Regulatory Requirements for Medical Devices including In Vitro Diagnostics in India (Version 2.0)

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Lecture – L6
Clinical Investigation of Medical Devices, Regulation of Investigational Medical Devices

Welcome to Regulatory Requirement for Medical Devices Including in Vitro Diagnostics in India version 2 Lecture 6 that is the Clinical Investigation of the medical devices and Regulation of Investigational Medical Devices learning objective.

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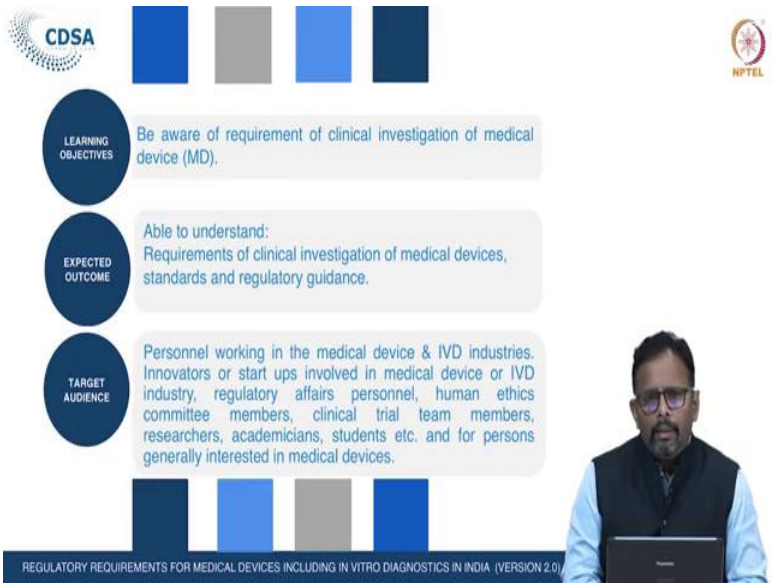

We will aware what is the clinical investigation of the medical devices, what is the difference between clinical investigation of the medical devices and the clinical trial of the drugs. expected outcome we will able to understand the requirement of the clinical investigation of the medical devices the standards and the regulating guidance for conducting the clinical investigation of the medical devices.

Target audience the personal working in the medical devices and in-vitro diagnostic industry, innovators of the medical device industry. And in-vitro diagnostic industry regulatory affair personnel's, human ethics committee members, clinical trial team

members, researchers, academicians, students and the person generally interested in the medical device and in-vitro diagnostics.

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What will we learn in this lecture? We will discuss what is the clinical investigation, what are the regulatory requirement for clinical investigation of the medical devices. The standards for clinical investigations, applicable standards and guidance. The types of the clinical investigation in study of the medical devices and the comparison of the medical devices clinical investigation with the clinical trial of the drugs include all these chapters.

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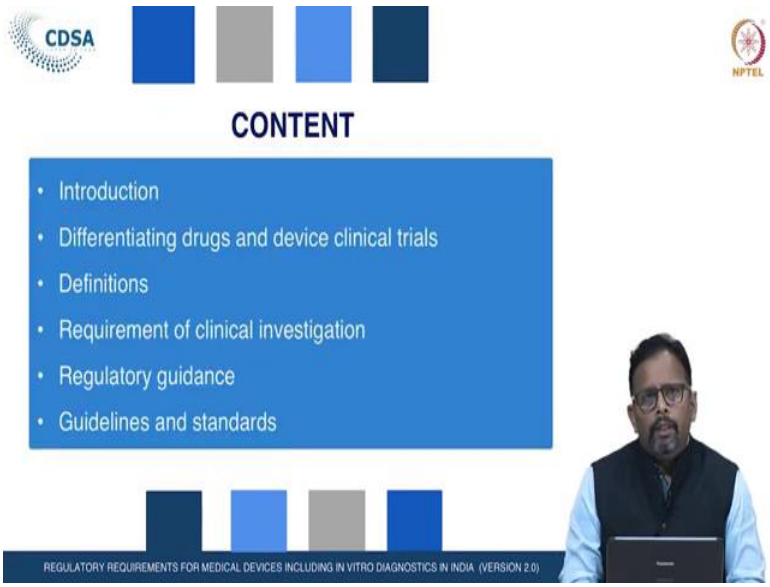

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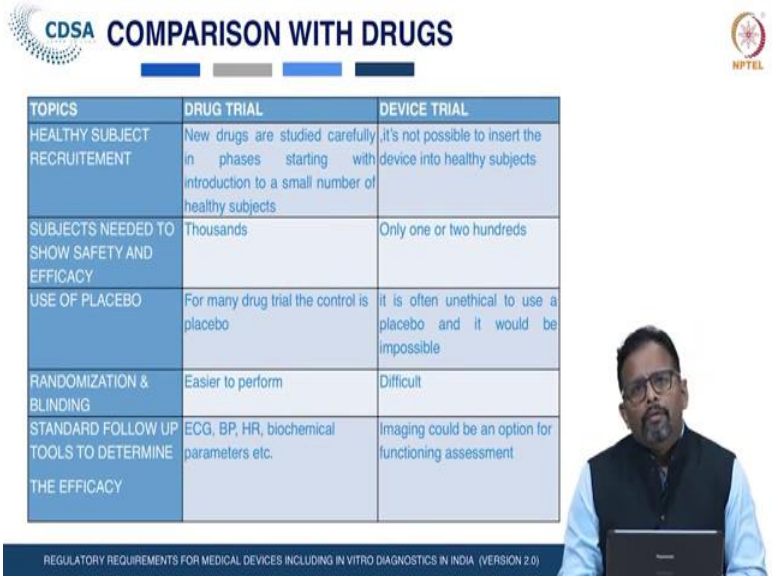

Now, first come to the comparison with the Drugs. In the previous lectures, we have discussed what is the difference between the drugs and the devices, also we have discussed the requirement of the clinical trial of the drugs as well as the requirement of the clinical investigation of the drugs.

So, in case of the medical devices the clinical trial is not applicable, the clinical trial is applicable actually for the drugs where in the different phases of the trials is required to be carried out to estabished the safety and efficacy of the drugs. However, in the medical devices the pilot study and the pivotal study that is required to be carried out to establish the safety and performance of the medical devices. So, what are the difference? If you see the difference and compare the medical device with the drugs ir respect of the trials. You will see the drug trails, the healthy subjects recruitment is there for conducting the trial on the drugs. Initially in the phase 1 trial, the drugs are to be used on the healthy patients, however the medical devices it is not possible to insert the medical devices on the healthy subjects.

If you see the subjects needed for establishing the safety and efficacy of the drugs, it has to be carried out in the larger population to prove the safety efficacy of the drugs. However, in the devices this can be established the safety and performance can be established by conducting the study on around hundred patients. In the drug cases in that study clinical trial study generally placebo are to be used, however for the medical

devices, it is unethical and it is not possible to use the placebo. If you see the design the drug trial randomization and blending you can do, however in the device trial it is very difficult.

The standards follow up tools to determine the efficacy of the drugs. Various instruments like ECG machine, BP apparatus and other equipments to determine the biochemical parameters of the patient. However, for the medical devices imaging could be an option for the functional assessment. Therefore, the clinical trial that is phase 1, phase 2 and phase 3 trial is not applicable for the study of the medical devices.

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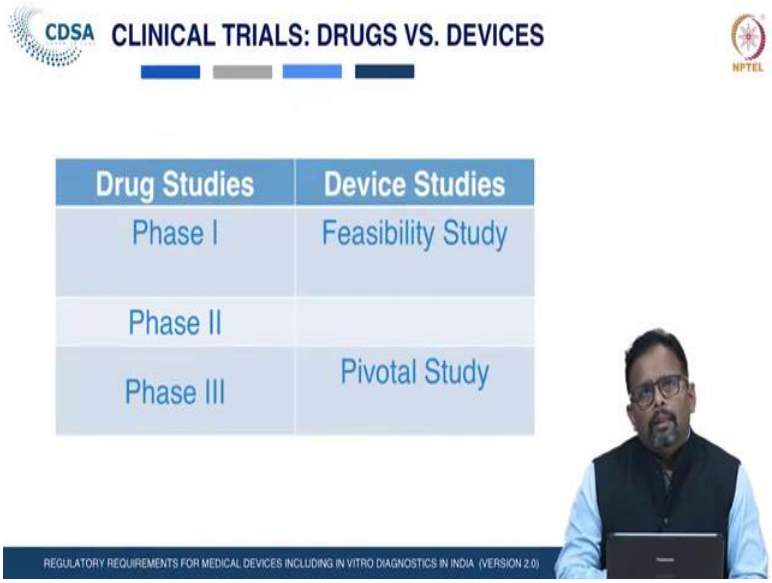

In the drugs trials the phase 1 trials phase 2 and phase 3 trial is to be carried out.

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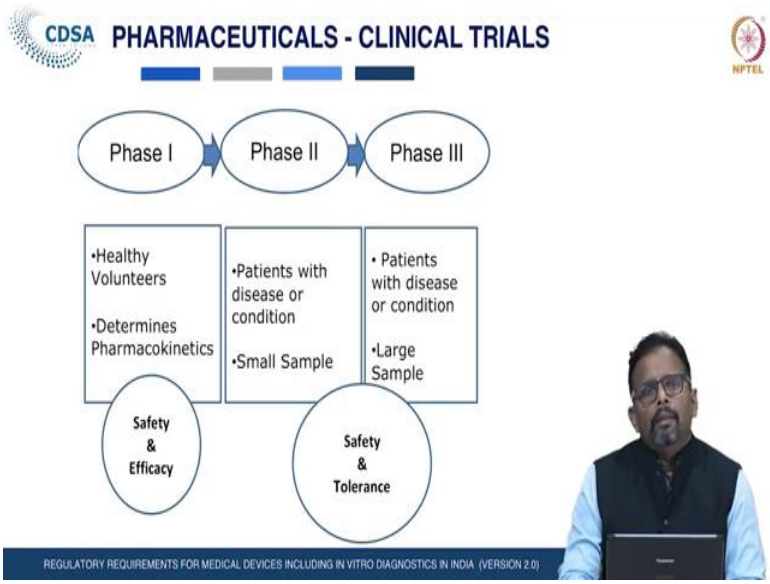

First initially to establish the safety and efficacy then only phase 1 trial is to be carried out in the small number of patients. Then phase 2 to establish the safety and tolerance and after establishing the safety and tolerance of the dose, in the phase 3 that is the confirmatory study for establishing the safety and efficacy of the drugs.

However for the medical devices the feasibility study that is the pilot study which is to be carried out on the small number of patient. And after establishing the safety in the small patient based on the pilot study data the pivotal study is required to be carried out to prove the safety and performance of the devices for it is intended use. As already discussed the pharmaceutical clinical trial Phase 1 Phase 2 and phase 3 trials are generally carried out.

Phase 1 is carried out on the healthy volunteers and it determines the pharmako kinetics and it safety and efficacy is to be established phase 2 and phase 3 phase 2 may be carried out on the patient small sample size and phase 3 also need to be carried out on the patient with the large sample size and to establish the safety tolerance and efficacy of the drugs and pharmaceuticals

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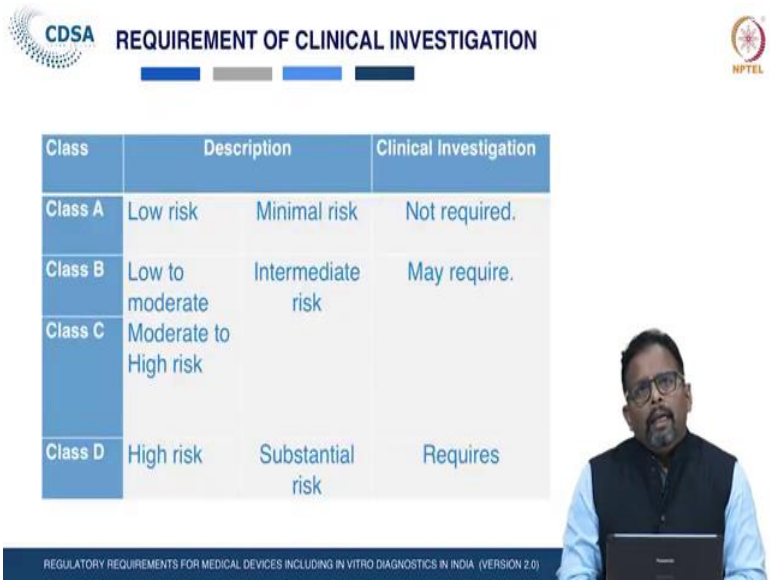

And for the medical devices as already we have discussed the clinical investigation is required, where there is no concept of the phase 1 phase 2 or phase 3 trials only the concept of the feasible study and the pivotal study. And the requirement of the clinical investigation of the medical devices, we have discussed that devices have been classified into different class based on the criticality and the intended use of the devices class A is the Low risk devices, class B Low to moderate risk devices class C Moderate to high risk devices and class D is the High risk devices. So, for the clinical investigation, if the risk of the devices is minimal then there is no requirement of the clinical investigation.

If there is a intermediate risk associated with the medical devices, then clinical investigation may required or may not be required and for the high risk medical devices the clinical investigation is required to establish the safety and performance of the devices. And this clinical investigation is applicable only for the devices which falls under the definition of investigational medical devices, for the devices other than the investigational devices this clinical investigation is not required to be, it is not mandatory to carried out on the devices for which the safety and performance as well as the efficacy has already been established.

So, for high risk devices and the intermediate risk devices there is a requirement of the clinical devices and the low risk devices like class a devices there is no requirement of the clinical investigation.

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If you see the global scenario of the clinical requirement of the clinical trial or the clinical investigation of the medical devices, the USA, in USA the regulation of the medical devices is under the federal food and drug and cosmetic act. In Europe that is the medical device directive the premarket and post market supervision is required by the USFDA, the Centre for Device and Radiological Health(CDRH) is accountable for pre market and post market supervision of the devices available in the market.

In Europe the notified body they are the authority for grant of the CE certification, the risk classification as per the USFDA. The medical devices have been classified into three tier system class 1, class 2 and class 3. Where the class 1 devices is the Low risk there is no requirement of the clinical trial or the clinical investigation, class 2 and class 3 where the intermediate risk or the high risk there is a requirement of the clinical investigation.

in Europe the medical devices have been classified based on the risk class 1 that is the low risk devices class 2 a that is the low to moderate risk devices class 2 b that is the moderate to high disk devices and class 4 that is. In Europe the devices have been classified into four category class 1 devices that is the low risk devices class 2 a that is the low to moderate risk class 2 b that is the moderate to high risk and class 3 devices that is the high risk devices.

Approval system for class A in USA it is under general control class 2 that of pre market notification process, class 3 that is the special control premarket approval is required. In

Europe the manufacture need to establish the CE to exhibit the CE marking in order to ensure that the device is safe, fit for it is intended use.

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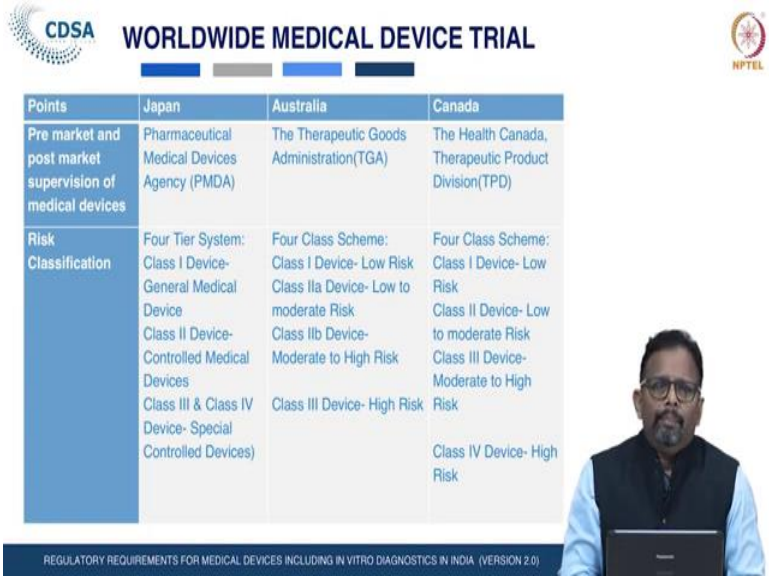

If you see the regulatory requirement for the clinical investigation of the medical devices in Japan, Australia and Canada. The Japan, the PMDA is the responsible is the authority to monitor the safety and efficacy of the medical devices in their country. In Australia it is Therapeutic Goods Administration (TGA) and in Canada Health Canada (HC) the Therapeutic product division which is responsible for monitoring or supervision of the medical devices marketing in their country.

They have classified the medical devices based on the risk, in Japan the medical devices have been classified into class 1, class 2, class 3 class 4 wherein class 1 is the low risk devices and class 4 is the high risk devices require a special control and in Australia also the classification system is in the line of the European system. Where the class 1, class 2 A class 2 B class 3, class 1 is the low risk class 3 is the high risk. Canada the classification the scheme is again class 1 class, 2 class 3 and class 4 devices, where the class 1 is the Low risk devices and class 4 is the high risk devices and the low risk devices has already discussed there is no requirement of the clinical investigation.

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If you see the clinical requirement of the clinical investigation as per the medical device rules 2017. In the medical device 2017 the specific provision for clinical investigation clinical performance of the medical devices and the in vitro diagnostics kits have been made. the specific provision have been made in the medical rule 2017.

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Certain definitions related to clinical investigation has been defined in the medical device rules. The definitions which have been defined is investigation medical devices, the devices which does not have it is predicate devices or the devices which is claimed

for the new intended use or new population or the new material or the major design changes and is being assessed to establish the safety and performance as well as the effectiveness of the clinical investigation, such devices is defined as the investigational medical devices.

Predicate devices definition has been defined in the medical device rule 2017, predicate device means the devices first time and first of it is kind approved for manufacture for sale or for import by the Central Licensing Authority (CLA) and has similar intended use material of construction design characteristic as the device which is proposed for license in the country.

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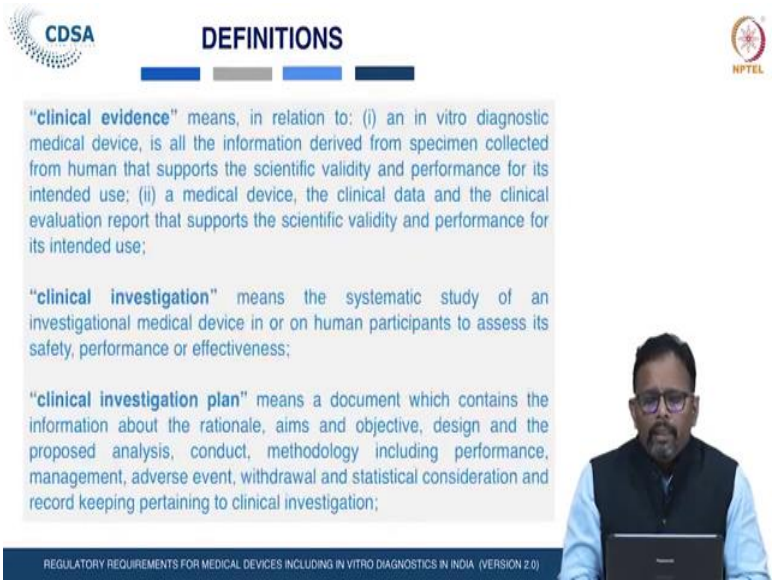

Clinical evidence, clinical evidence means in relation to in vitro diagnostics kits, the clinical evidence is the information derived from the specimen collected from the human that support the scientific validity and performance for it is intended use.

In case of the medical devices the clinical evidence means the data, the clinical data and the clinical evolution report that support the scientific validity and performance for it is intended use. Clinical investigation is also defined that is the systematic study on the investigational medical devices in which human participants to assess its safety and performance and effectiveness.

Clinical investigation means this systematic study of an investigational medical devices in or on the human participants to assess itssafety performance and effectiveness. Clinical Investigation Plan (CIP) means the document which contain the information about the rationale aim and objective designs and performance management adverse events withdrawal and statistical consideration and the record keeping pertaining to the clinical investigation.

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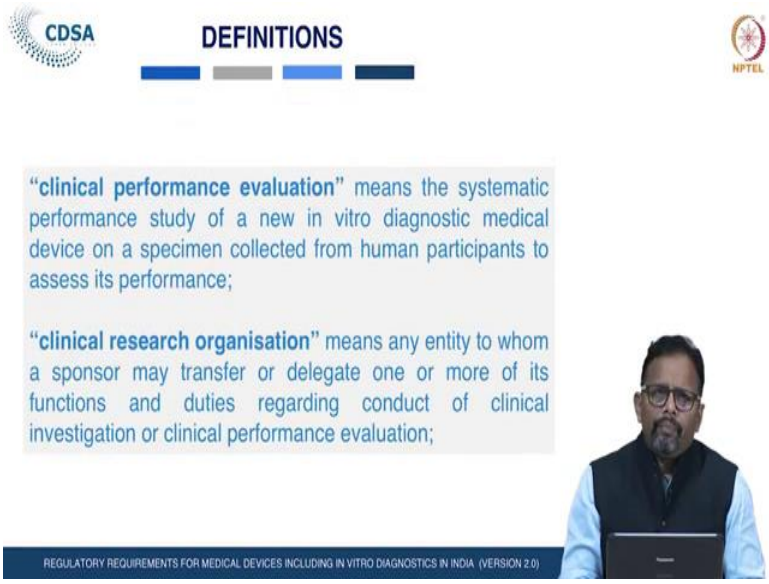

Clinical performance evaluation which defines the systematic performance study of the new in vitro diagnostics on the specimen collected from the human participants to assess itsperformance.

Clinical Research Organization (CRO) it means an entity to whom a sponsor may transfer or delegate one or more of it is function and duties regarding conduct of the clinical investigation or clinical performance of the evaluation of the in vitro diagnostics. All those definitions has been defined in the medical device rule 2017. Now, as we have already discussed for the establishing the safety and performance of the medical devices, the pilot study is required to be carried out in a small number of population , a small number of the patient to establish the safety of the devices.

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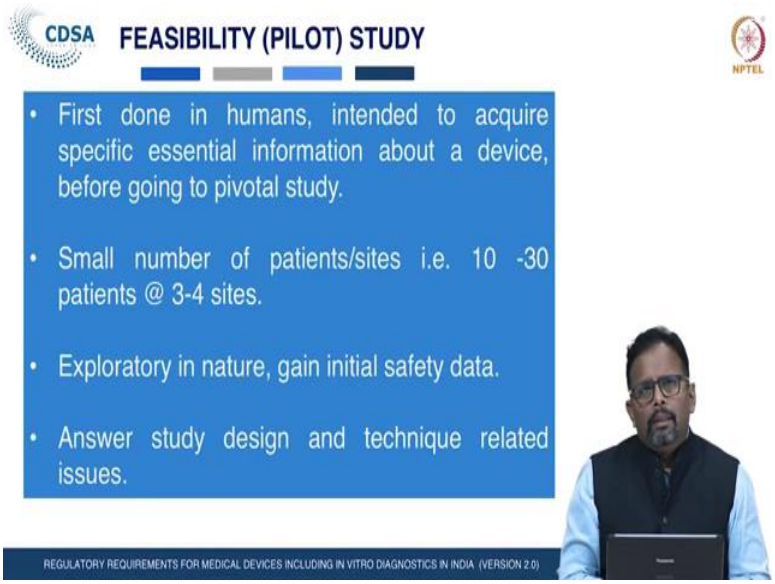

normally this studies to be performed approximate 10 -30 patients in small side 3 to 4 sides.

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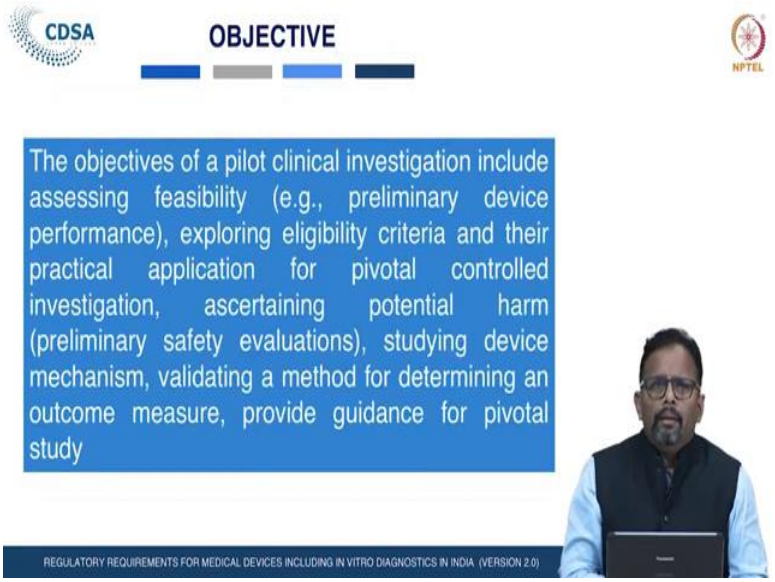

The Objective of the pilot study, enclose the assessing feasibility exploring feasibility criteria and their practical applications for pivotal control investigation. The data the objective of this study is ascertaining the potential harm is studying device mechanism validating a method of determination and outcome measures and also provides the guidance for the pivotal study.

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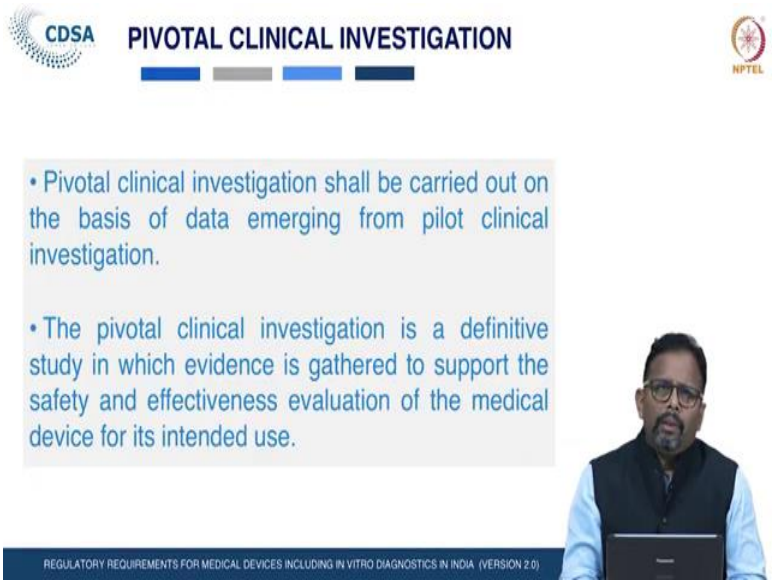

Now, come to the Pivotal Clinical Investigation (PCI), the pivotal clinical investigation shall be carried out on the basis of the data emerging from the pivotal study pivotal clinical investigation study. The pivotal clinical investigation is the definitive, it is a confirmative study in which evidence is gathered to support the safety and performance or effectiveness of the medical devices for itsintended use.

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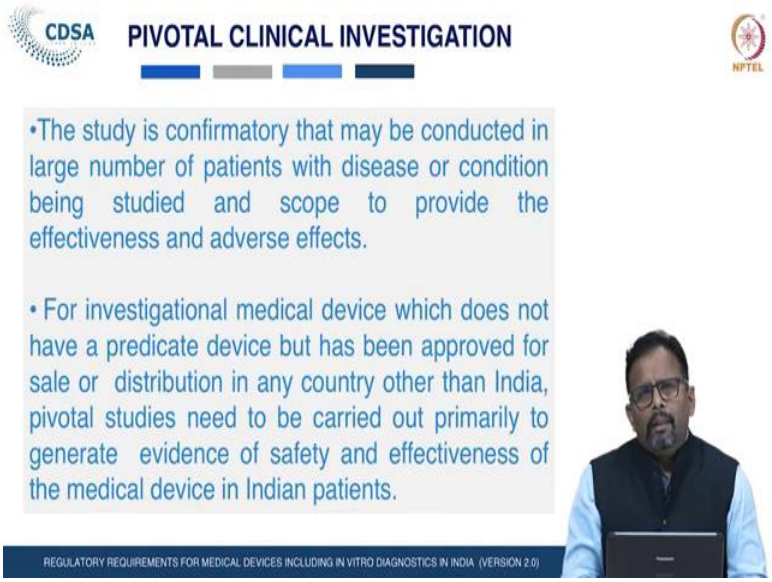

This is the confirmatory study that may conducted in large number of patients with disease or the conditions being study and scope to provide the effectiveness and adverse

effect. For investigational medical devices which does not have a predicate devices. But have been approved for sale and distribution of any country other than India. Pivotal study need to be carried out primarily to generate the evidence of the safety and effectiveness of the medical devices in the Indian population.

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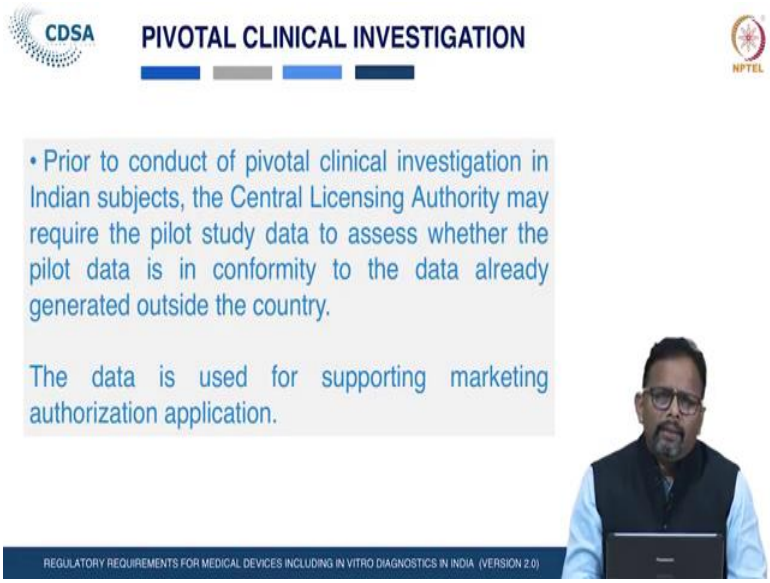

Prior to conduct of the pivotal clinical investigation in Indian subject, the central licensing authority (CLA) that is the DCGI the controller in general India may require the pilot study data to assess. Whether the pilot study data is in conformity to the data already generated outside of the country the data is used for supporting marketing authorization applications.

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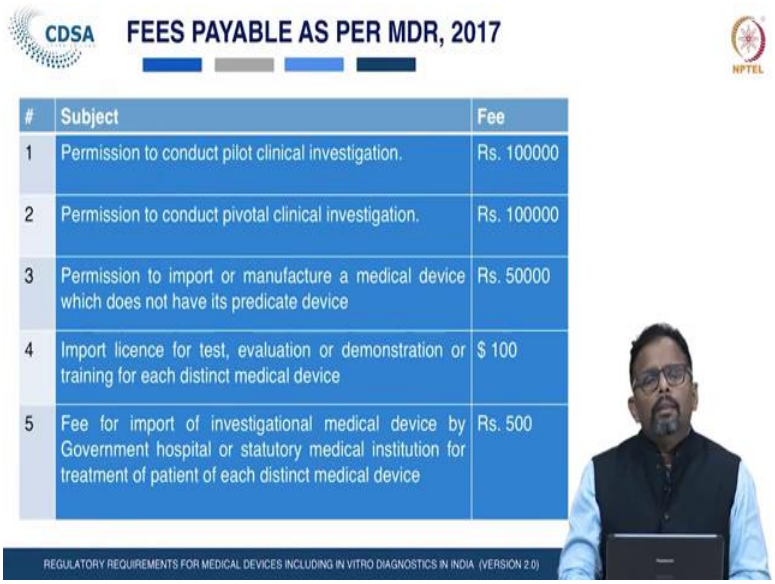

The fees for various activities with related to the clinical investigation. If the clinical investigation is need to be carried out on the investigation medical devices for pilot study rupees 100000 is there. For pivotally study 100000 is there, for obtaining the import and manufacturing permissions for the devices which does not have predicate devices 50000 fees is there import license that is dollar 100 and for the investigational devices import by the government hospitals 500 Indian currency is required.

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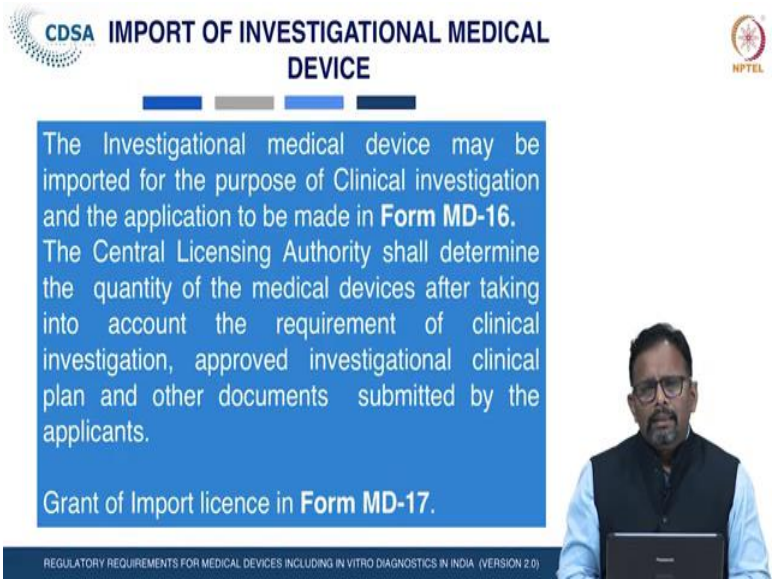

Import of the Investigational Medical Devices, the investigation medical devices may be imported for the purpose of clinical investigations and the application in form 16 along with the documents for which the studie is to be carried out, they need to be submitted by the applicant. The central licensing authority (CLA) will grant the import license for conducting the clinical investigation of the investigation medical devices in MD 17.

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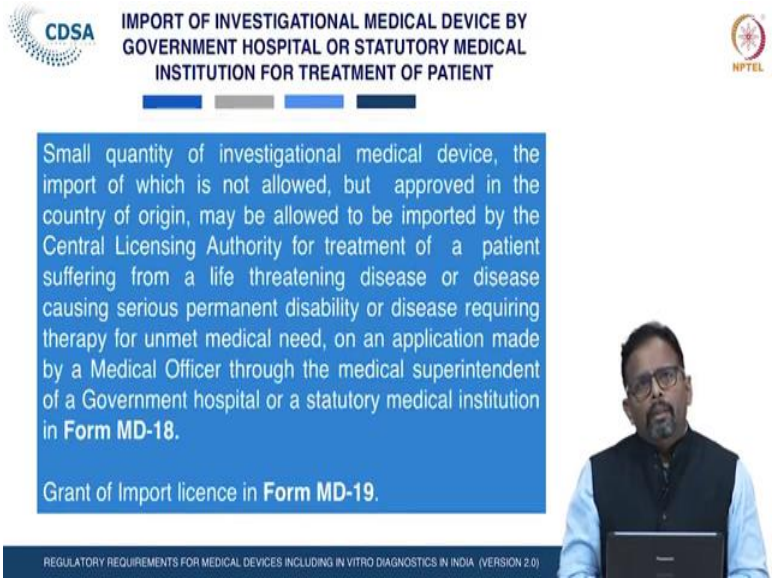

The import of the investigation medical devices by the government hospitals for the treatment of their patient, the small quantity can be imported by the hospitals and the application in MD 18 along with the fees, requisite fees and the details of the patient and disease conditions that has to be submitted to the licensing authority. And the licensing authority shall grant the import license in MD 19 after satisfying the requisite information.

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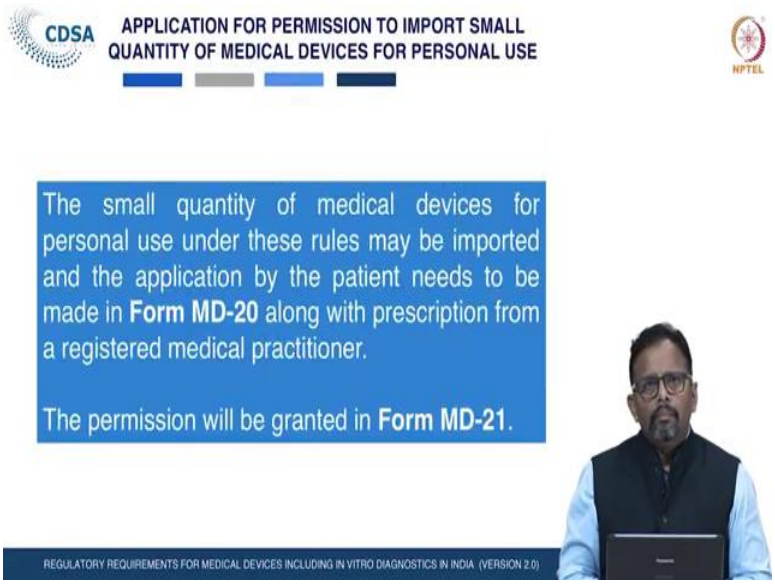

The import of the investigation medical devices by the government hospitals medical institution for the treatment of the patient, the application in MD 20 along with the requisite fees and the document required to be submitted. And the permission will be issued in MD 21 by the central licensing authority (CLA).

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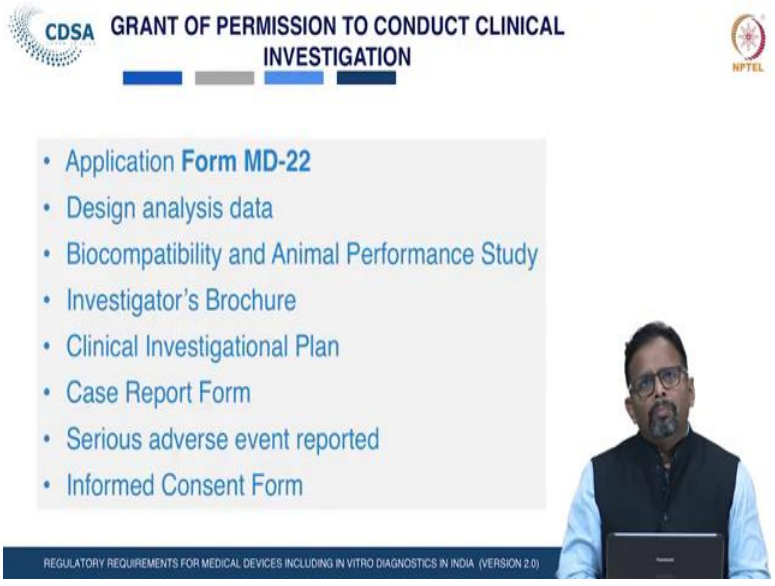

Grant a permission to conduct the clinical investigation of the investigation medical devices, the application has to be submitted to the central licensing authority in MD 22 along with the design analysis data. Biocompatibility and animal performance study data,

investigator brochure (IB), Clinical Investigation Plan (CIP) case, report forms, Serious Adverse Event (SAE) reported the informed consent form.

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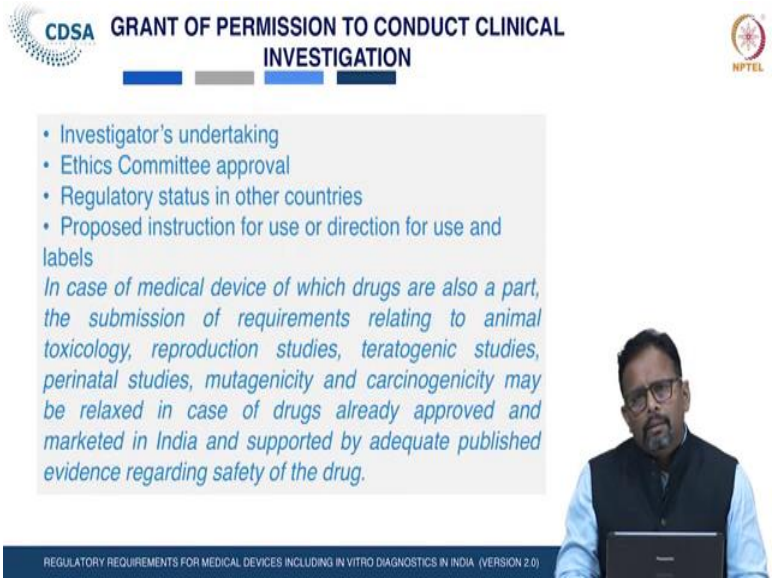

Investigators undertaking, ethics committee approvals, regulatory status in other countries and the propose instruction for use and direction for use and label. In case of the medical devices of which drugs are also a part the submission of the requirement relating to animal toxicology study, reproduction study, teratogenicity, perinatal studies, mutagenicity, carcinogenicity all those data also required to be submitted along with published data to the central licensing authority(CLA)

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And after satisfying the permission for conduct of the clinical investigation in MD 23 shall be issued by the central licensing authority. If the data is not satisfied the application can be rejected for the reason to be recorded in writing.

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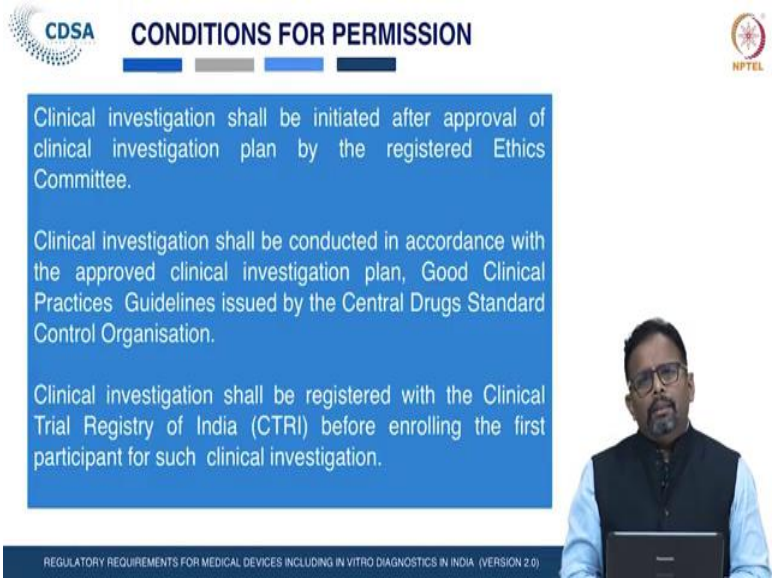

The conditions for permissions, the permission is issued by the central licensing authority to the applicant, to the sponsors with the conditions; the conditions of the permission that is the investigation shall be carried out after approval of the ethics committee, which is registered with the Central Licensing Authority (CLA). Another

condition that is the a study the clinical investigation study shall be carried out in accordance with the clinical investigation plan CIP) and Good Clinical Practice (GCP) guidelines issued by the central licensing authority that is the CDSCO. Another condition it shall be registered with the Clinical Trial Registry of India (CTRI), before enrollingthe first patient of such clinically investigation.

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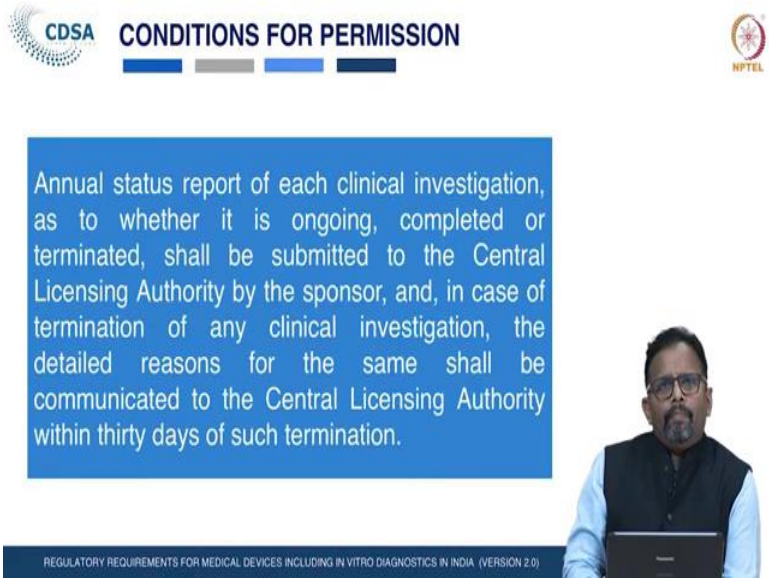

Another condition is the annual status report of each investigation is clinical investigation as to whether it is ongoing completed or terminated, shall we submitted to the central licensing authority (CLA) by the sponsor. In case of termination of the any clinical investigation the detailed reason, for the same shall be communicated to the central licensing authority within a period of 30 days.

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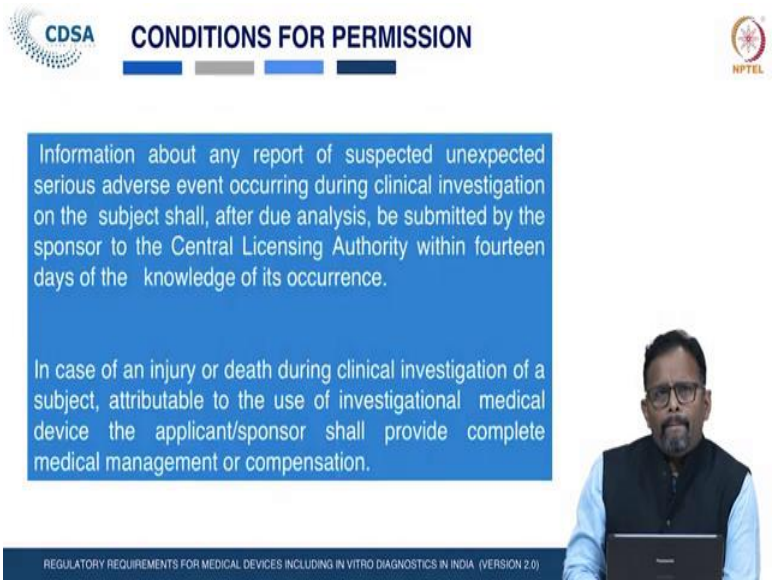

The information about any unexpected serious adverse event, occurring during the clinical investigation within 14 days that details has to be submitted to the central licensing authority (CLA). In case of injury death during the investigation, the use of the investigation medical devices, the applicant or the sponsors shall provide the complete medical management and compensation.

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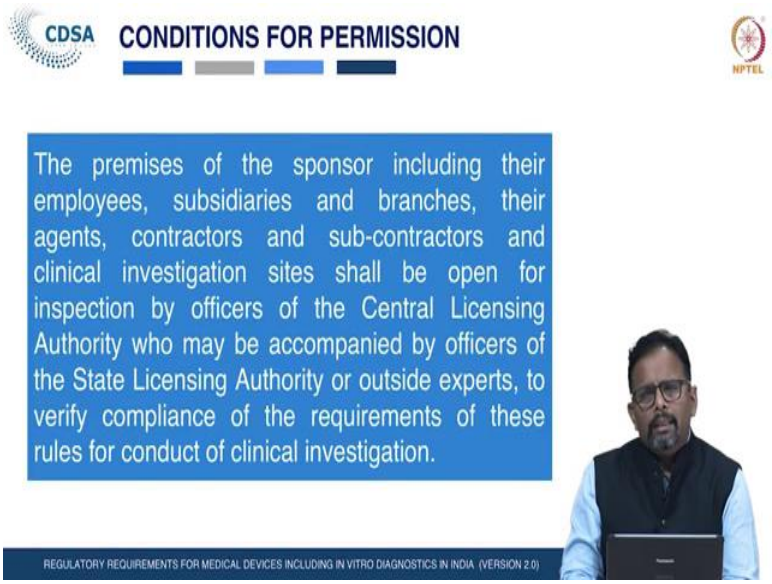

The premises of this sponsors including the employees, subsidiaries and the branches their agents, their contactors subcontractors at the clinical investigation sites shall be

open for inspection by the officers of the central licensing authority (CLA). To verify the complaints of the requirement of the medical device rules for conduct of the clinical investigations.

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The clinical investigations shall be carried out by enrolling first patient within a period of one year from the date of grant of the permission, failing which prior permission is again required to be obtained by the applicant from the central licensing authority (CLA). The sponsor holding the permission shall maintain the data, record, registries and other document for the period of seven years after completion of the such investigation. These are the conditions of the clinical investigation permissions obtained from the central licensing authority (CLA).

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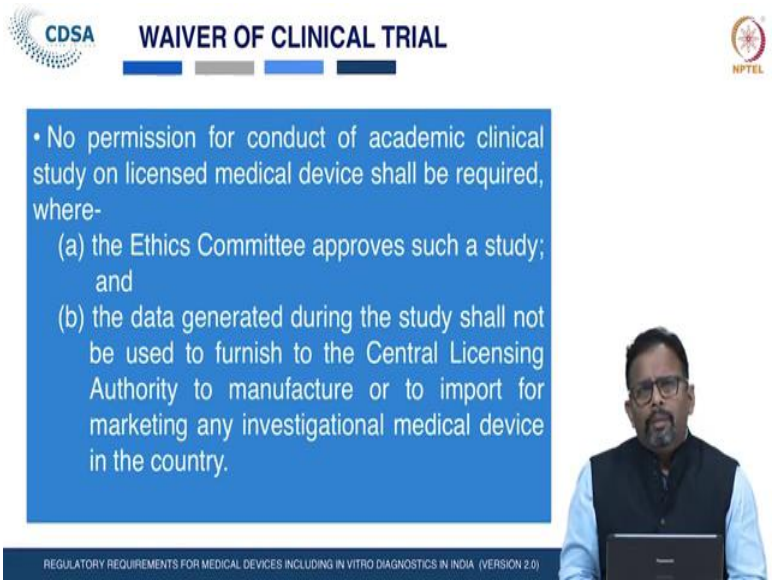

There is also certain cases waiver of the clinical trial of the investigation medical devices, no permission for conduct of the clinical investigation for academic purpose is required from the Central Licensing Authority (CLA). However, such investigation shall be approved by the ethics committee approved for such study. The data generated during the study of the academic study shall not be used for the used for the purpose of commercialization of their product.

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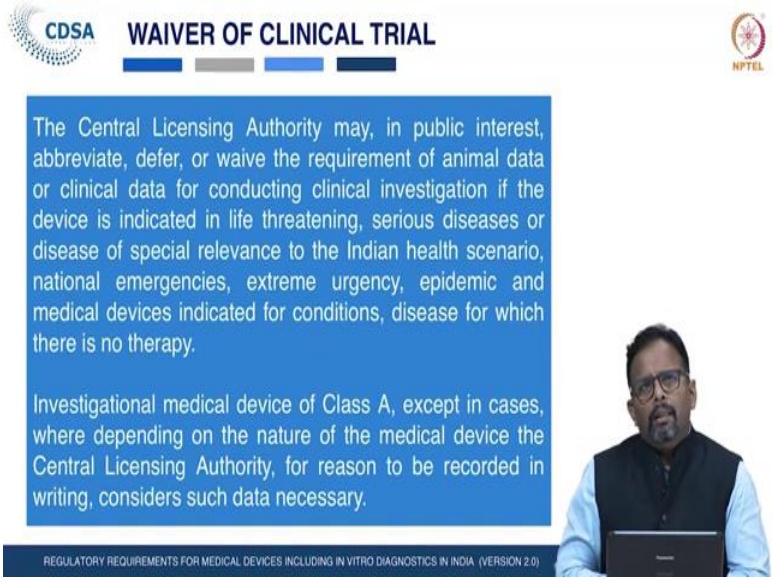

The clinical investigation is also not required to be carried out, in case if the Central Licensing Authority (CLA) may see that if it is in the public interest, the data animal data the clinical data for conducting the clinical investigation. If it is indicated for the life threatening or the serious disease or the disease of the special relevance to the Indian population or the national emergency or in case of esteem agency, epidemic or the medical devices indicated for the conditions disease for which there is a no therapy. In such cases the licensing authority may consider the application for waiver of the clinical investigation of investigation medical devices.

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The result of the clinical investigation may not be required to be submitted, where the investigational medical devices is approved by the regulatory authority either by the UK or USA or Australia or the Canada or Japan. And the said devices has been marketed in those country at least for two years and the Central Licensing Authority (CLA) satisfy with the data of the safety performance and pharmacovigilance of the devices.

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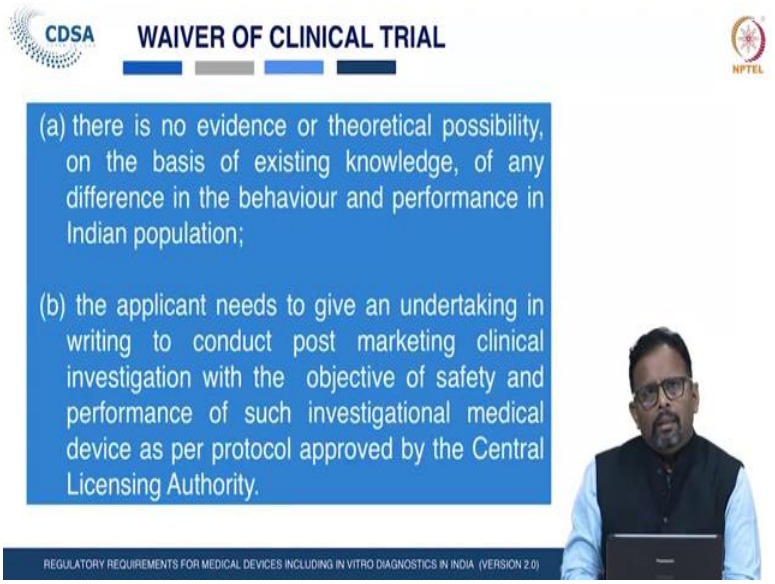

And there is no evidence or the theoretical possibility on the basis of existing knowledge or any other difference in the behavior and the performance of the Indian populations. The applicant need to give an undertaking in writing to conduct the post market clinical investigation with the objective of the safety and the performance of such investigation medical devices, as per protocol approved by the Central Licensing Authority (CLA). So, in such cases the requirement of the clinical investigation may be waived off.

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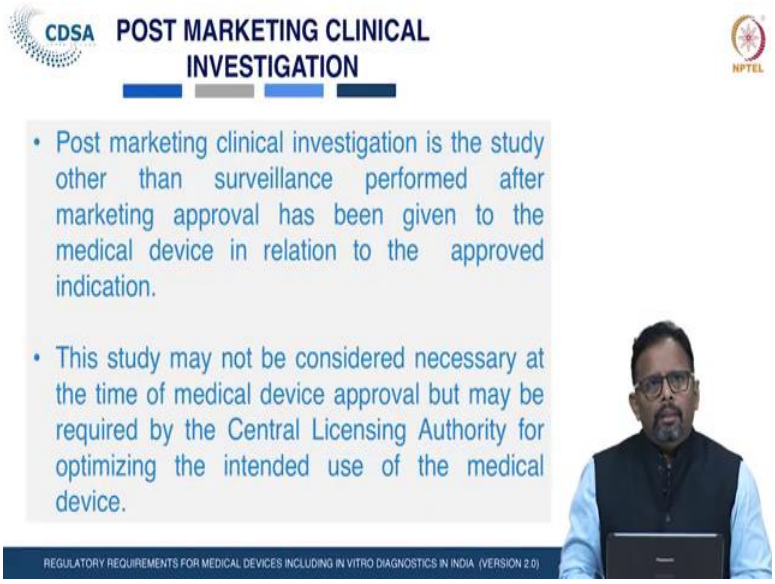

The Post Market Clinical Investigation (PMCI), the post market clinical investigation is the study other than the surveillance performed after the marketing approve marketing approval has been given to the medical devices in relation to appropriate indication. This a study may not be considered necessary at the time of medical device approval, but may be required by the central licensing authority (CLA) for optimizing the intended use of the medical devices.

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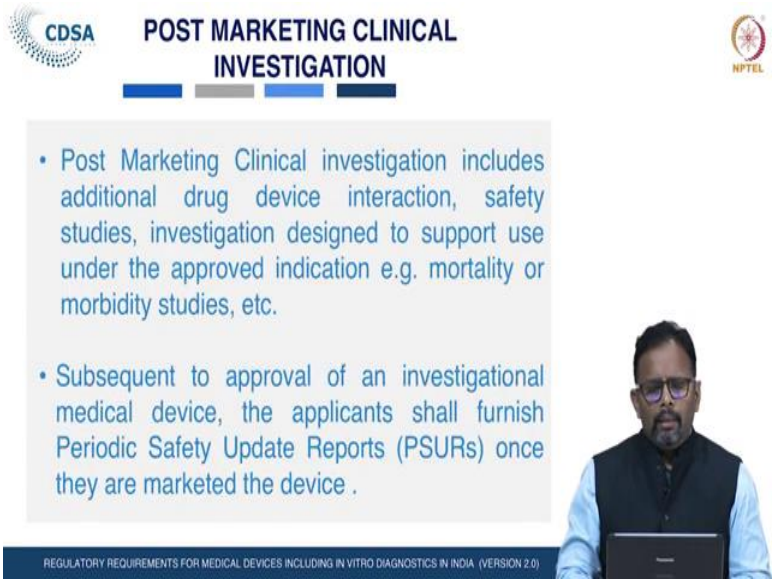

The post market clinical investigation include additional Drug device interaction, safety studies investigation design to support use under the approved indications. The subsequent of the approval of the investigation medical devices the applicant shall submit periodic safety updated report, once the products are marketed into the country.

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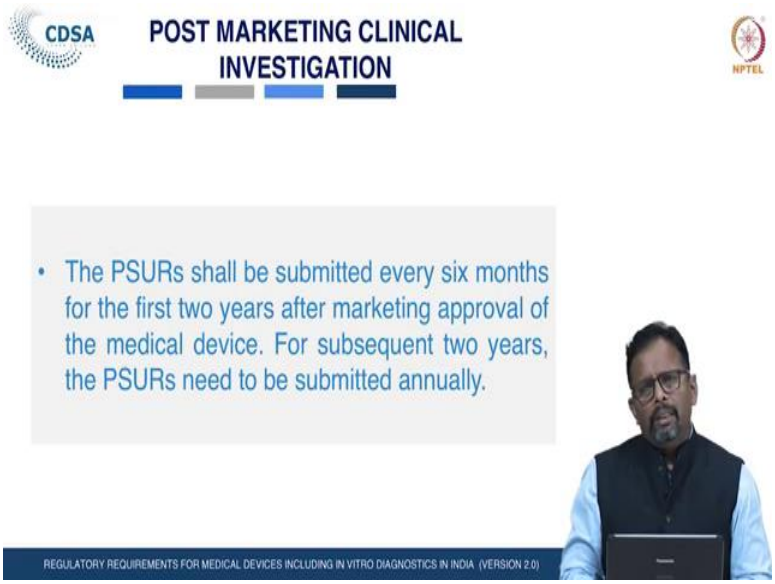

The PSURs shall be submitted every six month initially for the two years and another two years annually they need to submit the PSUR. The permission to import or the manufacture medical devices which does not have predicate devices.

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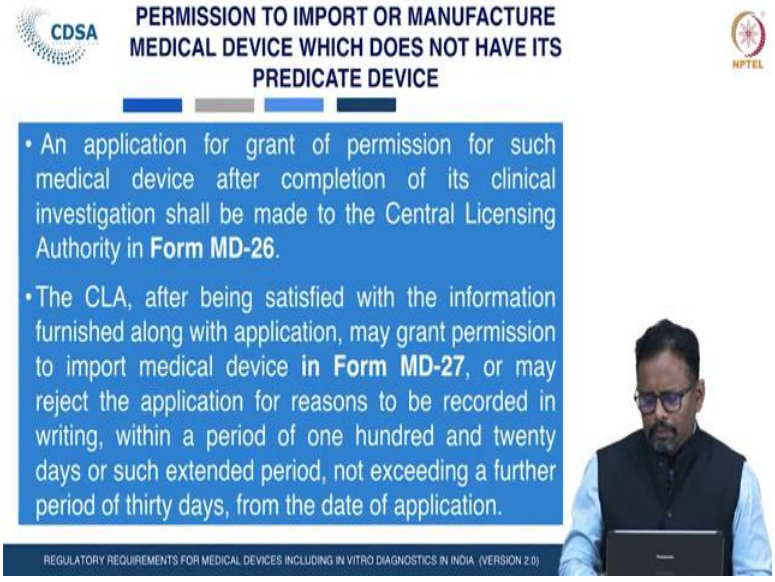

We have discussed in the previous lecture for this the applicant has to submit application to the central licensing authority (CLA) in MD 26. The requisite fees and the data as mentioned in the fourth schedule of the medical device rule 2017 has to be submitted to the central licensing authority along with the clinical data, biocompatibility biological

evolution data, validation data, stability data and other chemical details mentioned in the fourth schedule of the medical device rule 2017. After satisfying the requirement the central licensing authority (CLA) shall give the permission in form 27 to the applicant.

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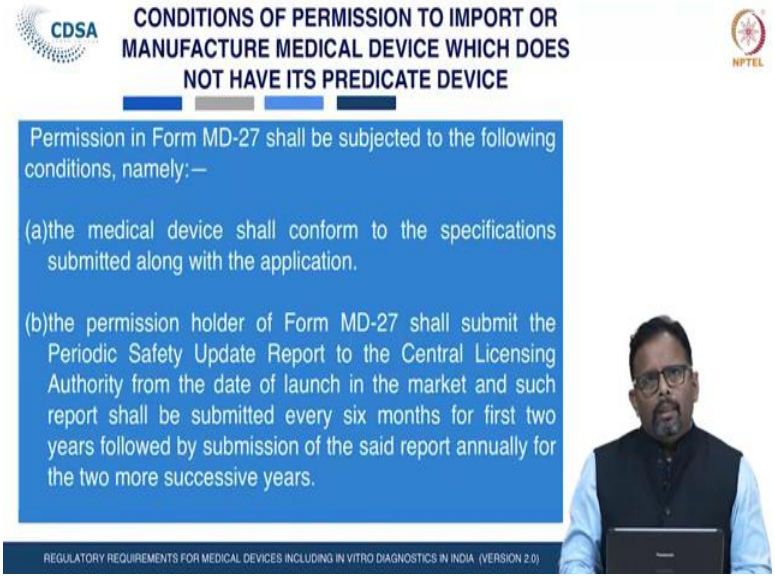

Also there is certain condition in the permission given by the central licensing authority for the devices which does not have the predicate devices. They have to submit the periodic safety updated report every 6 month for initially 2 years and then annually for another 2 years the medical devices shall confirm the specifications submitted along with the applications.

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The permission holder shall inform the date of launch of the devices in the market to the Central Licensing Authority, they shall submitted the suspected unexpected serious adverse event (SAE) within the 15 days of the awareness of the event of such incidents to the central licensing authority.

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The guidelines for the conducting clinical investigation has already been prescribed in the 7th schedule of medical device rule 2017,which is in the line of ISO 14155: 2011 that

is the clinical investigation of the medical devices for human subjects good clinical practices.

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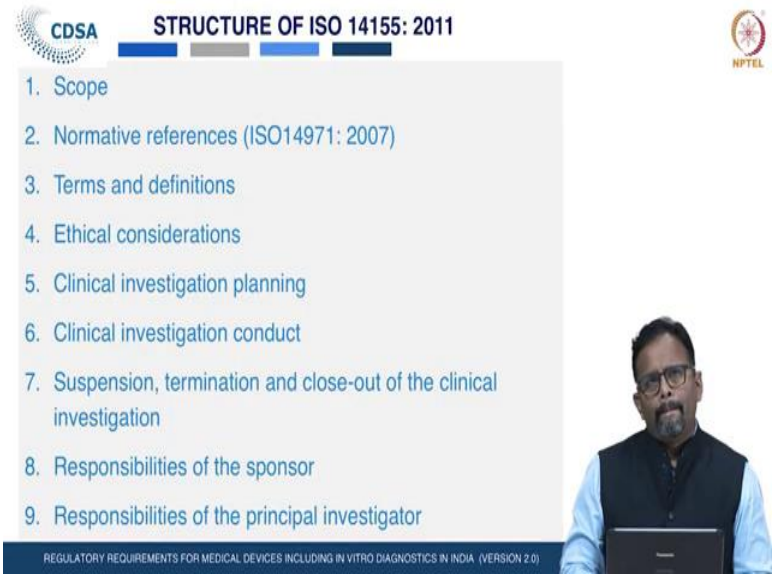

Now, let us have look on the structure of the ISO 14155: 2011 this guideline have 9 components one is scope, part two that is a normative reference which is based on the ISO 14971 Risk Management Process (RMP). The standards includes terms and definitions part 4 the ethical considerations clinical investigation planning, clinical investigation conduct, suspension termination and closed out of the clinical investigations, responsibility of the sponsors, responsibility of the principal instigators all those details and guidelines have been described in this standards and the same guidelines the 7th schedule of the medical device rule 2017 have the similar guidelines for conduct of the clinical trial , clinical investigation.

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The guidelines and the standards available globally with respect to the clinical investigation of the medical devices or the clinical trial of the clinical devices. In USA the ICH and GCP guidelines and also they recognize the ISO 14155 in European there is a directive medical device directive 2005/28/EC-GCP guidelines and the medical device directive guidelines 2001/20 as well as the ISO 14155.

In Japan the Japan Medical Device GCP guidelines which is also in the line of ISO 145155:2011 the health Canada GCP under the Canadian medical device regulations, Australia GCP as per CPMPICH 135/95. These are the guidelines and standards related to clinical trial of the medical devices or the clinical investigation of the medical devices

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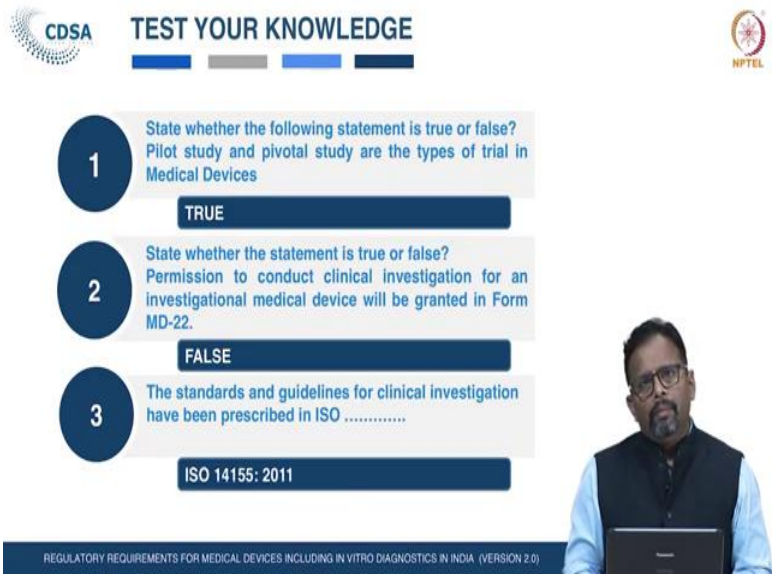

Now, let us have some question answer session. Now, again please read this statement whether it is true or false, the pilot study and the pivotal studies are the types of the trials in the medical devices it is true or false.

It is true it is applicable for the medical devices.

The permission to conduct the clinical investigation for an investigation medical devices will be granted in form MD 22 is it true no.

it is not a true, it is a application the permission is granted in MD 23.

Now, can you fill up this statement complete this statement the standards and guidelines for the clinical investigation which have been prescribing in the ISO, which ISO standards it is prescribed yeah it is ISO 14155/2011.

Thank you.