Current Regulatory Requirements for Conducting Clinical Trials in India

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Lecture – L7
Good Clinical Practice (GCP)

[FL]. Welcome to our online course called Current Regulatory Requirements for Conducting Clinical Trials in India. Today, I will take you through the lecture 7 which is Good Clinical Practice.

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What do you understand by good clinical practice? Let us try to learn through this seven areas. One is the pre-requisites for the study. Before that we should know what is GCP? Why we should follow the GCP? Then we will understand what is pre-requisites for doing any clinical study. What are the responsibilities, responsibilities of various stakeholders? Then we will understand what is record keeping and data handling. We will understand quality assurance, statistics and address special concerns. Although the Indian GCP, do not have principles of GCP we will try to cover them in our overview.

So, the GCP which is good clinical practice is actually divided or focused on two areas; one is ethics, another is the data and the results. The ethics focus on this right, safety and wellbeing or study participants, whereas the data focuses on the credibility and accuracy

of the data which is generated. It is very important for us to know that why we should study GCP.

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It is a standard, it is an international standard for clinical studies or trials that encompasses many of the areas the design, the conduct, the monitoring, the termination of the study in between if it happens, the audit, the analysis, the reporting and the entire documentation of the studies. When you conduct a GCP study or GCP compliant study, you ensure that the studies are implemented and reported in such a manner that there is an assurance given to the public that all the data that are generated are accurate and that the right, safety and well-being of all the study participants are well protected.

GCP also ensures that the studies are scientifically authentic and that the clinical properties of the investigational product which is called as IP or IMP are properly documented. We will cover the Good Clinical Practices for Clinical Researchers in India, which is by CDSCO Central Drugs Standard Control Organization, 2001.

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So, what does this mean to us? If you see the graph here or that diagram here, GCP means how the study is designed, how well it is conducted, how it is recorded, how it was monitored, how it was analyzed and how it was reported. And it focuses on the two areas we discussed, the rights, safety and wellbeing of the study participants or subjects and the data quality and integrity.

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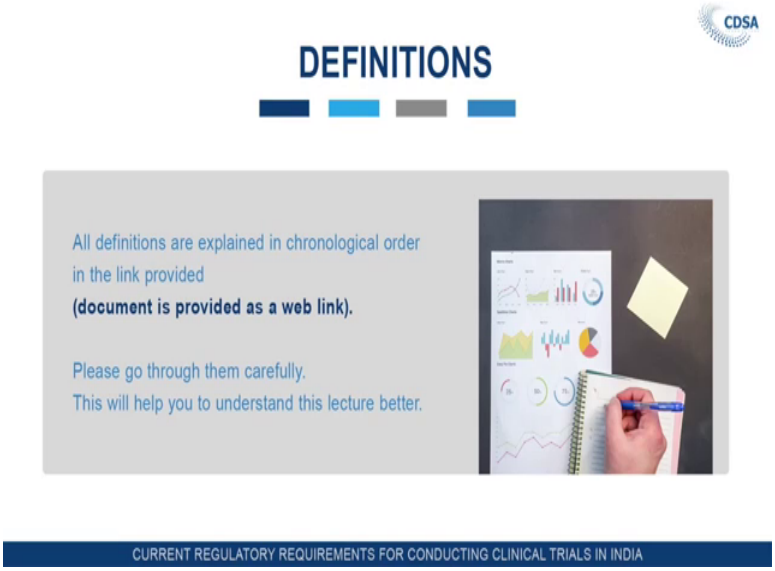

Let us first understand the definitions. All the definitions are given in the word document which is provided as a web link to you. Please go through them carefully. All these

definitions are extremely important to you and if you do not understand the definitions, you will probably not understand this chapter better. Once we have understood the definitions, let us try and understand what are the pre-requisites for conducting any clinical trial or study.

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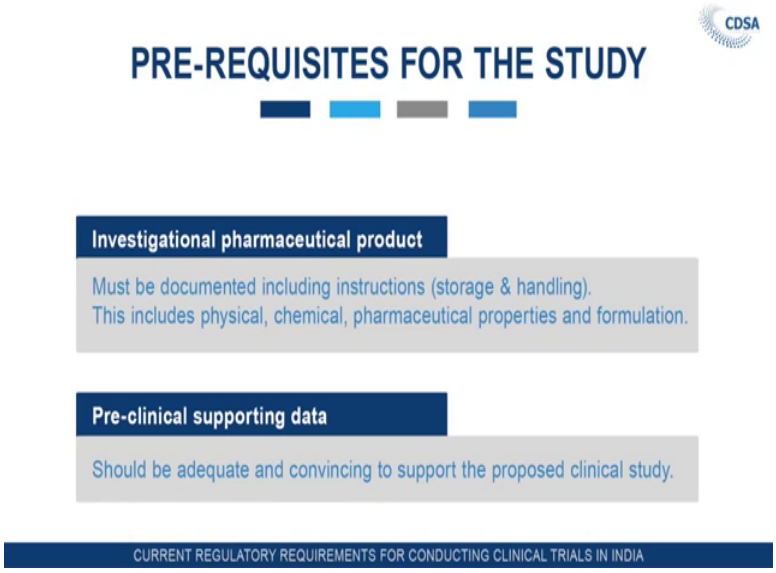

The first pre-requisite is the product. The product which is to be used for the clinical trial; it is known as IP. IP means investigational pharmaceutical product. It should be documented, that means, how it was produced, what are the physical properties, what are the chemical properties, what are the pharmaceutical properties, how the formulation was met. All this should be documented including the instructions of storage and handling.

Pre-clinical data; pre-clinical data can be many types. It can be pharmacology; it can be toxicology; it can be regulatory toxicology; it can be animal pharmacology. So, this two areas cover the pre-clinical and there are wide ranges of pre-clinical studies, and they are all well defined in schedule Y. They should all the pre-clinical data should be adequate, and they should convince to support that the proposed clinical study is correct.

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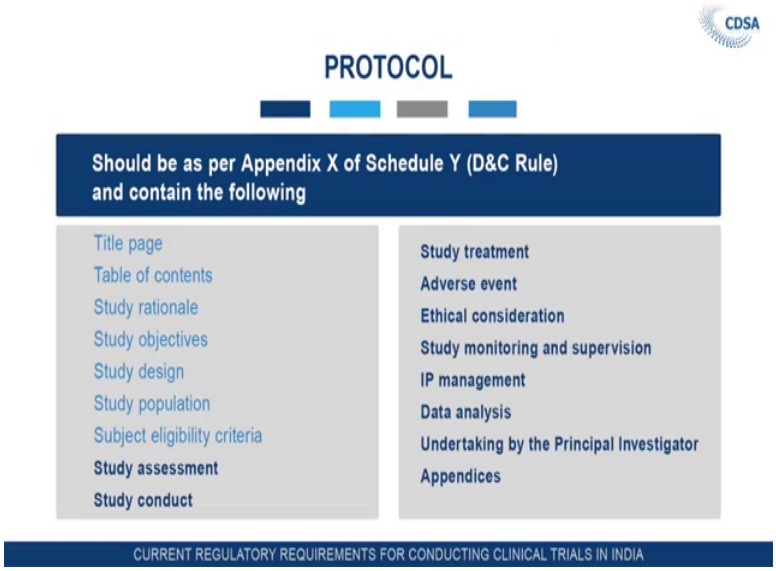

When you begin a clinical study or a clinical trial, the first document is the most important document and that is the protocol. The protocol which is designed, it should be as per the appendix 10 of schedule Y which is under Drug and Cosmetic Act. The protocol should have many areas like the table contents, the title page, the study rationale, the objective, the design, the population. It should also tell the eligibility criteria which includes inclusion and exclusion criteria. It should tell how you are going to assess, how you are going to conduct, what are the adverse events, what are the ethical considerations, how will you monitor a study, who are the supervision you will do, how are you going to do an IP management, how the analysis of the data will be there and how the principal investigator undertakes gives the undertaking.

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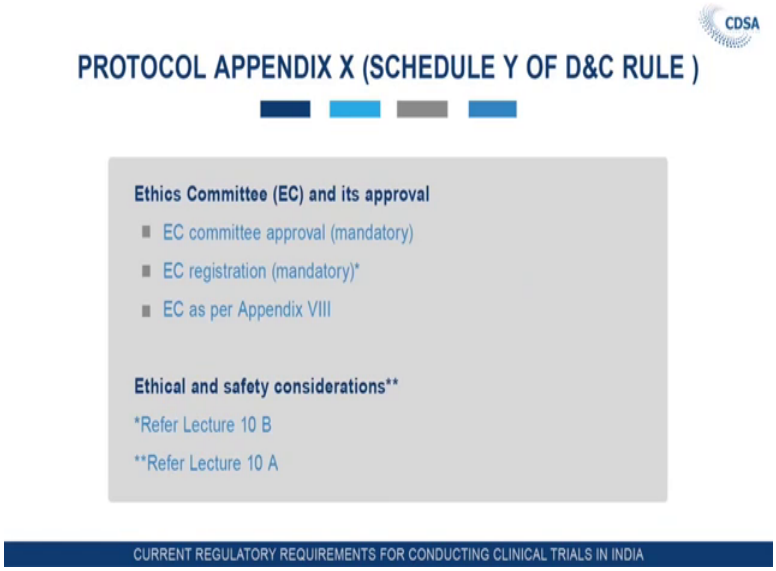

Also we need to understand about the ethics committee, because we are involving human participants in this study. The ethics committee its approval are mandatory when you do a study and the registration of all the ethics committees which conduct clinical trials should be registered to CDSCO and that is a mandatory requirement. And the ethics committee should be formed as per appendix 8. We will also study about the ethics and safety considerations. Before that let us understand the third part which is responsibilities.

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In a clinical trial, there are many stakeholders. And all the stakeholders play a very, very crucial role in the success or failure of a clinical trial. The first one is a sponsor. A sponsor can be an investigator can be an institution and the sponsor is the one who selects an investigator, and selects an institution very carefully. He is the one he or she or the in sponsor is the one who has all the information related to the investigational product. They supply, they store and they know how to handle the investigational product.

They also ensure that the protocol is compliant as per the GCP and the regulations of the country. The sponsor is responsible legally for the implementation of quality assurance system. As a result sponsor undertakes all the monitoring and auditing activities. Sponsor is responsible for submission of the status report, periodic updates, reporting of the adverse events and serious adverse events. And also the main important thing the financial compensation wherever there is a case of an injury or death.

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The ethics committees are responsible for the review and approval of trial protocol. We have a separate chapter called 10 a and 10 b, which deals specifically on ethics committee. I hope when you go through this lecture 10 a and 10 b, you will have a very good or a brief idea about the ethics committee and the registration and the process of review and approval.

So, here we speak about the responsibilities of the ethics committees. It is the review of all the ongoing trials, review of the periodic study progress reports, reporting of the serious adverse events, they also are responsible for forwarding the serious adverse event reports to the licensing authority. Here the licensing authority is the CDSCO. They are also supposed to report any changes.

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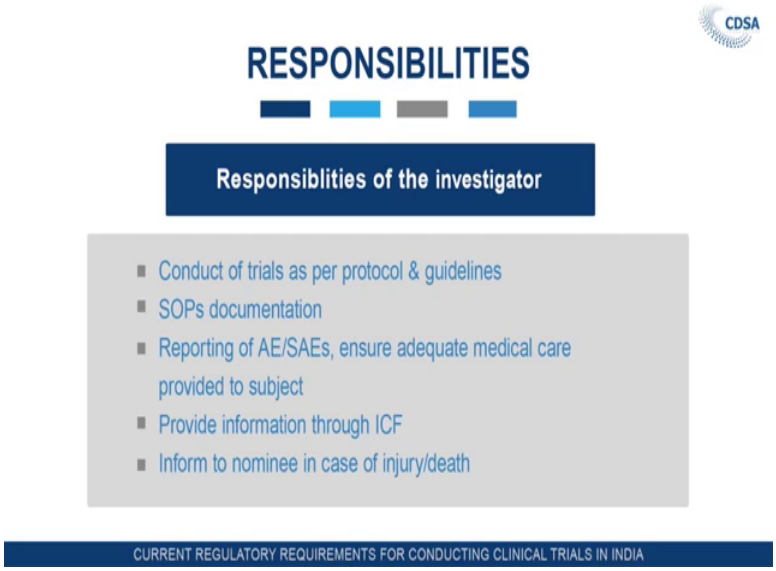

Now, comes the most important stakeholder of a clinical trial, it is the investigator, the physician, the clinician. Let me tell you briefly that many people have this (Refer Time: 08:06) have a belief that good clinical practice is about clinical practice. It is a misnomer. Good clinical practice is actually good clinical research practice. It is nothing to the clinical practice it has nothing to do with the clinical practice. It has nothing to do with the patients you see every day. It has nothing to do with the OPD you handle every day. It is to do with the clinical research where you handle a patient with a new type of medicine or a new dosage form or a new device or a diagnostics.

So, they are as your study participants and not a normal patient, so that is the difference between GCP and GC the real definition of GCP which people trying to sometime overlook. So, about the investigator the investigator is usually a trained qualified physician or a clinician as per the norms of the country, that means, has been from MCM has a degree from MBBS, MD, MS, degree from MCI they are responsible for the conduct of the trials as per the protocols and guidelines. They are supposed to follow all

the standard operating procedure supposed to report all the adverse events, all the serious adverse events, ensure that there are adequate medical care being provided to the study participants and provide information through ICF that is informed consent form.

Wherever there is a mention of subject, I try; I tend to use the word participant, because I feel the participant has got equal right in a study or a research or a trial where a subject is a king and a subject. So, wherever I say participant I actually mean participant or study subjects. Also investigators are responsible for informing the nominee of a study in case of there is an injury and death. For thus any clinical trial a physician is the person who has met the study participant.

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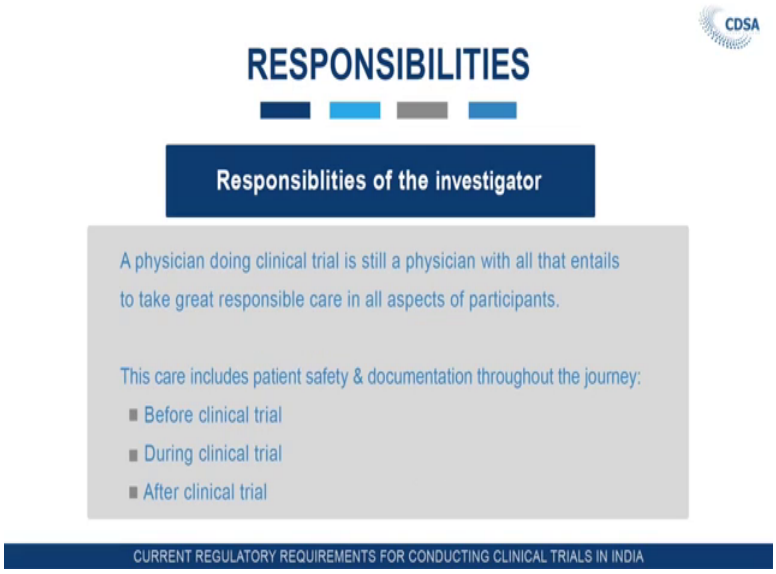

He is the one he or she is the one who has worked before the trial, during the trial and after the trial. And it is the only link to the study participant and it is the most important crucial element of success or failure in any clinical trial. So, the patient safety and the documentation throughout the journey of clinical trial should be best understood by a clinician and they should must be trained in good clinical practice.

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And the crux of any clinical trial is documentation. We see that clinical trial comprises of documents, documents and documents, and I am not wrong because it is the document which is which proves that you had done some work. We say whatever is not documented is not done. So, all the records which are generated in a clinical trial, it can be written documents, an electronic documents or magnetic and optical records, scans, X-rays, electrocardiograms, ECGs, they all should be in a form of a document where you can preserve them for a long time preferably 10-15 years. And they should be able to tell a story after the study is over and exactly leave a audit trail.

So, what you should keep, you should keep protocols copies of all the regulatory submissions, approval letters from the regulators, ethics committee is the consent form from the study participants, the monitoring reports, the audit certificates, the relevant letters, the reference ranges, the raw data which is so crucial and the completed case record forms and the final report.

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Whenever we do any clinical trial, please remember that you need to follow something which is called good documentation practice. The good documentation practice ensures that you do not document any data which can be forged or misconstrued later on. So, all the corrections in your case record form or any other study related documents should be made in such a way that it does not obscure the original entry. You should be able to correct put insert the correct data, give a reason why you changed it, and give a date, put your initials, and the initials should be of the authorized person to authenticate that the corrections is done by a person who is authorized to correct it. So, anytime you do any corrections in a clinical trial data, remember signing a cheque. When you sign a cheque, and the cheque goes wrong how you correct a cheque should be the one you should use it.

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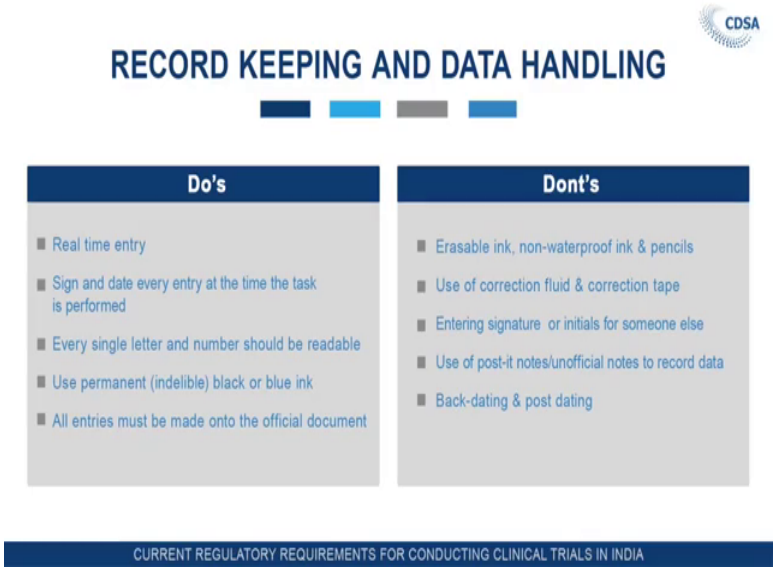

So, for a good documentation practice there are some do's and some don'ts. The do's is that you should never keep your work to tomorrow. You should always do real time entry sign and date every entry at the time the task is performed. Every single letter and the number should be readable. Readable and you should be using only permanent or indelible ink, preferably black or blue. All the entries should be made into an official document. You should never use erasable ink, non-waterproof ink, pencils, never use correction fluids or a correction tape. Entering the signature or initials for someone else is a very risky business in clinical trial. Using post-it notes unofficial notes to record data can create a lot of problem and never ever think of back dating and post dating in a record. So, good documentation practices also speak about something called ALCOA.

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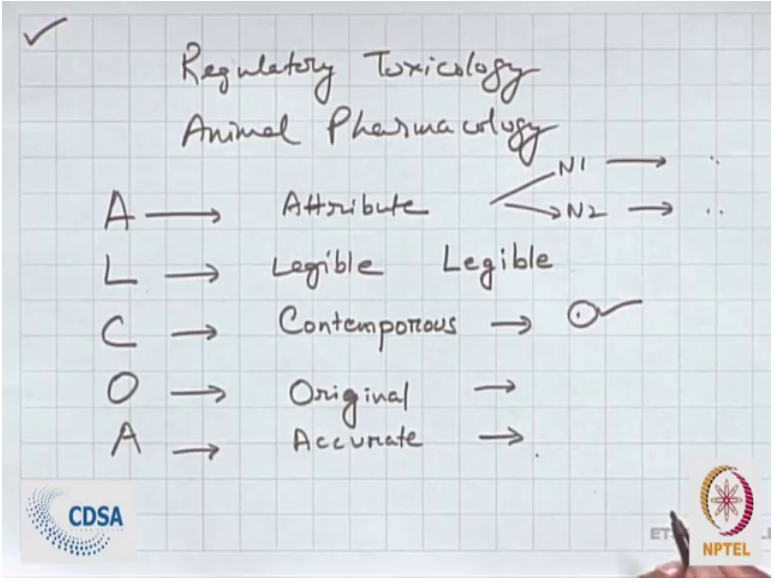

The ALCOA stands for A L C O A. A means attributable that means, anything which you do you should be able to attribute to anybody who has done it. Suppose a weighing a small child is being weighed by nurse 1, and the value of the child weight is written by nurse 2. So, you should write nurse 1 took the body weight and nurse 2 documented the body weight in the sheet. So, there were two nurses involved.

L stands for legible, what does legible means anything which you write like I am writing in such a weird handwriting, it is actually not legible. So, how you should write? You should write something which is a little better and all medicos have very very dangerous handwriting.

C, C stands for contemporous. What does the mean contemporous means contemporous means if you have done the work now you should do the documentation now, contemporous is at that moment. O stands for original that means, if you are writing something like this document it is an original document so, it is original. A stands for accurate. So, if you are writing anything, you must ensure that it is accurate.

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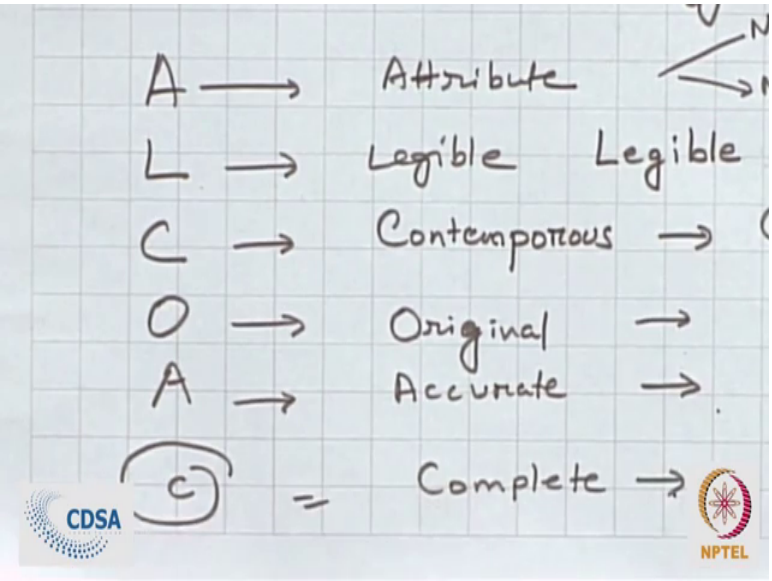

The reason 2016 edition of ALCOA also involves something called C, which is called complete. So, ALCOA has now become ALCOA C. And you should always remember when you do a good documentation practice.

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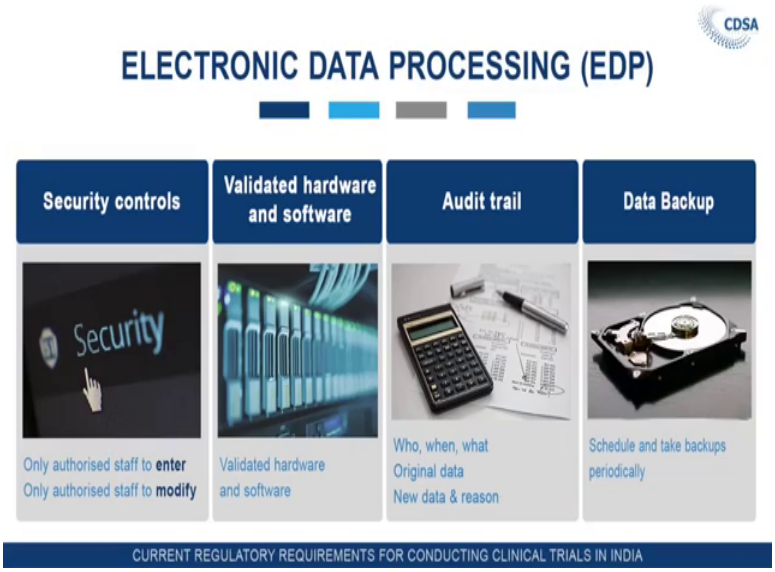

Now we are in era of electronic data and we have so many data that we have no other choice, but to use electronic data. So, whenever you use electronic data, please remember these four points. Your security control should be very strong, you should know who is authorized to enter the data and who is authorized to modify. The person who enters

should not modify. Your software and hardware should be validated and you should have a validation certificate. Usually, you should read about 21 CFR part 11 document to understand more about this. The audit trail, the document should be able to tell a story of 5 W and 1 H, who, when, where, what and how, and your original data and the new data and the reasons should be very very traceable. Data backup is extremely important because you do not know when you lose the data how to recover. So, do not forget to do that.

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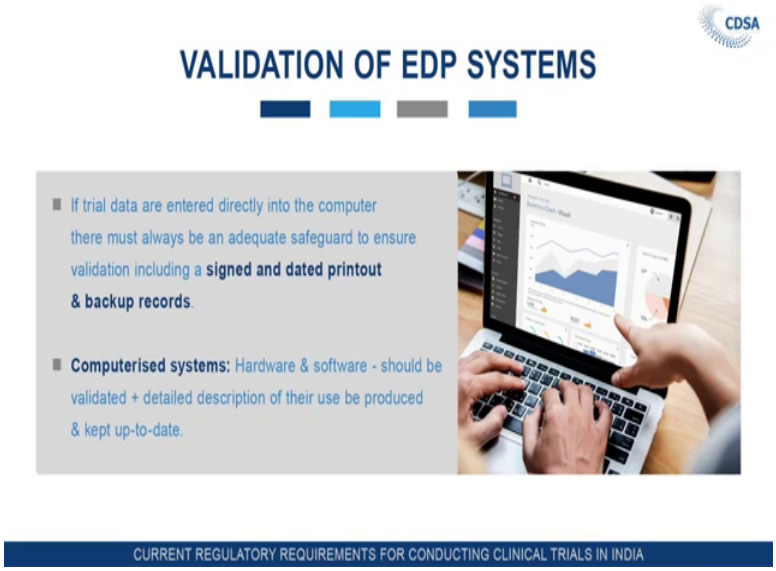

Validation of electronic data processing system is critical, because if they are trial data is entered directly into a computer, you must always be able to have sufficient safeguard to ensure that the system, your software system or hardware system is totally validated bug free, and it should have been assigned and dated and print out with backed up reports. So, that when you trust on the system, the system really makes to that. You do not fail while showing the data that means your computerized system which comprises of hardware and software should be validated with a certificate which gives a detailed description of the use, and how they should be kept up to date.

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Language, which language you should use. There is no certainty that you have to use English language, you can use any language all written documents or information or any materials used in a clinical trial should be in a language that is clearly understood by all concerned that is your study participants, the paramedical staff, the monitors, the clinicians, ethics committee members, the regulators.

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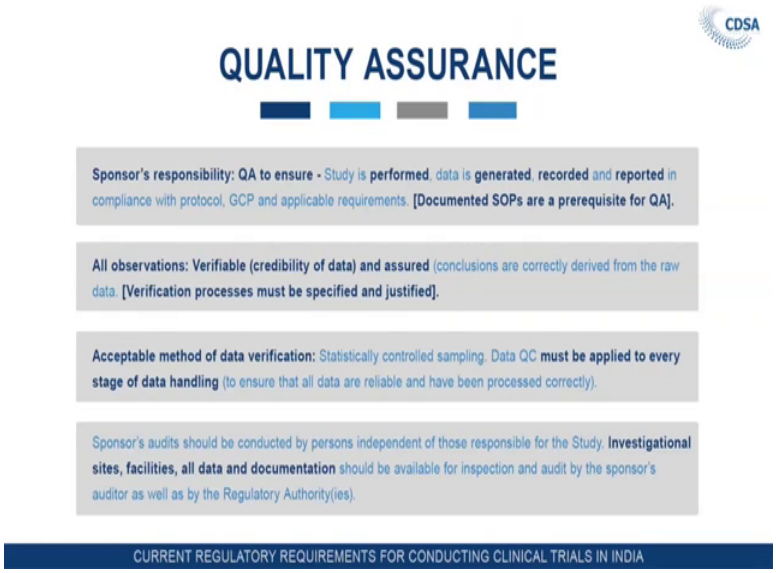

Let us come to the fifth subtopic called quality assurance. All the quality assurance is the responsibility of the legal responsibility of the sponsor, quality is a responsibility of

everybody in a clinical trial. A sponsor's responsibility is that the sponsor has to ensure that the entire study was first performed if performed the data was generated. If the data was generated, it was recorded; if it was recorded, it was reported. If it was reported, then all the things that was done is in compliance with the mother document which is the protocol, then the standard operating procedure, the SOPs, the GCP and the regulatory requirements.

And anything to have a good key way, you should have a very strong SOP system. All these observations should be verifiable, that means, you can do an audit trail and you can find, so that your data can be credible. All the data should be assured that means the conclusions are correctly derived how will you know, so their raw data should exactly speak what you are concluding to.

So, verification process must be very specified and should be justified. There should be an acceptable method of data verification, that means, you have to use statistically control sampling, you should have data QC in place where you should understand or check all the data whether the inputs are correct or not by do a single entry, double entry, whatever is your method of doing your data QC should be in place when you do this. And you must be able to assure that each and every data that has been put has been has undergone data QC and has been found to be true, and can be used for the data analysis. And this data is so important, because on the basis of this data the entire clinical trial data the report are generated. So, its reliability is of utmost or sacrosanct in nature. The sponsor conduct; sponsor as you know is officially or legally responsible for quality.

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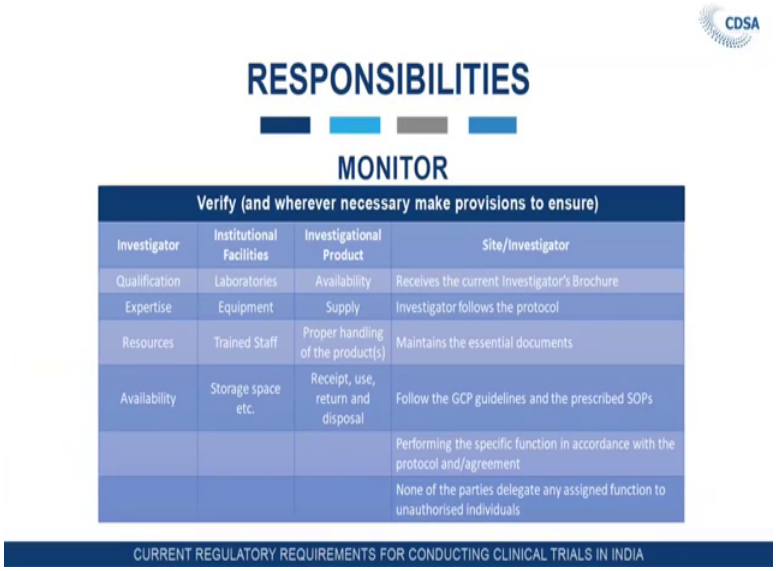

So, the sponsor ensures that there is a monitoring which is a quality control process in a clinical trial. And monitoring is a regular, rigorous and continual process which conduct which is continued over a period of the entire length of the clinical trial. Whereas, audits are compliance snapshots which are conducted by an independent person, whenever, whenever the sponsor feels or as defined in the sponsors SOP. The sponsors audits are usually conducted as I mentioned by independent persons, it can be site, it can be facilities, it can be data, it can be documentation, it can be any areas which the sponsor felt required an audit.

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It is a very important question as who is responsible for quality. Legally it is a sponsor who is responsible for the quality. But please remember quality cannot be the responsibility of one person when there is a multi-stakeholder working.

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But we heard from the father of quality Dr. Edward Deming. He said quality is everyone's responsibility. Now, let us come to a topic which is dreaded by many which is statistics.

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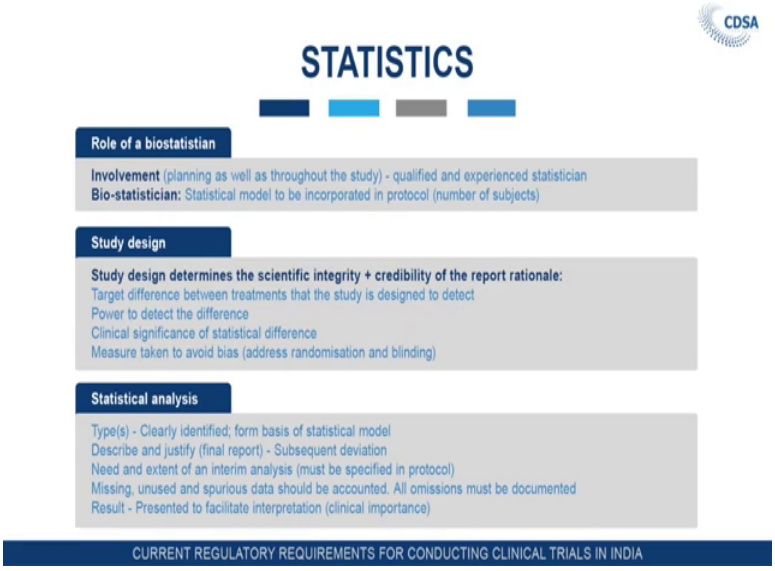

You require a good statistician in your clinical trial. Some time it is very it is too late to repair anything. So, the role of biostatistician is extremely important. The biostatistician should be involved in a clinical trial study from the planning stage, from the design stage and throughout the study till it is ends. Who should be the statistician? Anybody who is qualified, and anybody who is experienced and who has undertaken many of the statistical model which are incorporated in any study protocol to calculate the sample size in a study. The study design should be validated or the study design should have a rationale the study design actually determines the scientific integrity and the credibility of the data or the report.

So, there should be a rationale behind why you want to select a target, what is the target difference between the treatment that is study is designed to detect, what is the power of the study, the power to detect the difference, what is the clinical significance you are looking for the statistical difference. What are the measures you will take to avoid those, how do you address randomization and blinding. These are all part of study design and a trained qualified and experienced statistician is required to help you through this.

The statistical analysis is so important because all the data that you have received now has to undergo this kind of analysis and again a statistician plays a very, very important role. The statistical analysis talks about the types, they clearly identify form a basis of statistical model, they describe and justify in the final report they also describes a subsequent deviations.

The need and extent of an interim analysis when it is required, either during the study or it is specified early in the protocol is done by the statistician. The missing data, the unused data, the spurious data all are accounted. And all the omissions of data must be documented. The results which are presented to facilitate interpretations which are of clinical importance must be handled or must be dealt with by the a trained and qualified statistician.

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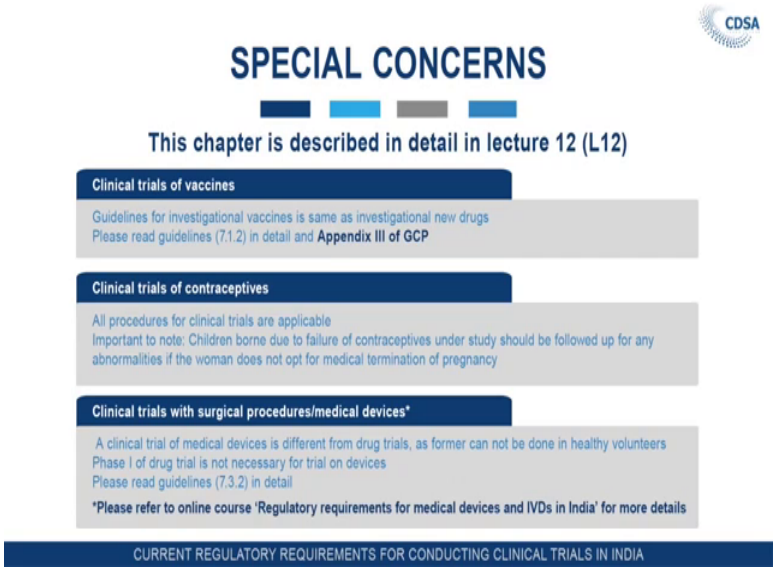

Now, quickly we will go through something special concerns. We have a special lecture called lecture 12 which addresses all the special concerns. So, I in this session will talk very very less about it, because we have dedicated one lecture only called as special concerns. So, that lecture which is lecture 12 will deal about the clinical trials of vaccines in detail.

I will just tell you very very less by telling that the there is a guideline to be followed for all investigational vaccines and it is same as that all investigational new drug. So, please read the guidelines which is provided, and also read the appendix 3 of GCP which has a detailed descriptions. The clinical trials of contraceptives all procedures of clinical trials are applicable whenever you are doing any contraceptive related clinical trial. The important note for this is the any children which are born due to failure of contraceptive during the trial should be followed up for any abnormalities. And if the woman does not opt for a medical termination of pregnancy, it is to be specifically cared for.

There are a lot of clinical trials with surgical procedures and medical devices. Please note that we have a different online course or a new another online course called regulatory requirements for medical devices and in vitro diagnostics in India. Please enroll for the course, please go through the course. And the course will have special address on medical device. For medical device it is not the clinical trial, it is a clinical investigation plan. One should remember that a clinical trial of medical device is not same as that of

drug trials, because here you involved sometimes healthy volunteers. The phase one of drug trials is not necessary for trials on devices. There is a special guideline called 7.3.2 which deals with it in very detail.

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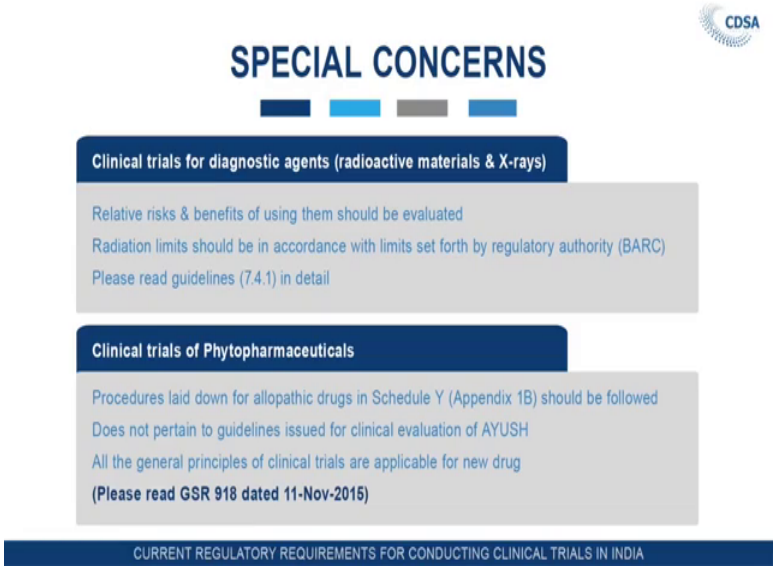

If you go through the clinical trial requirement for diagnostic agents which can be radioactive trials, it can be X-rays, then there are lot of relative risk benefits which the ethics committee should evaluate before allowing such permissions as a radiation limits to be set forth by the regulatory authority can be BARC. And you should read a guideline which is 7.4.1 which has lot of detail information to that. The clinical trials of phyto-pharmaceuticals, you should go through the GSR 918 which was dated 11th November, 2015 for this. There is a various procedures laid down for allopathic drugs in Schedule Y which comes under appendix 1B and you should read and follow those. It does not pertain to the guidelines which are issued by the clinical evaluation of AYUSH, and all the general principles of clinical trials are applicable for a new drug.

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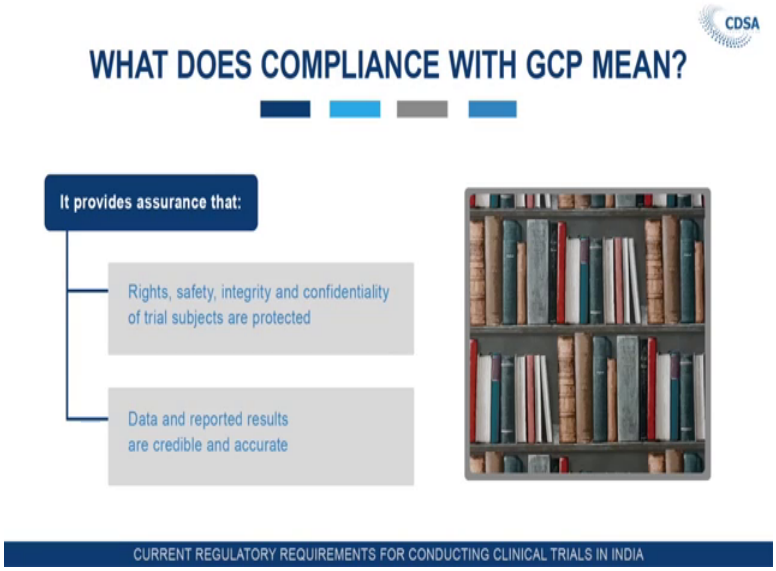

So, how do we, what do we address now, that we come to an end of this. If anybody tells you that are you GCP trained, you say I am GCP trained. When you do a clinical trial and your clinical trial is GCP compliant, what you and at the end ensure. You ensure by giving public an assurance about two very very critical areas the right safety and the wellbeing of the participants are well protected and the data generated from the clinical trial are credible and accurate. The CDSCO GCP 2001, do not address the 13 principles, but I thought of addressing you in very brief.

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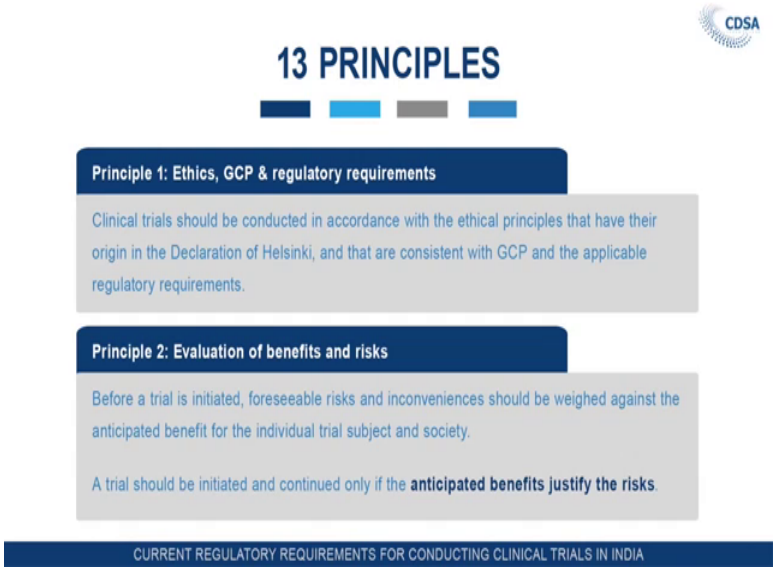

The first principle talks about the ethics, the GCP and the regulatory requirement says that the any clinical trial which should be conducted should be in accordance with the ethical principles and should have its origin from the Declaration of Helsinki. We have the lecture 10 A coming up and this lecture will give you a very very detailed descriptions about the ethical considerations through the ICMR new guideline. Also this course will take you through the evaluation of benefits and risk, you should understand that the clinical trials are evaluated by ethics committee. And before a trial is initiated, a permission is given there are many foreseeable risk and inconveniences which are weighed down and anticipated before a permission is granted. And the anticipated benefit should always justify the risk involved.

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There is always a debate about subject over science and society and that is the third principle. The right, safety and wellbeing of trial subjects should never be compromised, and should never prevail over the interest of science and society. The fourth principle talks about the pre-requisites which we have discussed very early. It says that if you do not have a proper document or proper data of the non-clinical which is regulatory toxicology and animal pharmacology, then you should not be allowed to conduct any proposed clinical trial, because the toxicology and pharmacology data gives you adequate information about the background of this investigational product.

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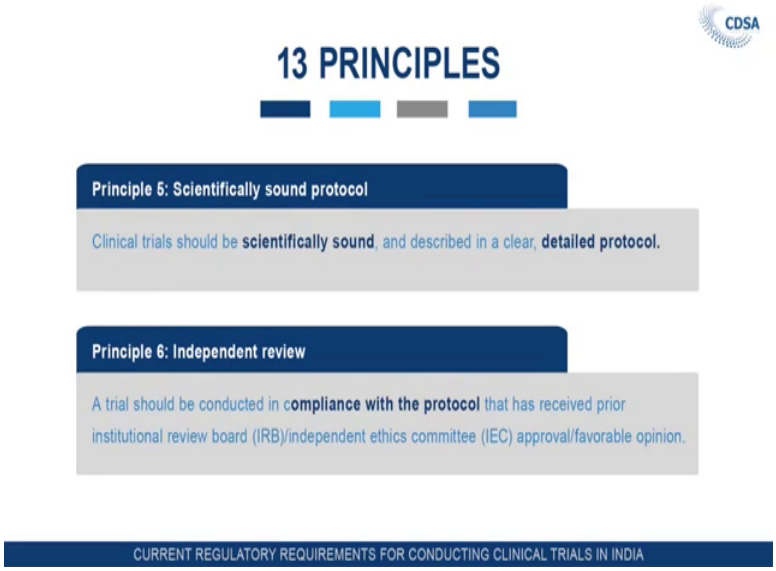

If the protocol the fifth principle talks about the protocol. It says if your protocol is not scientifically sound, it does not have a good study design and has does not have a clarity probably you are doing something wrong. So, a scientifically sound protocol is an extremely important requisite for doing any clinical trial. The sixth principle is extremely important. The ethics committee should be independent. There should not be any conflict of interest or competing interest. A trial should be conducted in compliance to the protocol, and the independent ethic; the institutional ethics committee should be registered to CDSCO who wherever the clinical trial is engaged. There is a special lecture called lecture 10 b which addresses how your ethics committee should be registered with CDSCO.

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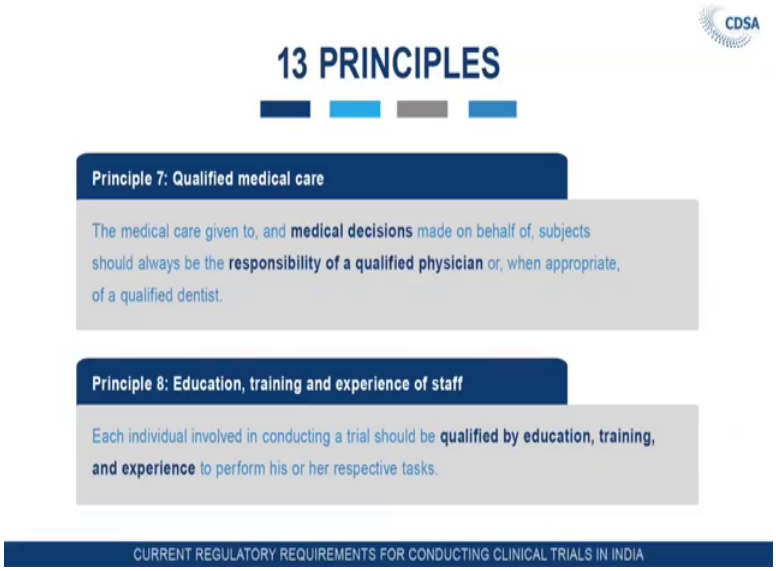

The seventh one talks very important. It speaks about the qualified medical care. The medical care which has given to sub study participants and the medical decisions which are made should be made by a qualified physician in India, it should be an MCI recognized degree and when it is a dental study it should be a qualified dentist. The principle eight talks about the education training and experience, my dear friends the education, training and experience are three different things. You may be educationally qualified, but you have to be trained. And you should possess an experience to perform your task rightfully.

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The lecture nine talks about the informed consent. An informed consent is extremely important. It is the weakest link of the entire clinical trial. Informed consent should be freely given, many people misuse the word or misunderstand the word called freely given. The informed consent should really be informed and we should ask how inform was the informed consent. And every study participants who were involved in the study must ensure that the informed consent form has been discussed in detailed by the study investigator and the team. And they were given an opportunity to ask questions and had the right to either select in a study get engaged in a study or a right to reject. The 10th principle is extremely important when the IC GCP got revised in 2016. This is the only principle which was retouched because record and documentation is extremely important.

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Fidelity of the records and documentation is what the principle ten speaks about. It speaks about that all the clinical trial information which are gathered, handled, stored should be in such a way that you can have a good audit trail, so that accurate reporting interpretation and verification is possible. The principle eleven speaks about very important factor which is called confidentiality. Any study participants who are engaged in a clinical trial, their identity is always protected. They are known by study identifiers or code words, because it is very very important to maintain the privacy and confidentiality of the study participants.

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The integrity of investigational product is the twelfth principle and this is entire clinical trial is of the investigational product. And if the investigational product itself is not having all the physicochemical properties intact or is its integrity is doubtful, then the clinical trial does not make any sense. So, the investigational product should be manufactured in an GMP facility and it should be as per whatever is mentioned in the regulatory document and approved protocol by the regulators and the ethics committee. The last principle ladies and gentlemen is about quality. It says that systems and procedures should be in place to assure quality, what is systems and procedures, they are the SOPs. So, their entire study should have lot of SOPs to ensure that the studies all areas have been addressed.

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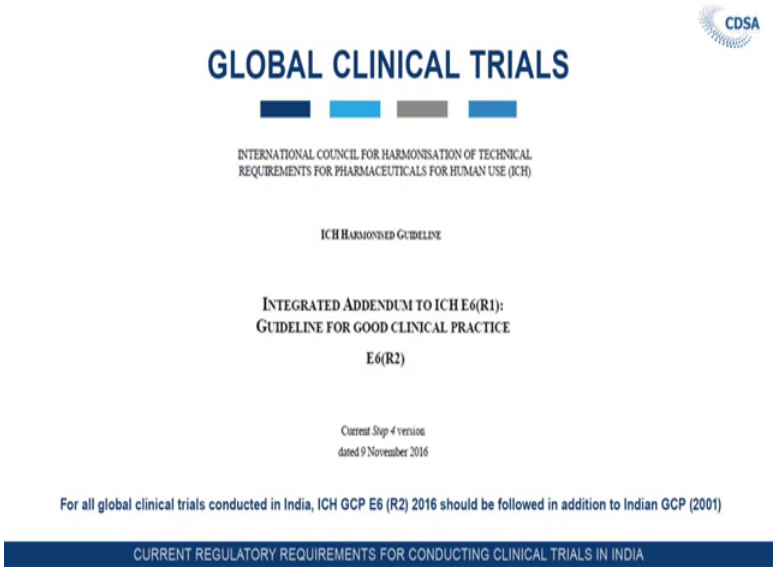

This is only one slide to tell you about the ICH GCP the E 6 which was revised in as R 2 in November, 2016. For all global trials which are conducted in India, it is mandatory that you should follow the law of the land which is the Indian GCP or many people refer it as CDSCO GCP 2001. And you should also additionally follow or show compliance to ICH GCP E 6 R 2, which is 2016.

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Why this ICH GCP, because there are many countries which are conducting clinical trials, and it is a method of ICH countries together to come together, so that they can

standardize the study conduct and requirements among all the countries. So, none of the studies which have been conducted in one country should be repeated in other country. So, ICH started from 1996, it got revised in 2016, it is formed by the European Union, the US and the Japan. And it is developed in accordance with existing standards across US, EU, Japan, Australia, Canada and Nordic countries. ICH stands for International Council on Harmonization of technical requirements for registration of pharmaceuticals for human use.

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You can also read about the WHO GCP which was released in 2002, and it underwent a long series from 1968, 1975 and 1995. ICH GCP also has 14 principles of ethical principles and the last again is the quality system. So, these are all these ladies and gentlemen. And now that you have understood let us try and see whether we can answer some of the questions which we undergone today.

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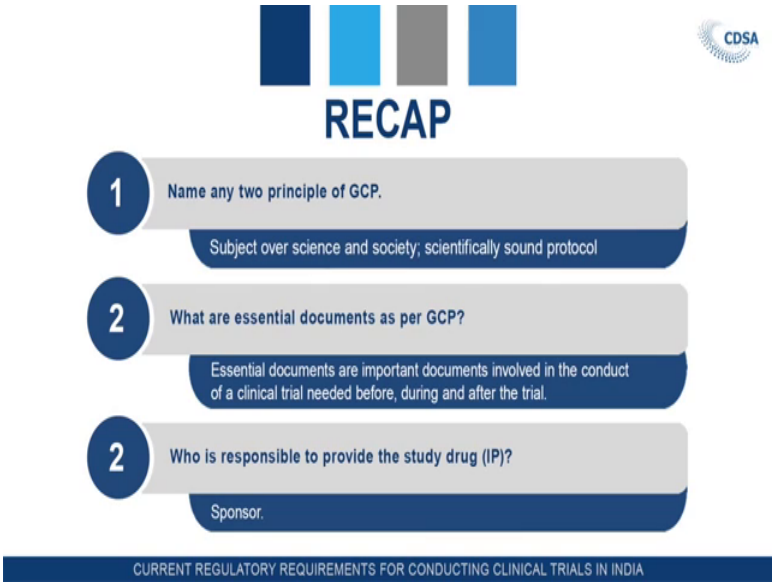

Can you name any two principles of GCP just now which you have gone through, any two, any two ok. For example, the principle one principle speaks about subject over science and society you can say, another can be the protocol the scientifically sound protocol you can say anything you can say education training and experience even which did we speak about something called essential documents. If I not, then I should not ask this question, but this is a very good way to answer something which has not been touched.

Essential documents as you know are very very important documents. The name itself says essential documents. They are the documents which are involved in the conduct of the clinical trial before, during and after the trial. This can be protocol, investigation brochure, the regulatory approvals, the CRF case record forms, the clinical trial liability insurance and all the documents have been listed at the end of the GCP guideline. Can you tell me who is responsible to provide the study drug that is investigational product for a clinical trial study. Yes, you are right, it is the sponsor it was told that it was sponsor's responsibility.

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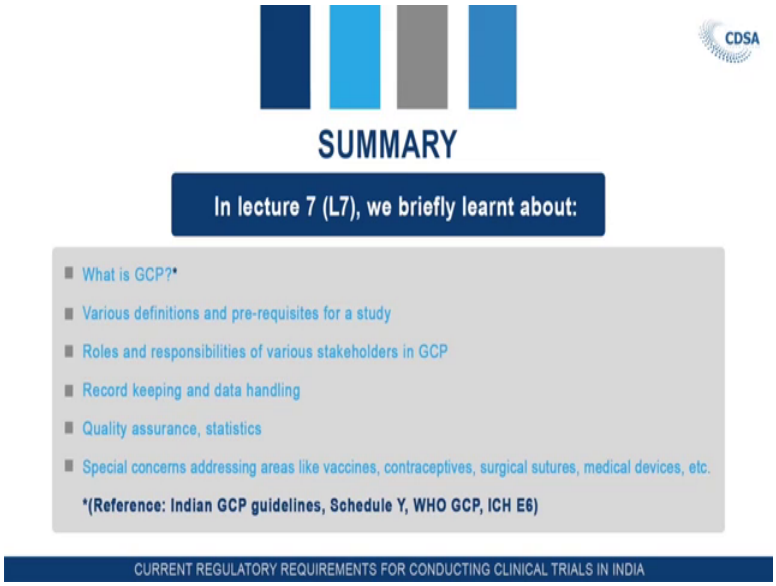

So, that is it ladies and gentlemen, my dear friends in today's lecture, lecture 7 we understood about what is GCP, why we should study this, what are the various definitions, the pre-requisites of the study, the roles and responsibilities of various stakeholders like investigators, sponsors, monitors and ethics committees. We understood what is record keeping and data handling. Quality assurance statistics we also touched upon the special concerns addressing areas like vaccines, contraceptives, surgical sutures, medical devices. There is all which we spoke were actually from the Indian GCP guideline 2001.

Thank you so much for listening to this today's lecture and I hope you enjoyed the lecture.

Thank you and [FL] and [FL].