming to the rule 41, when we consider, so, how you say how you do this causality assessment or how you decide whether the clinical trial injury is related to the clinical trial whether the injury or the death or permanent disability whatever are related to trial are related to this particular clinical trial of the new drug or the investigational new drug. To decide on these it has been the conditions for the various reasons where it should be it should be considered that it is related to the new drug or the related to the clinical trial, it is said that in case the adverse effect when there is a adverse effect of the investigational product, it would be considered that it is related to the new drug.

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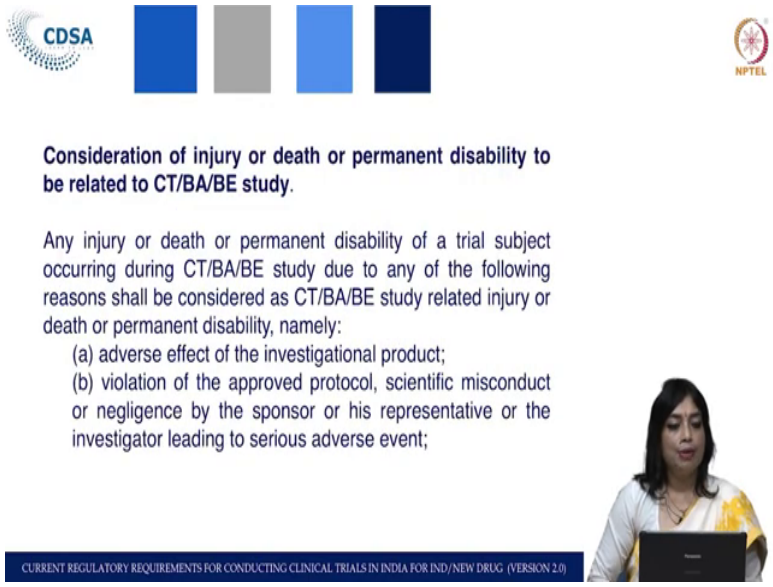

Similarly, when there is a violation of the approved protocol, scientific there is a scientific misconduct or negligence by the sponsor and it is proved then in that case which may which may have led to the serious adverse event. So, in that case also it would be considered that the injury or the death or the permanent disability is related to the study. It is occurring during the clinical study, due to any of the following results. So, any injury or death or permanent disability of a trial subject occurring during the clinical trial due to any of these following reasons shall be considered as a clinical trial study related injury or death or permanent disability.

So, what are these conditions, what are the reasons? Adverse effect of the investigational product, when there is an adverse effect due to the investigational product, when there is a violation of the approved protocol. And there is a scientific misconduct or negligence by the

sponsor or his representative or by the investigator which has led to the serious adverse events. So, that would be also considered related to the clinical trial.

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When there is a failure of the investigational product to provide the intended therapeutic effect and where there was a standard care or rescue medications already included in the protocol. But, that was not provided to the trial subject, it would be considered as a clinical trial related injury.

And also, in case the standard care has not been provided; though it was included in the clinical trial protocol in a placebo control trial, when it was required. And, also any adverse events or adverse effects due to the concomitant medications, which is included as a part of the clinical trial protocol. And, if such medications also has led to some adverse effects it would be considered as a clinical trial related injury.

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Also when there is an adverse effect on a child in-utero because of the participation of the parent in the clinical trial. So, that case also it is it has to be related to the it is related to the clinical trial. And, any clinical trial procedures which is a part of the protocol that has led to this such injury. What does the rule 42 says? Procedure for compensation, in case of such injury.

The procedure means what is the timeline of reporting, how the decision would be taken by the regulatory authorities on the basis so, the roles and the responsibilities of the various participants of the clinical trial – the sponsor, the investigator, the ethics committee, the regulatory agency.

So, the investigator shall report all serious adverse events to the central licensing authority; that is central drug standard control organization to drugs controller general India or and the

sponsor and the ethics committee. The investigator has to report all serious adverse events to the regulatory authority, to the sponsor or its representative who has obtained permission from the licensing authority, for conduct of clinical trial and also to the ethics committee who has accorded approval to the study protocol within twenty four hours of their occurrence.

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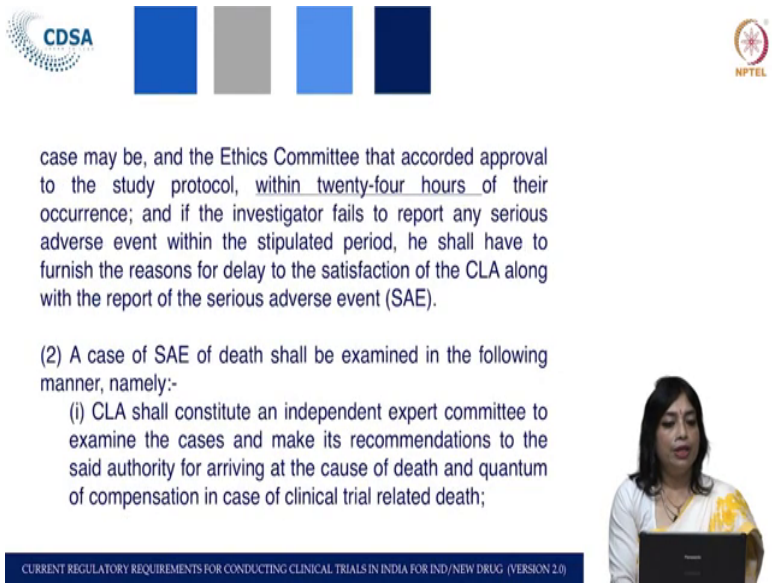

And, if the investigator fails to report this adverse events within this stipulated period of twenty four hours then he has to furnish the reasons for such delay to the satisfaction of the Central Licensing Authority and along with the report of the SAE. In case the SAE has been reported then such SAE has to be examined by an independent expert committee which has which would be constituted by the Central Licensing Authority to make examine the cases and to make its recommendation to the safe side authority for arriving at the cause of death and quantum of compensation which has to be given.

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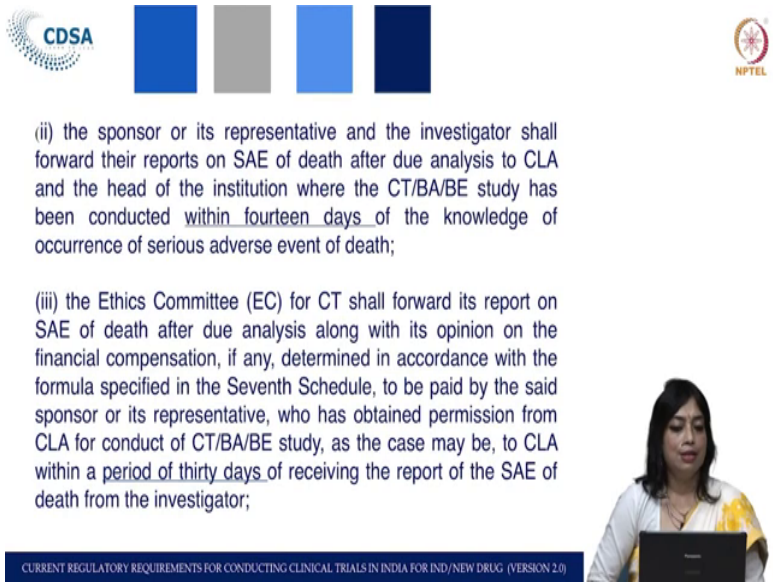

The sponsor or the representative of the investigator or the or its representative and the investigator shall forward the reports on the SAE, along with the due analysis of such SAE to the head of the and the head of the institution where the clinical trial has been conducted within fourteen days to. So, the sponsor and its or its representative and the investigator has to forward its report on SAE of death after due analysis of the after they due analysis causality analysis whatever is possible in the circumstances to the central licensing authority and, the head of the institution within the fourteen days of the knowledge of occurrence of serious adverse events.

And, similarly the ethics committee whom the investigator has reported supposed to report within twenty four hours, has to furnish its reports along with the analysis on its opinion on the financial compensation to the as and the financial compensations how it has to be calculated is

given in the Seventh Schedule. So, along with this opinion this has to be give this has to be furnished to this Central Licensing Authority within a period of thirty days.

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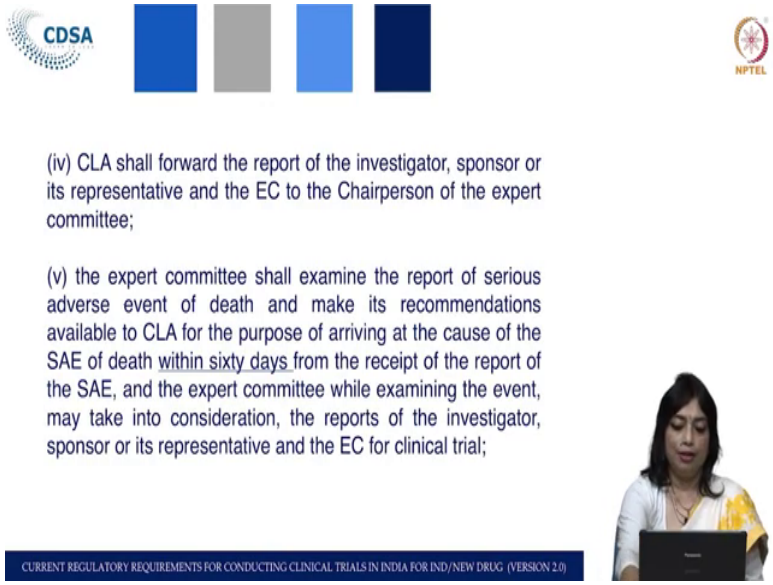

The central licensing authority shall forward the report of the investigator sponsor or its representative and ethics committee to the chairperson of the expert committee for the analysis. And, the expert committee shall examine and give their views within sixty days. And, the expert committee while examining this event may take into consideration the reports of the investigator sponsor, as well as the report of the ethics committee who is responsible for giving permission to this study.

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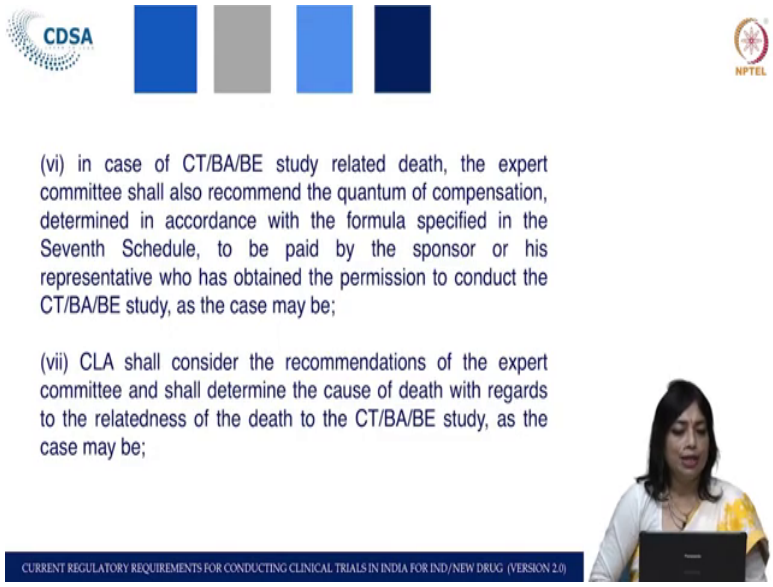

In case of clinical trial related death, the expert committee shall recommend the quantum of the compensation determined in accordance with the formula which is specified in the Seventh Schedule. and based on the recommendation of the expert committee the CLA shall consider these recommendations and shall determine the cause of death with regard to the relatedness of the death to the clinical trial as the case may be.

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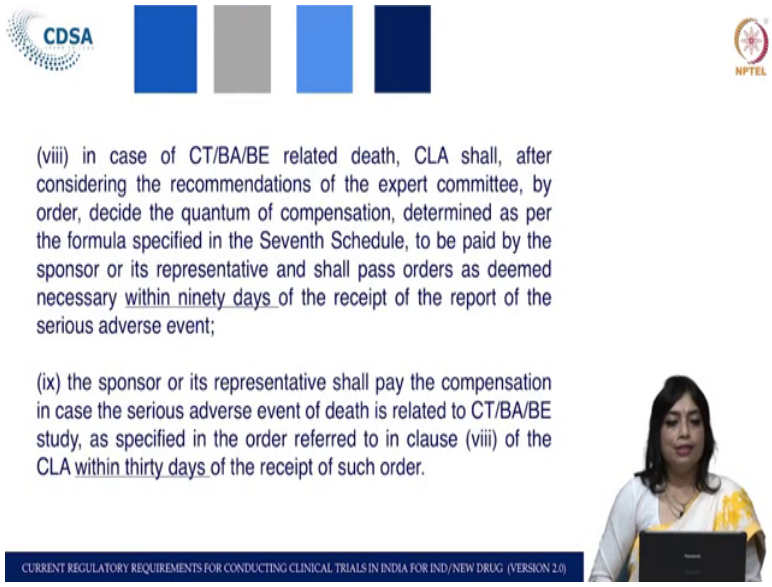

In case of clinical trial related death, the CLA after considering all these recommendations, it is required to pass an order within ninety days; if this order has to be sent to the sponsor or its representative. And, the sponsor or the representative after getting such order from the CLA shall pay the compensation within a period of thirty days. So, the timelines for the various actions are specified in this compensation rules.

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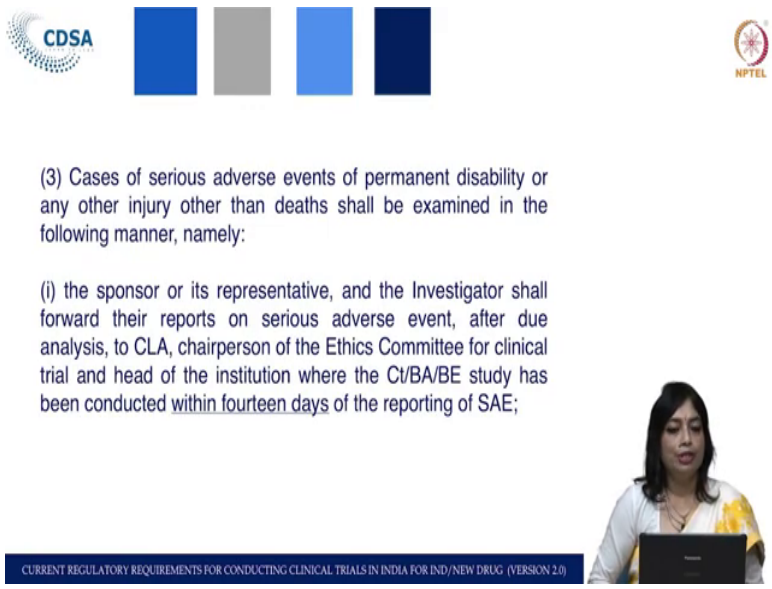

In case of serious adverse events of permanent disability or any other injury other than the death, in that case the same the timeline would be the same for reporting the reporting the serious adverse events. And, in that case, the sponsor or its representative and the investigator shall forward their reports with the of the serious adverse events after due analysis to the central licensing authority to the chairperson of the ethics committee for clinical trial and the head of the institution within the fourteen days of reporting of the SAE.

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The ethics committee in the similarly after due analysis shall forward their report within thirty days to the Central Licensing Authority about their opinion and about their opinion on the financial compensation. The ethics committee will give specific recommendation after the due analysis of such report, within the on with its opinion on the financial compensation. And the CLA after this determining after considering all the report they shall determine the cause of the injury and person order as per the or in that case.

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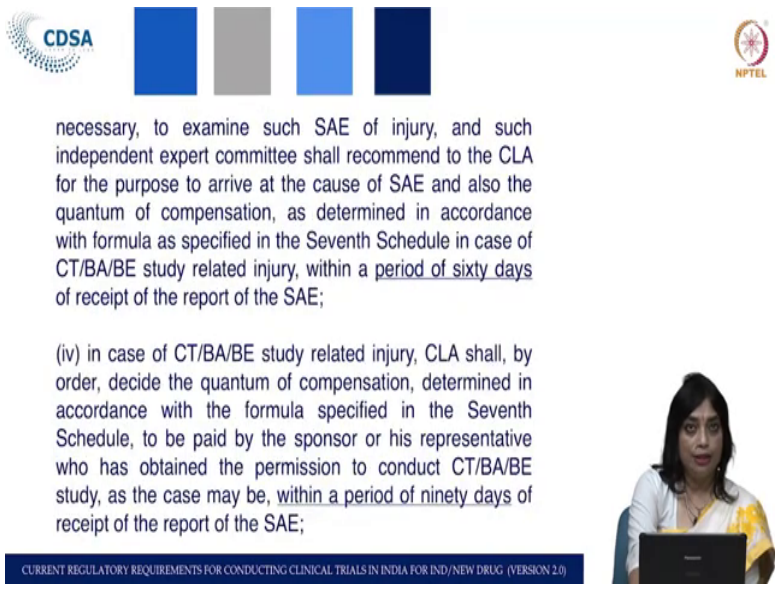

The process which is to be done is that such order the CLA themselves may pass or may constitute an independent expert committee to decide on this particular to examine the SAE or the related injury report. And such expert committee may recommend to the CLA for the purpose to arrive at the cause of the SAE and also the quantum of the compensation. This was to be done this independent expert committee will examine this SAE report within a period of sixty days of the report receipt of the report.

In case of the clinical trial related injury the finally, the decision on the quantum of compensation and the other decision would be made based on the various recommendations of the various the various entities it has to be made within a period of ninety days of the receipt of the report of the SAE. Once the report of the a report for a payment of compensation is received by the sponsor, the sponsor has to pay the compensation within thirty days.

So, these are the various timelines of twenty four hours, fourteen days, thirty days, sixty days, ninety days and the payment of the compensation of thirty days, which are specified in the new drug and the clinical trial rules.

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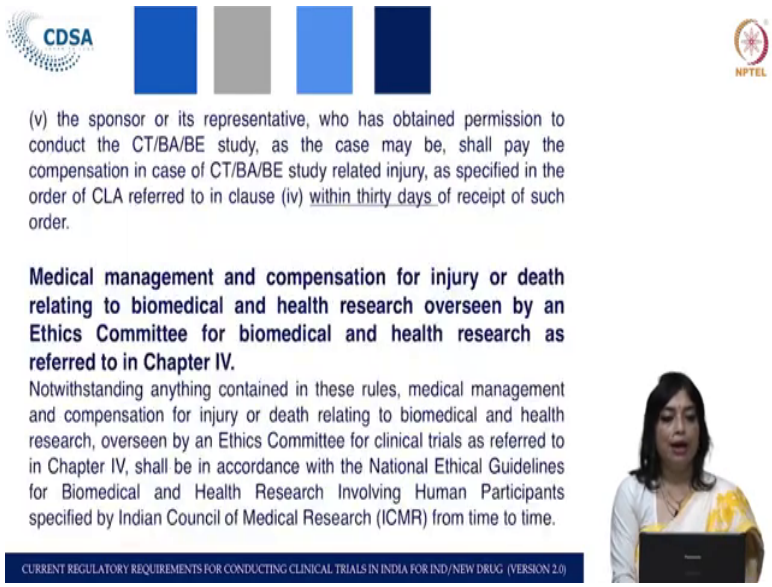

To ensure that the patients is looked into the clinical trial subjects are taken care of and whenever there is a harm due to the when there is a harm caused or there is a safety concerns or when there is a harm caused due to a clinical trial to a subject adequate compensation has been paid to the trial subject. To ensure that adequate compensation, proper compensation and proper care has been taken to the clinical trial subject. This compensation rules has been made with specific timelines and also with the various formula for calculating the compensation.

When we go to the Seventh Schedule, we will see the how the compensation formula is calculated in case of SAE the death, due to the SAE when there is a permanent disability, due to the SAE serious adverse events and in case there is other than permanent disability, but there is still non-SAE non-death case and the death case. So, there are death SAE causing death and there is an SAE which may not cause death, but there is a permanent disability. So, such cases how the compensation formula has been made, which is very exclusive and unique for the unique in this global regulations and it is only very much it and it is applicable only in case of India.

It is a Indian rule and the Indian law which has made a very specific compensation formula. Coming to the rule 43, which talks about the medical management and the compensation for injury or death relating to the biomedical research and health research. So, when there is a research, when there is a clinical trial, which we do not which do not which is not a regulatory clinical trial. But, it is conducted by various research institution for the purpose of the research or which is related to the various academics or the hospitals which are do some studies related to the already approved new drug for some specific new indications or for some specific use or for a new dosage form. Such kind of which is done for the purpose of the research, such clinical trial these are monitored and these are monitored by the ethics committee as per the National Ethical Guidelines for Biomedical and Health Research.

So, this National and the Ethics Committee are such Ethics Committee who look after this academic clinical trial or the clinical trial for the research purpose are also approved by the department of health research biomedical and health research. And the and in that case the compensations the whatever has to be provided are provided as per the National Ethical Guidelines for Biomedical and Health Research involving human participants which is specified by the Indian council of medical research.

So, all the rule 43, is the exclusive rule for the medical management and compensation in case of the clinical research. In that case the ethics committee which is approved by the department of health research, they look after this compensation. The compensation which is to be provided in case of such trial subject who are involved in the clinical research. That means, it

is not for the new drug it is already for the drug which is already approved and it is being used now for some other new indications or for research purpose in case of that the compensation is decided as per the national ethical guidelines for biomedical and health research and that is being monitored by the ethics committee constituted for such purpose.

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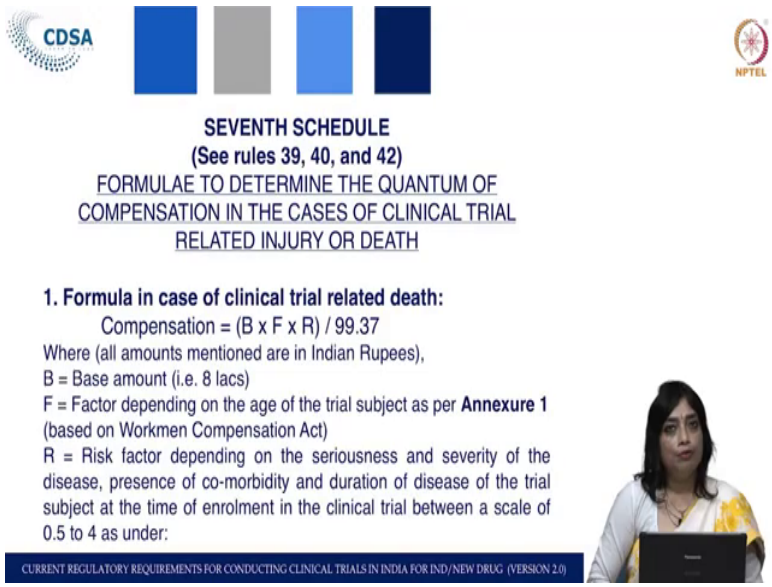

Coming to this clinical trial compensation formula, which is covered under the same rules 39, 40 and 42 mention about this clinical this compensation formula. And, this is under the Seventh Schedule of the new drug and the clinical trial rules; it gives the formula in case of the clinical trial related death. The compensation formula if you see, it says about a base amount that is which is which is being decided this 8 lakhs base amount, if you see the compensation formula, it says about a base amount which is 8 lakhs and it is decided on the basis of the wages of unskilled labor in the city of Delhi.

So, it is based on the based on wages calculation. There is a factor which is depending on the age of the trial subject and there is annexure subsequent to this, which based on this work Workmen Compensation Act. And, then there is a R is the risk factor depending on the seriousness and severity of the disease, presence of co-morbidity and duration of the disease of the trial subject at the time of enrollment in the clinical trial. And this is between this has been decided between a scale of 0.5 to 4 as under.

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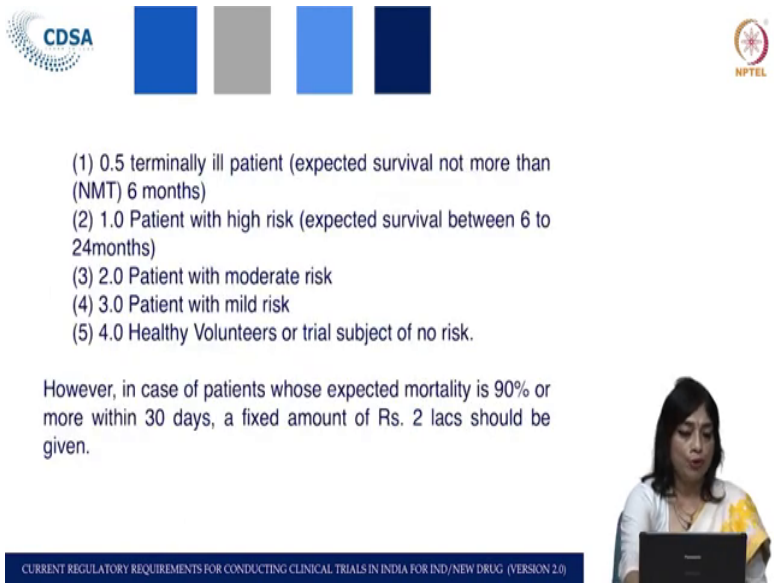

So, when we say 0.5 it means terminally ill patient expected survivable not more than 6 months. If when a scale of 1 means patient with high risk expected survival between 6 to 24 months; R 2 is a patient with moderate risk; a 3 is a patient with mild risk and 4 means healthy volunteers or trial subject of no risk. However, in case of patients was expected mortality is 90 percent or more within 30 days in that case a fixed amount of 2 lakhs to be given.

So, these are which is included in the compensation formula and the compensation amount which is being included in the Seventh Schedule.

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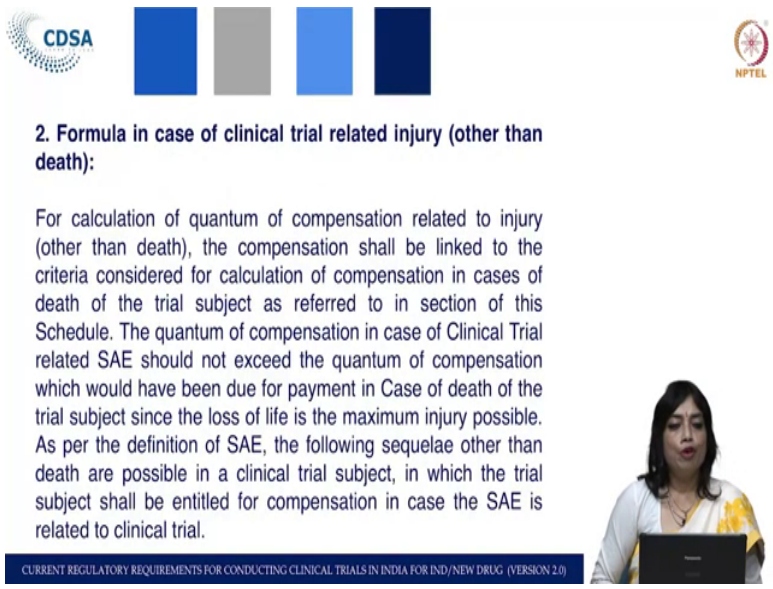

The formula in case of clinical trial related injury other than depth for calculation of the quantum of this compensation related to injury, other than death the compensation is linked to the criteria which is considered in the calculation of the compensation in case of death because why it is done? This is important to ensure that the quantum of the compensation in case of the clinical trial related SAE should not exceed the quantum of the compensation, which should have which would have been due for payment in case of death of the trial subject since the loss of life is the maximum injury possible.

So, always the compensation due to clinical trial related injury will be always less than the compensation due to due to death of a trial subjects which is paid to the legal heirs. As per the

definition of this SAE the following sequelae other than the depth are possible in a clinical trial subject in which the trial subjects shall be entitled for compensation.

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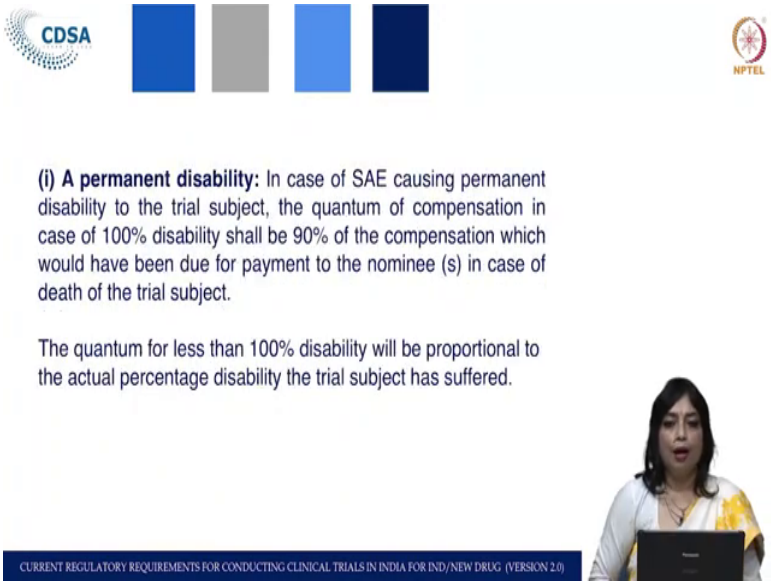

And, what is that? A permanent visibility – in case of the serious adverse events causing permanent disability to that trial subject the quantum of the compensation in case of 100 percent disability shall be 90 percent of the compensation, which would have been due for payment to the nominee in case of death of the trial subject.

So, as it is said that, it is been decided that always such compensation which is being paid, it should be less than the one if there was a death due to the trial subject. The quantum for less than 100 percent disability will be proportional to the actual percentage disability the trial subject has suffered.

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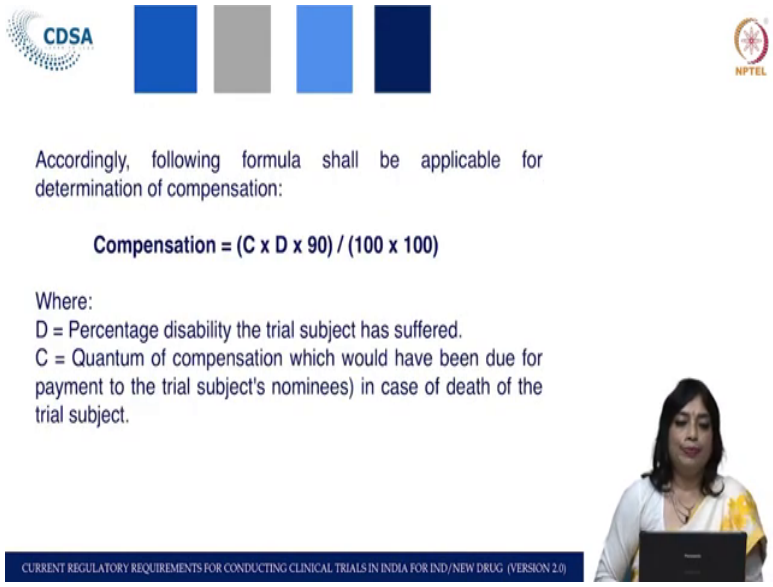

The and also there is a formula for this for the determination of the compensation where the percentage disability which has to be decided by the expert experts. This percentage disability of the trial subject is considered as D and C.

So, this is the compensation formula, if you can look into it and in that the quantum of compensation, which have been due for payment to the trial subjects nominee in case of death of the trial subject is the C. So, this is the compensation formula in case of permanent disability.

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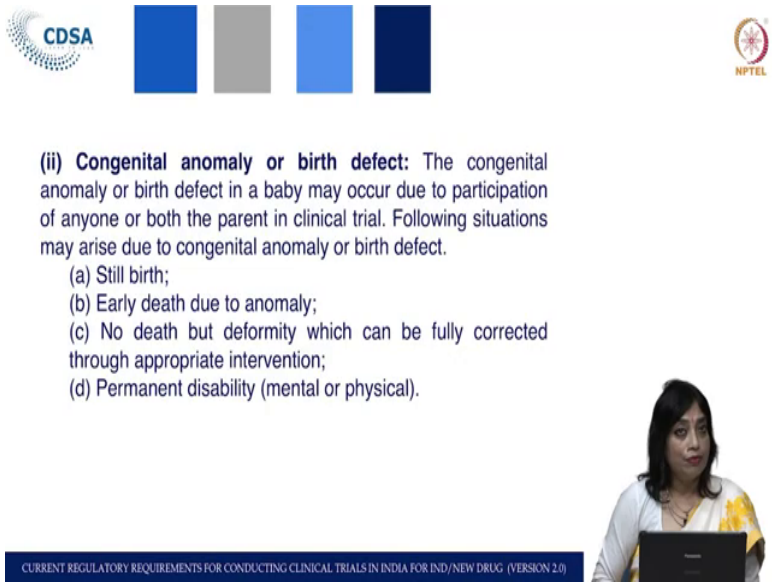

In case of congenital anomaly or birth defect, it has been decided that if such defect has occurred in that case. Following situations may arise due to the congenital anomaly or a birth defect like still birth, early death due to anomaly or no death, but deformity which can be fully corrected through appropriate intervention or there may be a permanent disability mental or physical.

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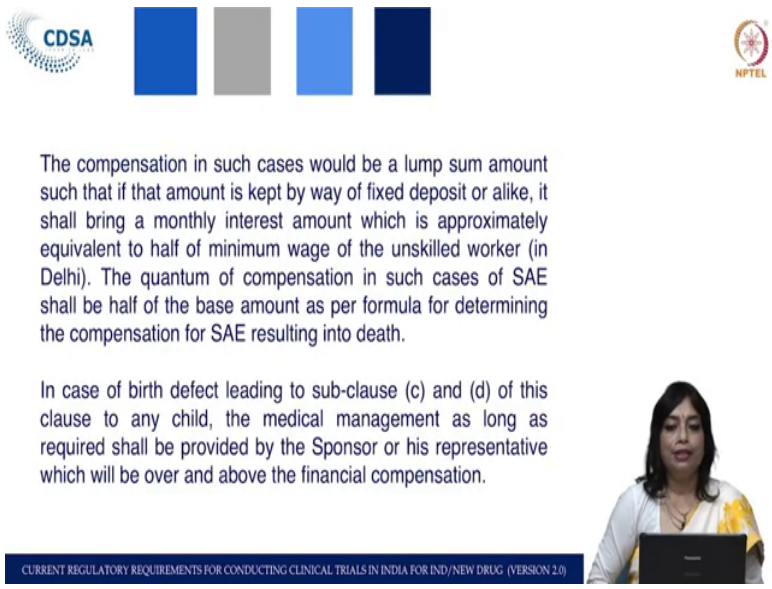

So, considering this four anomalities due to or a birth defect the compensation in such cases would be a lump sum amount, such that if that amount is kept by fixed deposit or alike it shall bring a monthly interest amount which is approximately equivalent to half of the minimum wage of the unskilled worker. So, that is the way the calculation has been made. And, in case in all cases however, the medical management as long as required shall be provided by the sponsor. So, that is the formula says.

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Also there may be chronic life threatening disease and reversible SAE in case it is resolved. In case of clinical trial related SAE causing life-threatening disease and reversible SAE in case it is resolved, the quantum of compensation will be again linked to the number of days of the hospitalization of the trial subject. And, accordingly based on the loss of which the calculation has been decided.

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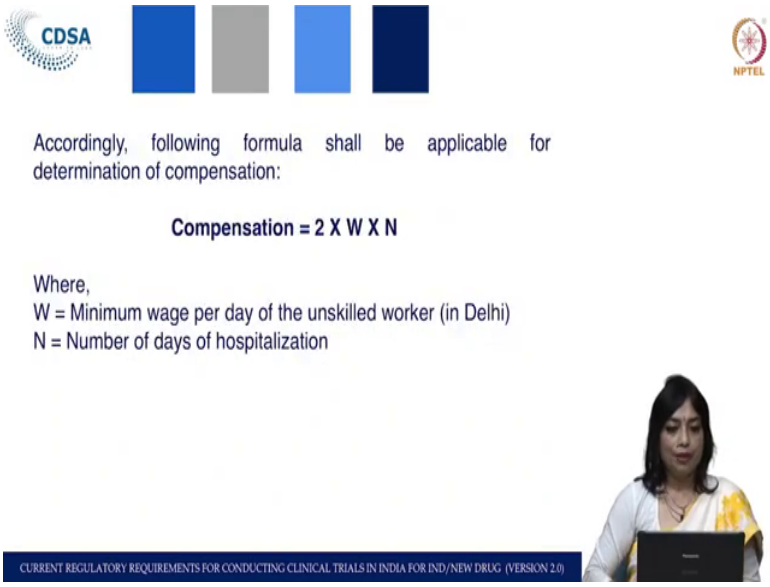

So, this is the formula which has been followed for this. This is the formula which is given in the compensation rule, where W will be the minimum wage per day of the unskilled worker and the number of days of hospitalization.

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Also coming to this, it can it is also said that the wage loss per day shall be calculated based upon the minimum wage of the unskilled worker. In case of hospitalization of any patient not only the patient loses his own wage, also there will be a direct or indirect losses of various kind including inconvenience wage loss of attendant etcetera. In that case the compensation per day of hospitalization, shall be double the minimum wage.

So, these are the calculations which have been provided. There was an executive order earlier previous to this new drug and clinical trial rules for making this compensation calculation for all the clinical trial related reported SAEs. And now this has been put into this Seventh Schedule of the new drug and clinical trial rule.

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This is the annexure with the risk factor, depending on the age how the risk factor has been put and also.

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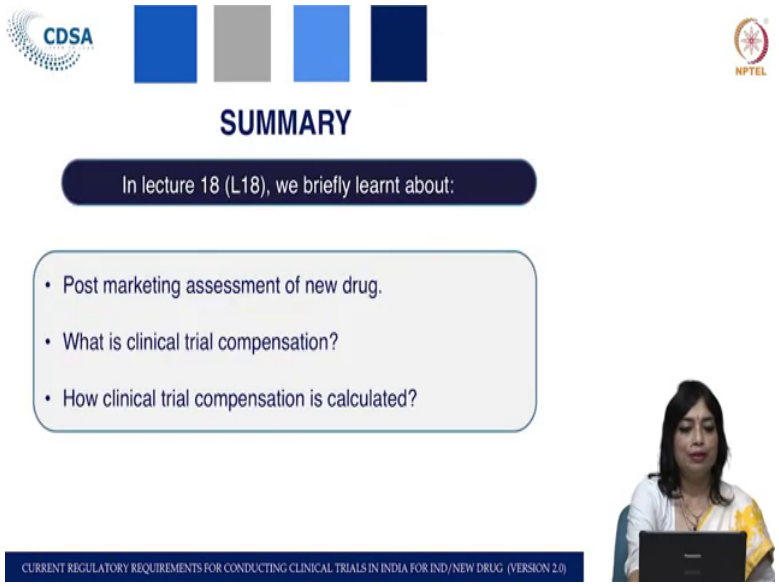

So, finally, coming to the summary what did we what we have learnt in this lecture 18? We briefly learnt about post marketing assessment of new drug; what is the clinical trial compensation, what we mean by clinical trial compensation; what are the different types of compensation; which are being given, in case of a death permanent disability or clinical trial related injury, when there is something which is when a disability has taken place due to the clinical trial, when there is a congenital birth defect, when there is a chronic life threatening disease and what are the different birth defects.

So, everything has been elaborately included in this formula, to understand and to make this compensation rule fruitful, how the clinical trial compensation is calculated is made based on this decision.

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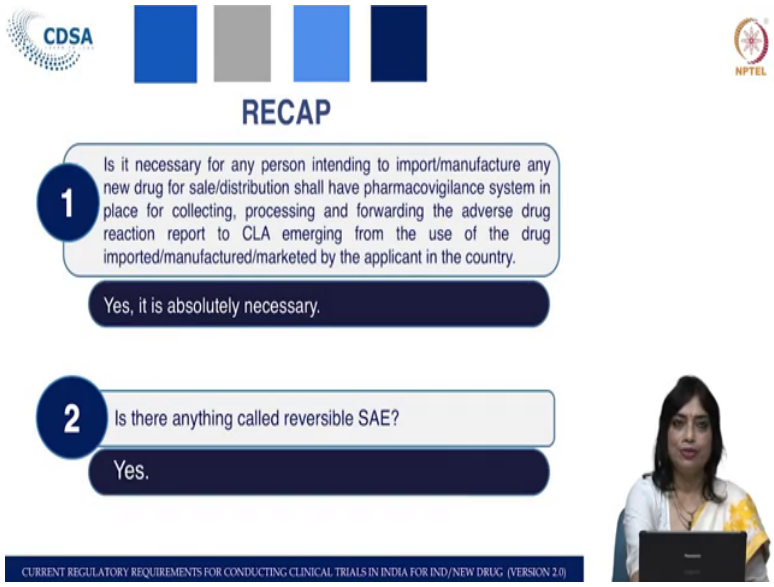

So, let us recap what we have learnt now. So, going to this let us go to the question number 1. Is it necessary for any person intending to import manufacture in any new drug for sale distribution to have a pharmacovigilance system in place for collecting, processing and forwarding the adverse drug reaction report to CLA emerging from the use of the drug imported manufactured marketed by the applicant in the country? I think you have by this time know the answer. So, the answer is ready. Let us see what is the answer. Yes, it is absolutely necessary. Is it not?

Is there anything called reversible SAE? I hope the answer is with you. Yes.

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Let us go to the next question. Is the clinical trial compensation related to death same as related to clinical trial related injury? You know the answer. What is the answer? No. Did you write yes? No, it is not the same. Clinical trial related compensation due to death is not same as related to clinical trial related injury.

Coming to the fourth question. State true or false. Post marketing surveillance is also carried out through periodic safety update reports. Very easy, you may give the answer. True.

I hope you have enjoyed the lecture. If you have any comments, any feedback, any suggestion you are free to write to us. Please give your feedback suggestion writing to us, so that we can improve upon it.

Thank you and all the best wishes for you.