Current Regulatory Requirements for Conducting Clinical Trials in India

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Lecture – L10A
Ethical Considerations

Welcome to the 10th lecture under the course Current Regulatory Requirements for Conducting Clinical Trials in India. Now, this will actually concentrate on the Ethical Considerations which are highlighted in the national ethical guidelines for biomedical and health research involving human participants and children. Of course, the disclaimer is that this presentation is based on my expertise and experience and represents only my views.

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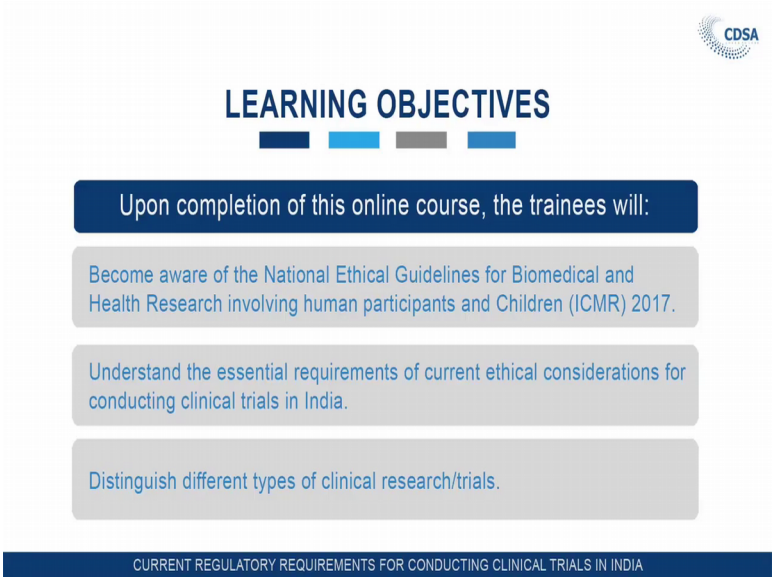

Learning objective of this particular lecture is that upon completion of this online session the trainees will become aware of these national guidelines, understand the essential requirements of the current ethical considerations for conducting clinical trials in India. And, also distinguish between the different types of clinical research and trials.

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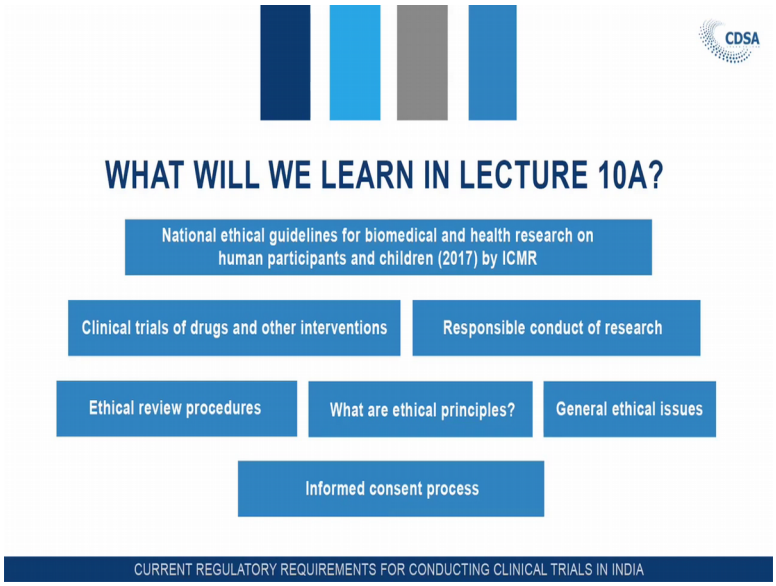

What will we learn in this lecture of course, it is based on the guidelines; but we will be talking about the general principles, the general ethical issues, the responsible conduct of research and concentrate on ethical review procedures as well as informed consent process and highlight what is written in the clinical trials section of this guideline.

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To start with the first guidelines in our country ethical guidelines was released in 1980, then we have the first division in 2000 and the second one in 2006 and the last one released in October 2017. Now, this latest guideline actually has 12 sections.

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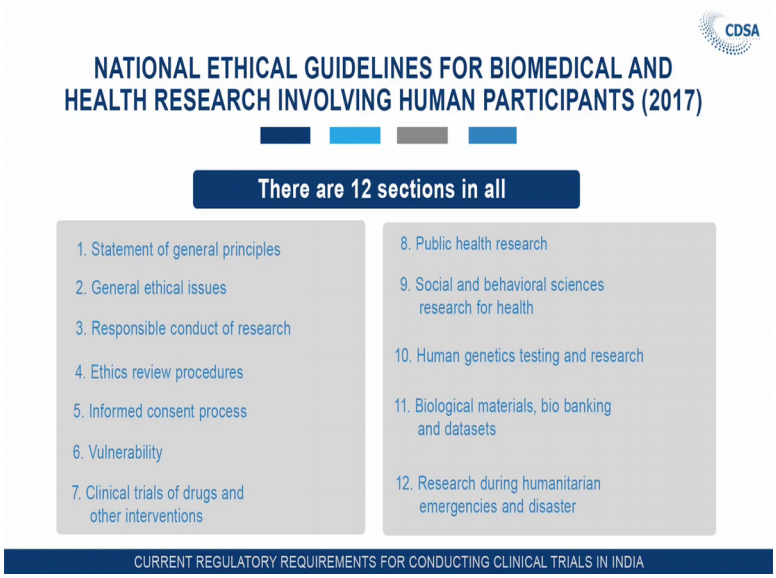

What you see in green are the new sections which have been added to this revision and also what you see in the red is actually it was already there in the 2006 version, but it has been expanded to such an extent that it require to be incorporated in separate section as it is.

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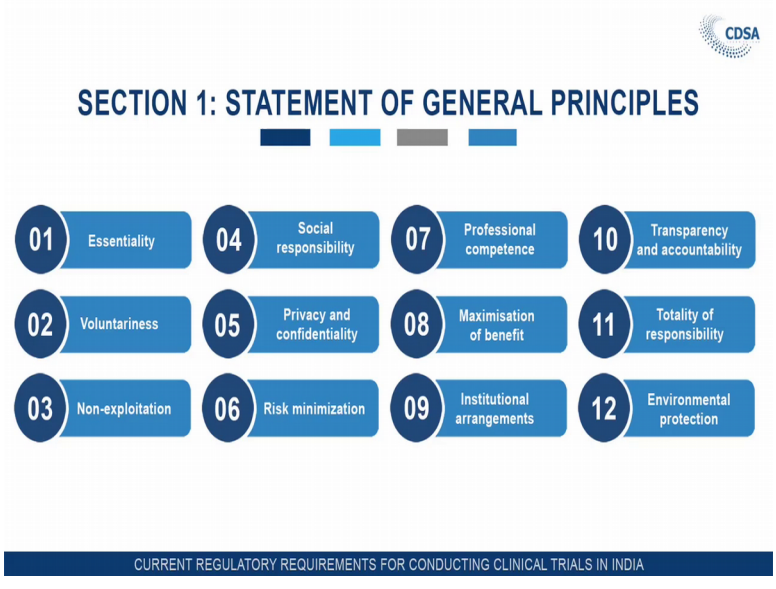

So, coming to the statement on general principles; there are 12 general principles. The first one on essentiality that is based on science which would be not harming the participants the whether the science itself; whether the research itself is essential to be

done or not. Voluntariness is based on the voluntariness of getting enrolled in a research, non-exploitation is self explanatory. Social responsibility means that there should not be any rift created in the society because, of one's research project.

Privacy and confidentiality will talk about it later and naturally one has to minimize the risk. The people who conduct research should be professionally competent and as far as possible one has to maximize the benefits that can come to the participant. They have to be institutional arrangements for allowing such research to be conducted in the institution. It has to be transparent and accountable and totality of responsibility is that the institution, the sponsor, the ethics committee, the researcher they all come into this fold they are totally responsible for whatever research they are conducting.

Environmental protection is important because new science has brought in a lot of elements which can actually pollute the environment. So, you required to have safeguards for this. The ones that you see in bluish green are the new principles that have been added to the 12 principles that were actually highlighted in 2000 and 2006 versions.

Now, coming to general ethical issues they have been described under 11 sub heads of which benefit risk assessment has been elaborated more, distributive justice has been added and importance of community engagement has been highlighted. So, these are what you see under green colour; the rest of it actually it describes very briefly about what you mean by informed consent process privacy and confidentiality payment for participation. Compensation for research related injuries, ancillary care, conflict of interest, selection of vulnerable and special groups and post research access and benefit sharing.

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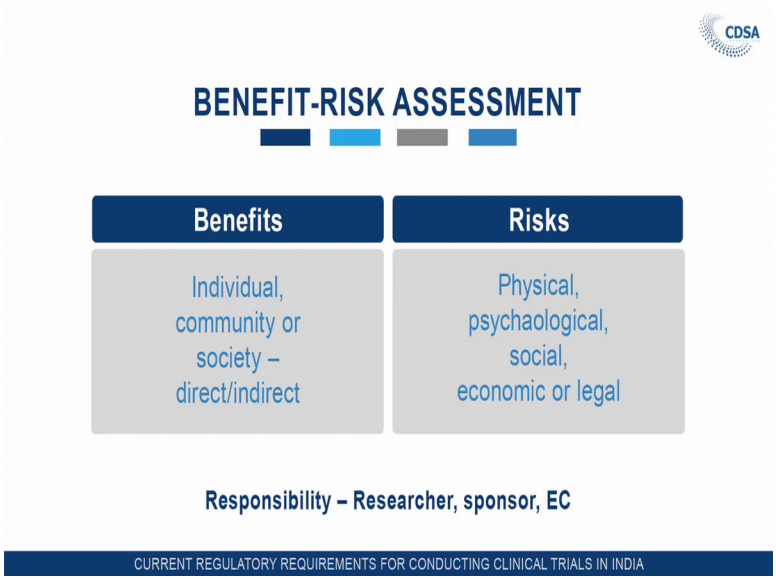

When you come to benefit risk assessment on one hand benefits can come to not only the individual, but also to the community or society and these could be direct or indirect. When we talk about risk is generally the physical risk that we pay attention to, but there could be actually psychological, social, economic or legal risk as well. So, one will have to have safe guard for that. So, this is the responsibility of all the three researchers, sponsors and ethics committees.

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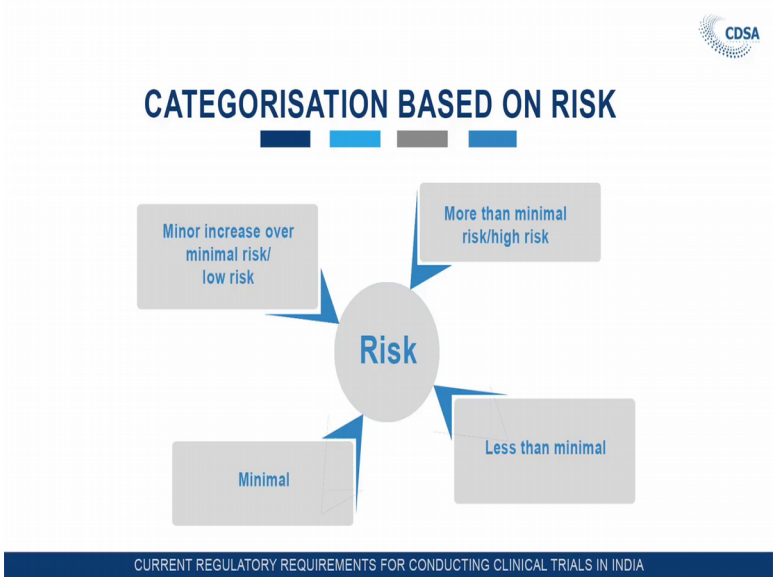

Now, if you want to base the risk on the level magnitude and probability then we classify them into four that is less than minimal, minimal, minor increase over minimal risk, more than minimal. Here the benchmark is minimal risk anything which is not identified person or data comes under less than minimal. Minimal risk is what you can encounter in daily routine life. Minor and more than minimal are actually when you use invasive procedures, but there could be a difference on that scale; one could be low risk on the other side of the scale could be very high risk.

So, which comes under low risk is like drawing blood from a healthy individual say 5 ml let us say minor increase over minimal risk, but if you were to do some other invasive procedures then it will come under more than minimal risk. Now, this classification is actually helpful for the ethics committees also because, the type of review that the ethics committee would do will be based on the risk categorization.

Coming to inform consent process it is the process of how you communicate the relevant information to the participant and ensure that the participant understands that; at the same time you have to see that the participant voluntarily gets enrolled. And, whenever the participant is not able to give you either due to legal position or due to cognitive deficiencies legally authorized or acceptable representative plays a big role in giving that consent.

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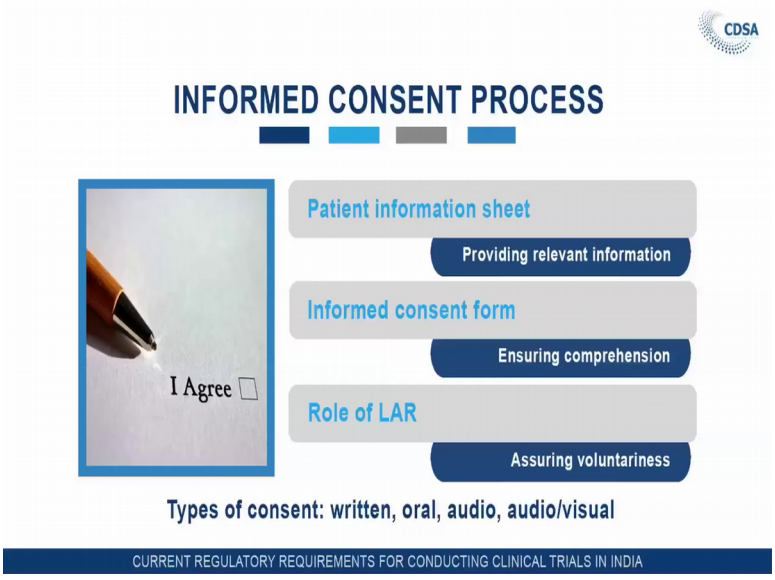

Now, the different types of consent are written oral audio or audio visual. When we come to privacy and confidentiality one should remember that privacy is actually the individual's right to protect that information, but there could be limitations to this. For example, if there is risk to oneself that is suicidal ideation or risk to others public health risk or when required by the court this privacy can be breached.

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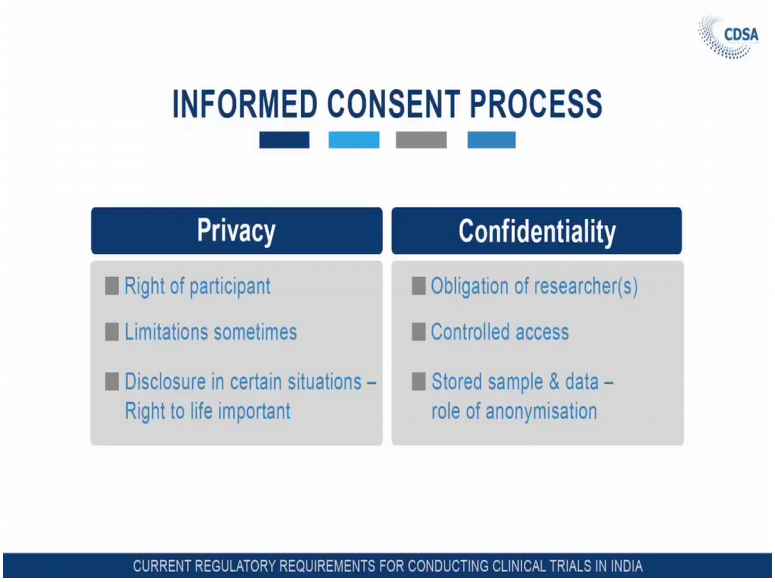

Confidentiality it is actually the obligation of the researcher and there has to be controlled access to the information which is gathered by the researcher and this is especially more important in case of stored sample and data. So, the role of anonymisation of the sample as well as data very important which we will talk about a in an subsequent slide.

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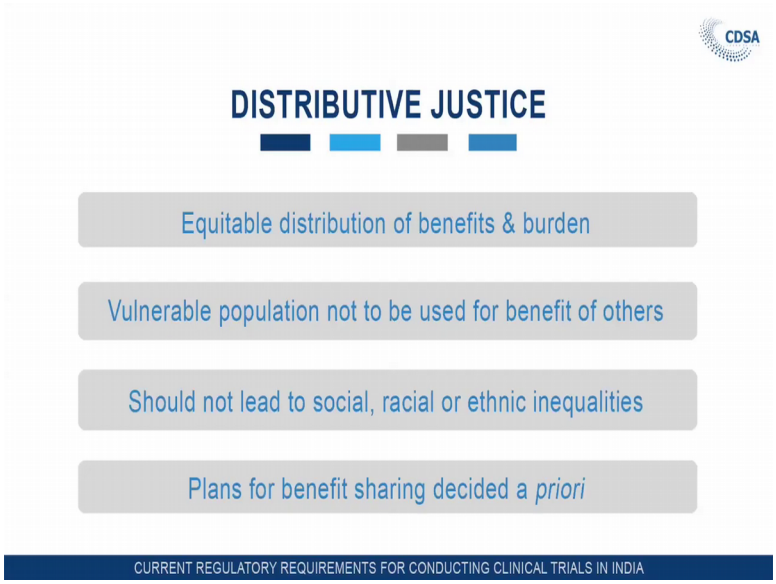

So, coming to distributive justice; to each according to the need that is the philosophy behind this and it means equitable distribution of benefits and burden. Because, if you are going to use vulnerable population they should not be used for benefit of others; at the same time if there is a beneficial outcome they should also be a part of that benefit and it should not lead to any social, racial or ethnic inequalities. And whenever there is a benefit sharing aspect it should be decided a priori before initiating the research.

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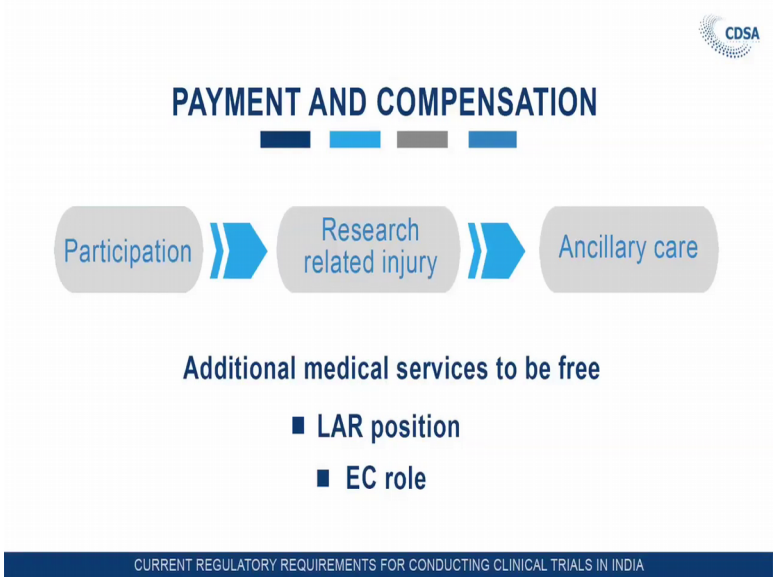

When it comes to payment and compensation; payment for participation is loss of wages, travel expenses and incidental expenses whereas, research related injury actually depends on the quantum of the injury. And, when it is non research related injury it is called ancillary care. Whenever additional medical services are to be used in a study they should be free of cost for the participant. Here whenever the money plays a role you have to be very careful about the legally authorize representatives position, many a times you know it could be exploited.

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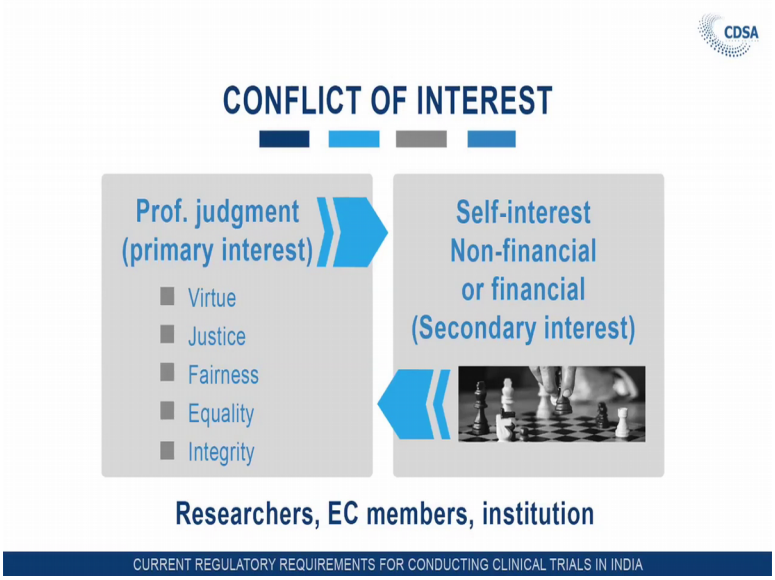

Now, ethics committees rule in this instance is very very important and when you talk about conflict of interest is a primary interest and a secondary interest. Primary is the professional judgment for carrying out the research, the values, the justice, fairness, equality, integrity are all part of that judgment process. But, if these are influenced by self interest, non-financial or financial then this is called secondary interest.

There is nothing wrong in having this, but one has to declare that whether you are an ethics committee member or researcher. So, this also brings in the role of institution because, sometimes the institution may have a conflict of interest in pushing through some sort of research in which they are actually interested from the financial point of view.

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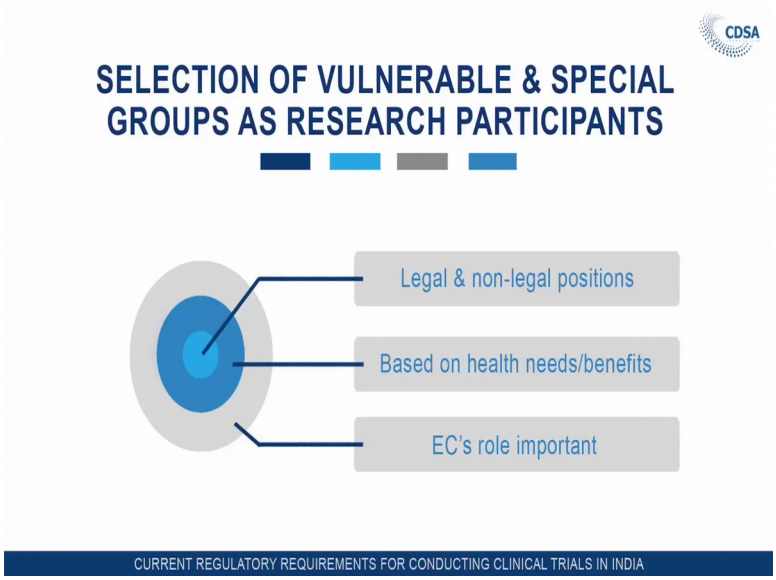

When it comes to selection of vulnerable and special groups, when we talk about special groups we mean women and children. Now, here they may have non-legal position for example, children cannot give consent. So, they do not have a legal position to give consent. So, one has to see that and people who are unconscious or cognitively impaired they also would require somebody else to give consent on their behalf; such research should be actually conducted only if it is addressing their health needs and or a benefits come to them. So, here again the ethics committees role is very important.

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The other general issues ethical issues that are discussed in this section is about investigator initiated research and student research. Community engagement is very important when the participants are drawn from particular community. How you communicate research findings is also equally important and post research access and benefits sharing; as you may find these aspects being repeated again and again in several other sections.

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Coming to the responsible conduct of research, what it means? It is actively promoting honesty, accuracy, efficiency, objectivity and transparency in research. Actually this should be otherwise known as responsible practice of research by adhering to ethical principles and professional standards. Now, these are various points that have been elaborated in this section.

When we talk of values of research all that had been described earlier stands true. Policies is anything to do with animal research one has to follow the ethical principles regarding that, if it is human research one has to follow the ethical guidelines that are prevalent in the country and any regulations pertaining to this also have to be followed. When you collect data it is very important from where you collected. So, you need you may need authorization permission for that.

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And, when you record how you preserve it, how you archive it is also equally important. The person from whom you get the knowledge actually the owners of that knowledge and what you have collected, you have collected as a custodian of that knowledge.

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So, when you review and report research it has to be honest, transparent, public I mean results which are to be published and when you talk of publication the authorship issue comes in.

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And, the ICMR guidelines actually adhere to the ICMJE guidelines, that is the International Council for Medical Journal Editors. Institutional or department policies if they are in place they have to also be, followed peer review itself has certain issues. When an especially when you are coating your own papers etcetera is very important how you go about it and these are described in the section. Registration of clinical trial registry is also very very important we will come to that later.

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Now, how do you handle research misconduct or scientific misconduct? You need to have policies and the institution is supposed to have those policies in place. Any investigation that may have to be conducted should be timely and it one should also see that the whistleblower as well as accused have to be protected. Because, unless the accusation has been proved the accused has to be protected because, there could be false allegations as well. And, when we talk of research misconduct the three elements: fabrication, falsification, plagiarism come into play. We will not going into detail about that, it is all given in the ICMR guidelines.

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Registration with clinical trial registry of India is mandatory for all regulatory clinical trials whereas, it is voluntary or any other types of research. But, when you actually register there are number of elements that you have to answer. If they are unanswered your proposal will not be registered.

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When it comes to collaborative research one should understand that the collaborative partners are supposed to function as equal partners, one should look out for any elements of exploitation or harm and any benefits of burden should be equally distributed among them.

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It is the responsibility of the ethics committee, researcher and institutions to see that they are socially and culturally contextualized and the research has the required expertise, the

participants are protected well. And, there is participatory designing among the partners and it safeguards interest of the participants researches as well as the institution.

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When it comes to international collaboration one should adhere to the guidelines and the regulations that are required to be followed in India. So, who owns the samples, analysis, dissemination all these elements come under that. There has to be if any material has to be transferred there has to be a material transfer agreement between them and also MoU which the health ministry's screening committee would go through in approving the research.

Coming to the fourth chapter on ethical review procedures there are number of items which have been highlighted there and it is a good guidance for many ethics committees for reviewing proposals. When you talk about ethics committee one should know how it is structured and whether the members are competent enough to be members of the committee or reviewing the proposals.

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They should know how to function also and their decision should be independent of the management's influence. So, that why we say independence, but it is a fact that many a times there is a subtle influence on them. So, one has to be as far as possible independent of such influences.

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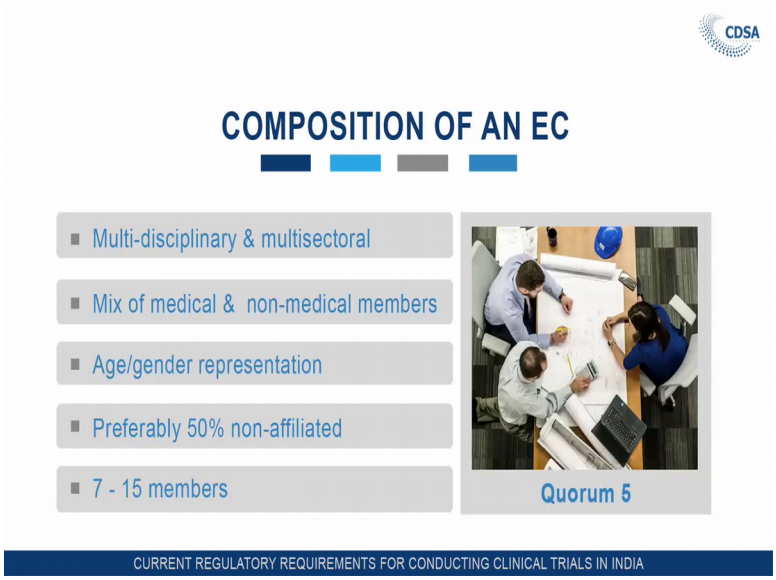

The competition of course, it has been multi-disciplinary, multi-sectoral age and gender balance, 7 to 15 members and they have to have at least 50 percent non-affiliated members. And, also there should be a mix of medical and non-medical members. The

quorum has to be 5, but for regulatory purposes this quorum has to be a fixed representation of clinician, basic scientist, legal expert, social scientists and group of people coming under that and the lay person.

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Now, you talk special situations in ethics review, an institution if it has got many proposals it can have more than 1 ethics committees. And, if an institution does not have or agency just now is a small one it does not have an ethics committee, it can use the ethics committee of another institution which would be called as post institution.

For multi-centric research there could be a common ethics committee, I will not going into details about that and for stem cells you need to have institutional on stem cell research which would review the proposal first and then only it has to go to the ethics committee for the ethical aspect to be removed. Independent ethics committees are actually commercial ones which charge for review of each proposal.

They are only allowed to see BA BE's studies from the regulator point of view, none of the other proposals which come under the purview of the drug con controller general of India can be reviewed by the independent ethics committee.

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The role of ethics committee to actually safeguard the rights safety and wellbeing of participants and all type of biomedical and health research can be seen by the ethics committee whichever it pertains to not humans, but their biological material and data as well.

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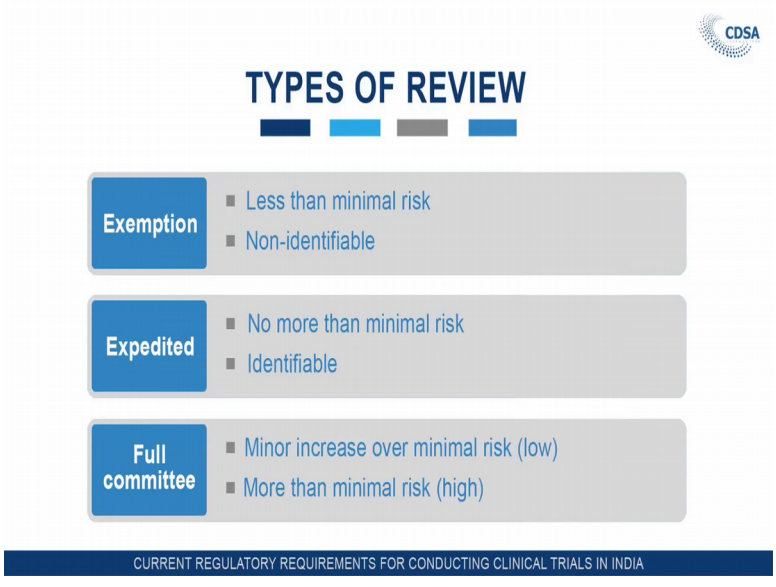

What are the types of review? As I have told you earlier it depends on what type of risk is being encountered in a particular proposal. All those which fall under the category less

than minimum risk can be exempted and as I overemphasized the fact that it should have known identifiable information pertaining to persons or data.

When there is no more than minimal risk say minimal risk there is identifiable information there and the harm would be something which may encountered in daily routine life. These go under the process of expedited review, anything else minor increase or more than minimal risk go to the full committee for review.

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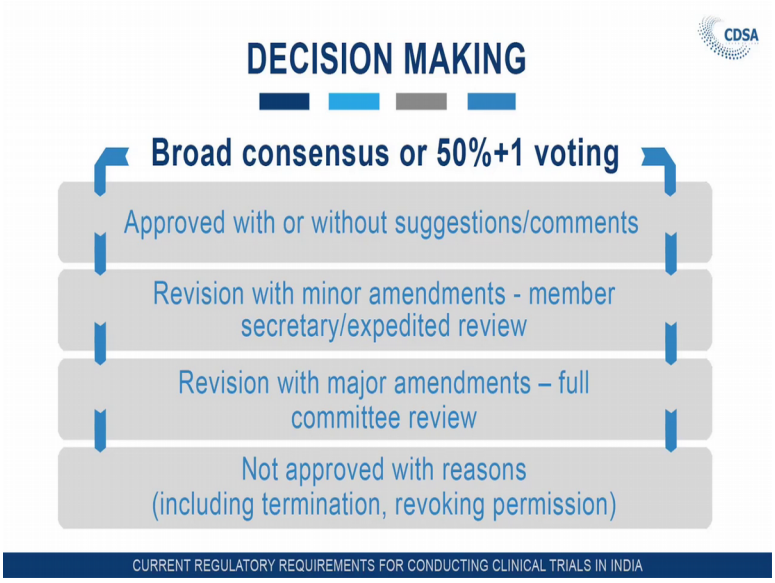

Now, how is the decision made? You either approve a proposal with or without suggestions or you give revision with minor amendments and revision with major amendments. These are important because, the one with minor amendments go to expedited review and the one with major amendments go for full committee review. And, if you are not approving a proposal you have to give the reasons including if you have terminated the project or revoked permission there also you have give reasons.

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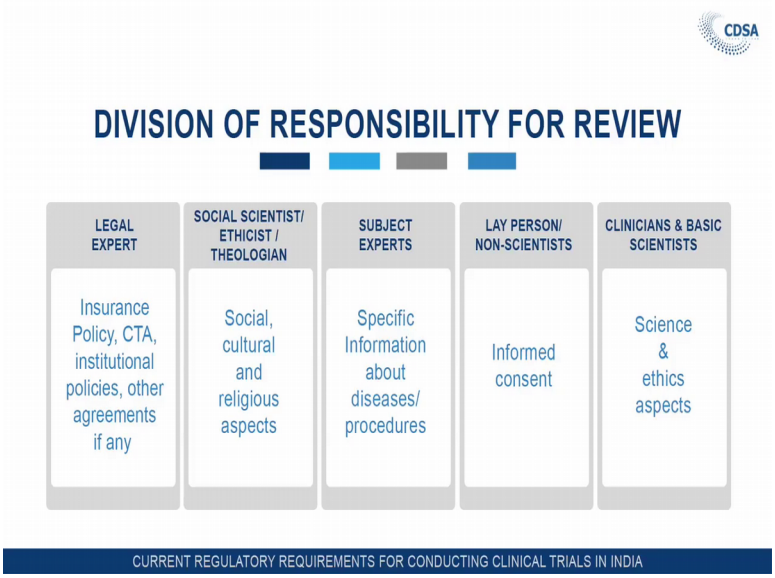

Now, how do you divide the responsibility? The legal expert each member has a particular role to play. The legal expert will look into the legal documents like insurance policy, the clinical trial agreement, institutional policy and any other arrangements if they are there. Social scientist will look at the social cultural and religious aspects. The subject experts would be giving information to that particular aspect in the proposal for which they have been invited to give comments, and the layperson and non-scientist a very very important members of the committee to comment on the informed consent document.

The clinician on the basic scientist of course, would actually give the scientific not only the scientific comments, but also on ethical aspects if any.

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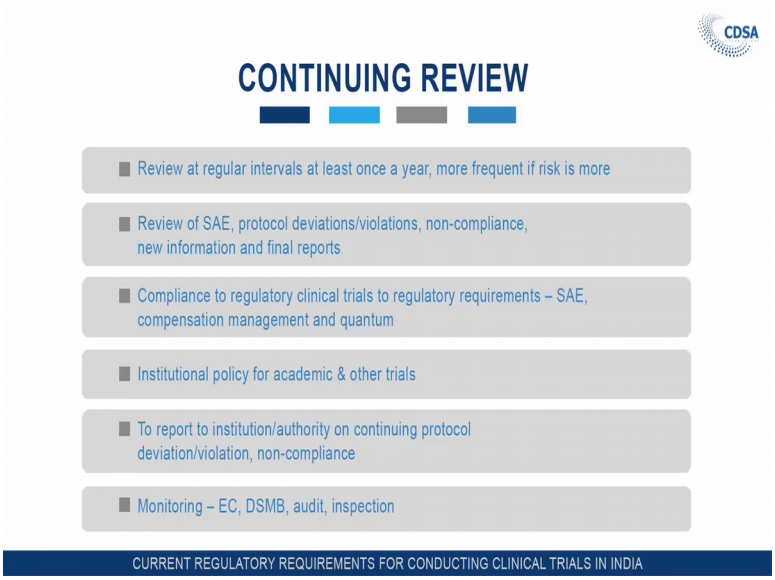

Continuing review is important because; and it is not enough if you just have the initial approval what we say the initial review. So, at regular intervene one has to keep on reviewing the progress at least once a year or more frequent if the risk is more. And, review of severe adverse events, protocol deviations, violation, non-compliance, new information and final reports is all done under the head containing review.

Compliance regulatory aspects as well as guideline etcetera are also part of that especially when it comes to severe adverse events, compensation management and quantum, what quantum has to be given is a major task of the ethics committees. Any institution policy for academic or other trials are also reviewed during this process. And, any violation etcetera which concerns the ethics committee can be reported to the institution or the authority. Monitoring is another aspect which the either the ethics committee the data safety monitoring board, auditors or inspectors do is an important aspect to keep the quality of research that is going on in an institution.

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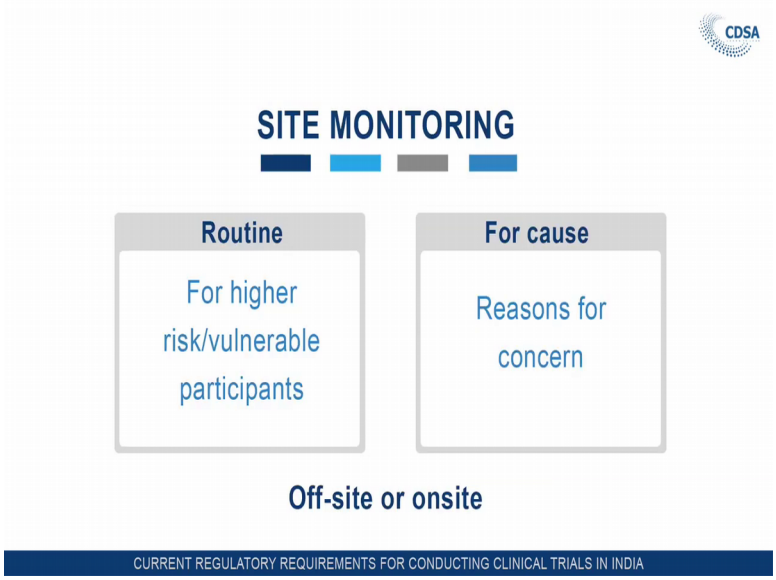

What is site monitoring? It can be routine or for cause and this could be off site as well as onsite. When it comes to record keeping it is an important aspect of ethics committee functioning.

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All documents and communications have to be dated, filed and preserved as per its SOP. Confidentiality has to be maintained who will have access, how do you divide them into active, inactive files, record whether they are hard copies or soft copies have to maintain for define period as it has been described in the SOP. And, it should be accessible for

inspection as well as we have also actually mentioned about electronic storage if it is feasible.

Registration of ethics committee is which review the regulatory clinical trials under CDSCO rule 122 DD have to register with CDSCO. And, this registration is valid for 3 years. Accreditation of ethics committee is to maintain the quality of the ethics committee functioning and also it helps to strengthen protection program, it also encourages the institutional commitment to scientific and ethically sound research with continuous improvements.

There are three agencies which actually do this two foreign that is the (Refer Time: 26:03) and SETQAA and the national one is NABH which actually certifies an ethics committee as accredited or recognized one. So, coming to 5th section on informed consent process as we had I have already described what it means.

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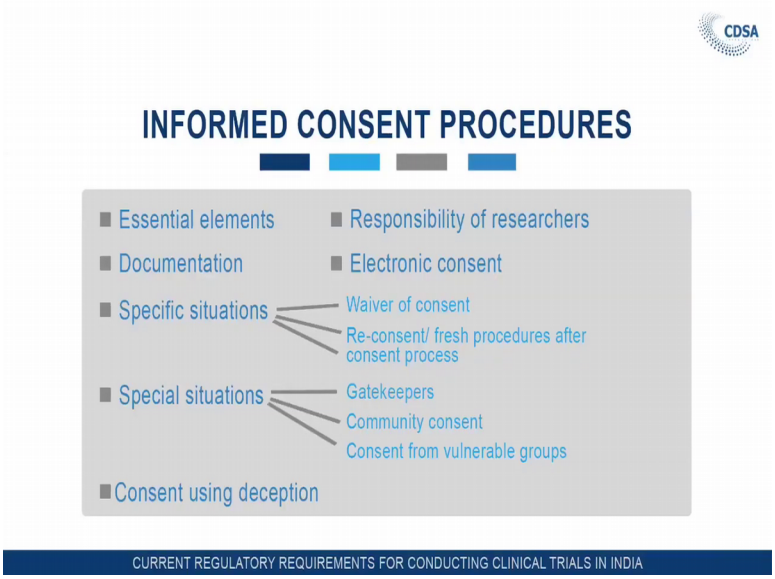

One needs to have the essential elements described in the informed consent document without that it is not a complete document. So, this is responsibility or researches as well and all these have been described in great detail ICMR guidelines.

The electronic consent process which is more getting more problem prevalent now has also been described there. And, the special situations when you can be waiver of consent have re-consent of fresh procedures after consent process and how in certain situations

you take permissions of the head of that particular institution called the gatekeepers; if it is a community the community consent and vulnerable groups consent from them as well.

There is also I mentioned of consent using deception will come to that little later.

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The types of consent of course, if the participants is a literate person, it is written and the if the person is illiterate it is thumb impression or in the case of oral consent in this instance you need to have an impartial witness. In both cases you can also have audio visual recording of consent process.

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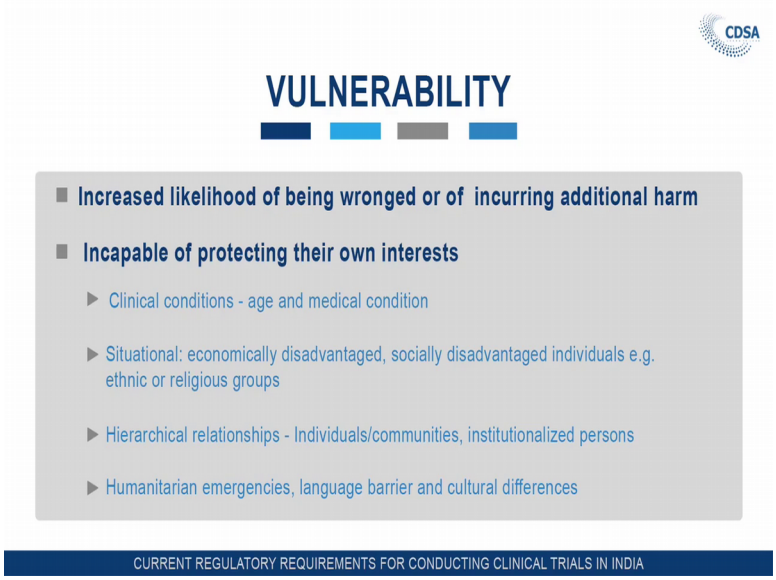

Coming to the 6 section on vulnerability these are people who have been actually wronged many times. So, they have increased likelihood of being wronged or of incurring additional harm. They are not able to protect their own interest due to various conditions, it may be clinical condition or situational like if they are economically disadvantage or socially disadvantage. Or, they could be hierarchical relationships where they have reduced autonomy and this may pertained to individuals as well as communities co institutional persons.

In humanitarian emergencies a language barrier and cultural differences again there is a lot of problem in obtaining truly properly administered informed consent. Now how do you manage this?

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Whenever you do research on vulnerable population, it should directly answer their health needs because they also have a right to be included for benefit in research. An EC should actually ensure safeguards, the researchers is also expected to provide that and if the researchers has not done that the ethics committee has to ensure that.

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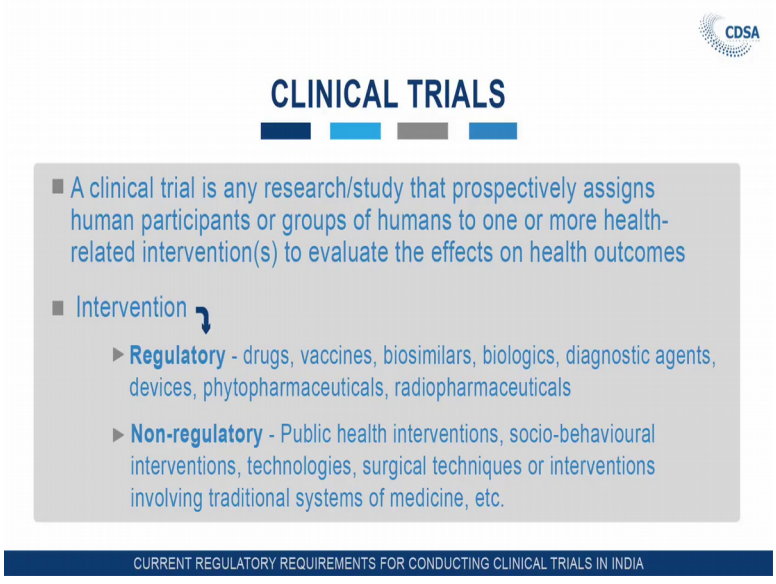

Coming to the 7th section on clinical trials of drugs and other internet interventions one should understand that clinical trial is any research or study that prospectively assigns

human participants or group of in humans to one or more health related interventions to evaluate the effects of health outcomes.

Now, these interventions need not be only regulatory in nature so, it can be non-regulatory as well. So, under regulatory we have the drugs, vaccines, bio-similars and so, on; under the non-regulatory you have public health interventions, social behavior interventions, technologies etcetera etcetera.

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So, there are a number of points actually described under clinical trial, it will be difficult to go each and every aspect of that.

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But the general principle pertaining to clinical trials have to be followed in all these cases.

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One should understand that clinical trials could be regulatory or non-regulatory; non-regulatory means it can be called academic or investigator initiated. Now, any new chemical entity, new indication, new dose, new formulation or new route of administration would come under the purview of regulatory authorities according to rule

122 E. There is a commercial objective behind that and any compensation for injury resulting as a in the research is the responsibility of the sponsor.

Whereas, for the same indication if it is done in an academic institution of purely academic interest the ethics committee has to inform the CDSCO about it. And, 30 days NOC from CDSCO is expected before the final approval is given and this is as per GSR 311 E dated 16 3 2016. The institution however, is responsible for the quality of data that is generated safety of the intervention and the compensation issues, coming to 8th section on public health research.

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Now, we have a number of points under this observational research experimental studies and so, on. Informed consent in each instance would be different verbal, oral etcetera and ethics committee is role is very very important in such instances is also the conflict of interest. The 9th section deals social and behavioral sciences research for health. Now, here the most important aspect is about deception in studies used in studies.

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So, the informed consent process can be very challenging; you have three types active, incomplete disclosure, authorized. The responsibility of the researcher is to actually disclose an aggregate data as de briefing at the end of the research project. The safety of the participant is important always, but also the research teams many a times in such situations. So, they also need protection and training before hand in order to protect them from the harm that could ensue as a result of the approaching the parties whom they interview.

Section 10 pertains to the human genetic testing and research, we should be aware of the fact that there is a very thin line as in public health research between service and research in this particular area.

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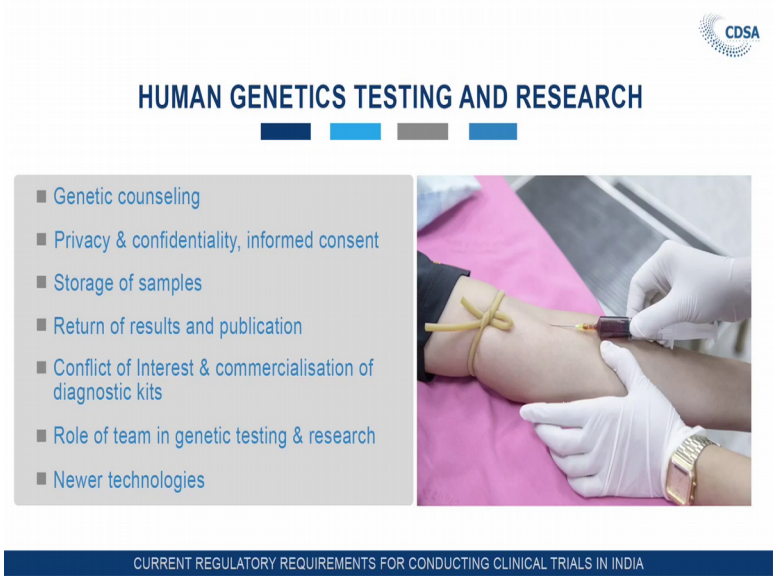

And most important aspect is that there has to be genetic counseling in place before you actually initiate research in this area. Newer technologies like Chinese experiment of designer babies is something which you have heard recently, the storage of samples return of results are also equally important. Section 11 deals with the biological materials by a banking and data sets, here also one has to be very very careful about who owns the data, who is the custodian and when can you use the same material for a secondary use; these are important aspects and how do you convey the results.

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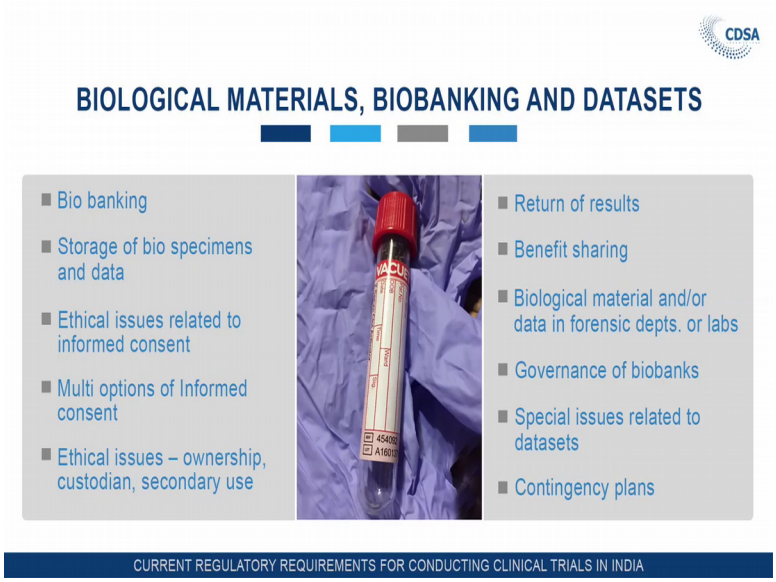

In some cases you may not be able to convey that, it all depends on how linked the data is or unlinked the data is. Again here we mean that if it is totally unlinked the aggregate data should be provided at the end of the project for developing strategies. Benefit sharing is another important area and security of data sets is something which is question these days very very much. There are any software available, but still with all artificial intelligence coming into play when really does not know how to protect such data.

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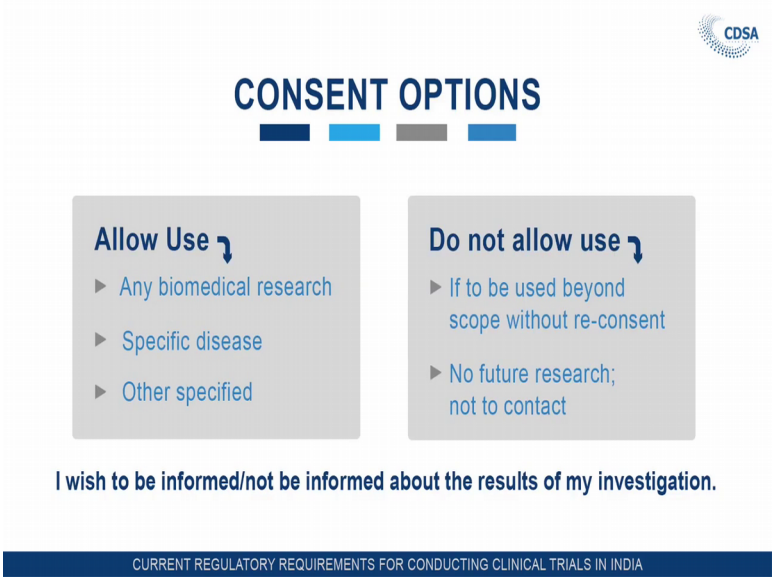

When you take consent in such instances you have to ask whether it is for any biomedical research, that they would allow the use of their samples or only for specific disease or any other specified research options. They should be given the choice to say that we do not allow use of our samples or data, if it is beyond the scope without taking re-consent from us or we need not consent for any future research or we do not have to be contacted at the end of the research.

So, that element also has to be part of the document; I wish to be inform not to be informed about the results of my investigation. Coming to the last sectional research during humanitarian emergencies and disasters we know very well the disasters that have happened in our country.

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There could be natural disasters as well as manmade disasters; the pictures show them very well the recent Kerala floods. For example, Ebola which our country has also has actually faced diseases like Nipah virus disease. So, one has to be very careful when one designs research on these aspects. One can actually have preemptive research preparation and be prepared for such an eventuality and get the ethics committee approval before hand. But, what happens in the situations are people are shell shocked and informed consent process can be quite challenging in the circumstances.

Whenever there is an international participation involved one has to be very very careful about the aspects regarding the stigmatization or benefit sharing etcetera.

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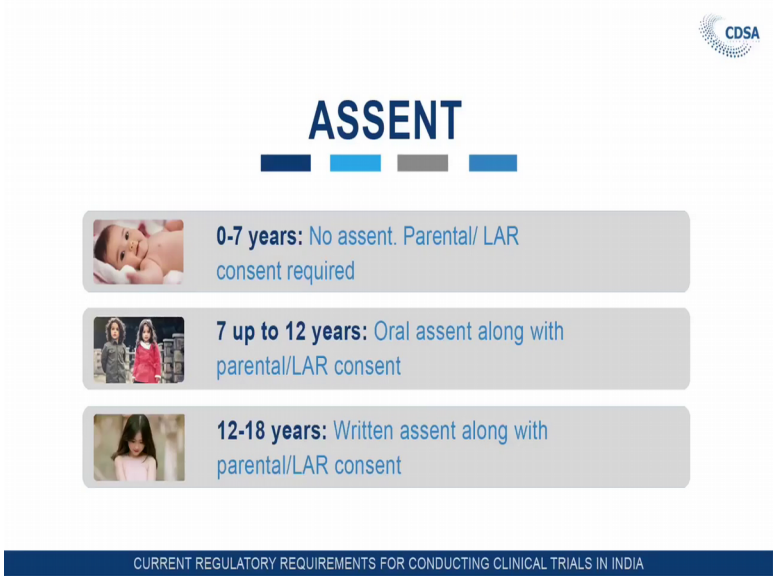

Coming to research on children 0 to 7 years there is no assent, only parental and legally authorized acceptable representation of consent in such instances. 7 to 12 years oral assent is required along with parental and LAR consent, 12 to 18 years written along with parental and LAR assent is to be taken into account.

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If a child refuses that child cannot be force to enroll in a study. There are other easier methods when or points to be taken into consideration when you collect samples from children.

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It has to be age and a body weight related sample drawing and always try to substitute with lesser in basic strategies for example, salival swab would be much better than more inclusive method. And, the timing of collection can be combined with when you draw the sample for routine care it can be combined with that. Appropriate facilities and material should be there and if there is pain one should provide the pain relievers as well.

And, it is a good practice to have a log book where you actually timing the samples and the number of sample sampling attempts that have been done in the process which defines the expertise in drawing samples in a particular case. In order to actually provide the safety measures to avoid such instances.

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Now, for a few questions: which are the latest ethical guidelines for human research released by ICMR and when? Yes, they are the national ethical guidelines for biomedical and health research involving human participants and for children in 2017. Is it mandatory to register the clinical trials in CTRI? Yes, it is mandatory for regulatory clinical trials.

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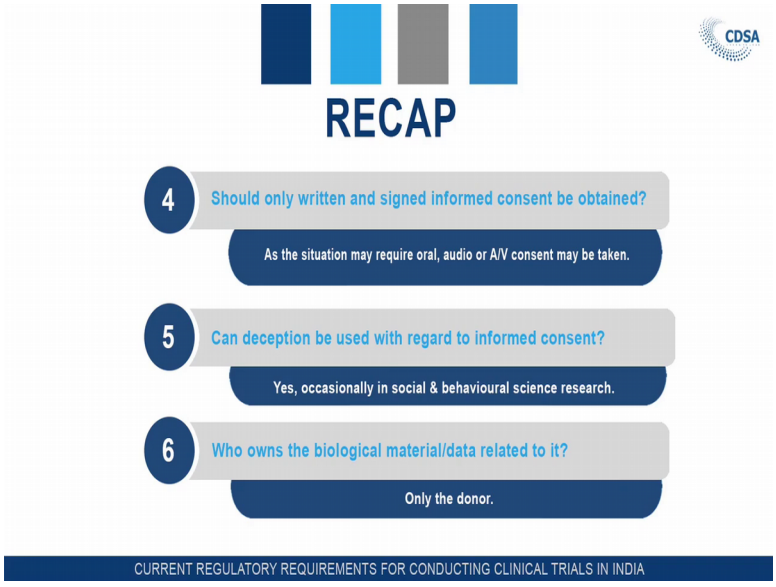

Is it mandatory for ethics committees to seek CDSCO registration? Yes, it is mandatory to seek CDSCO registration for ECs reviewing regulatory clinical trials. Should only

return and sign in form consent be obtained? As a situation may require oral audio or audio visual consent may be taken. So; that means, it is not necessary that in all instances to take written and signed informed consent.

Can deception be used with regard to informed consent? Yes, occasionally in social and behavioral sciences research you can use that. Who owns the biological materials or data related to it? The donor, only the donor.

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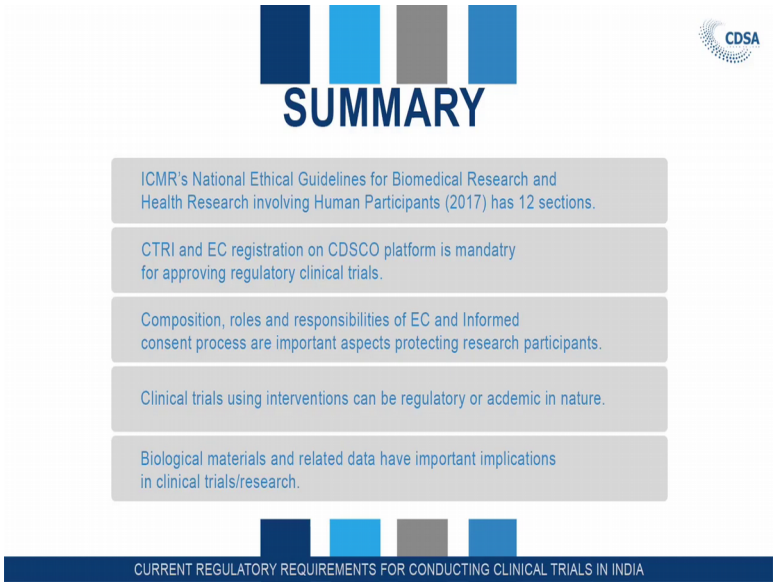

So, summarizing ICMR's National Ethical Guidelines for Biomedical Research and Health Research involving Human Participants has 12 sections. CTRI and EC registration on CDSCO platform is mandatory for approving regulatory clinical trials. The composition, roles and responsibilities of ethics committees and informed consent process are important aspects protecting research participants.

Clinical trial using interventions can be regulatory in nature or academic in nature. In biological materials and related data have important implications in clinical trials and research with regard to benefit sharing, who owns it and who is the custodian etcetera.

Thank you.