Legal and Regulatory Issues in Biotechnology
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Module - 01
Regulation of Biotechnology Research
Lecture - 04
Ethics in animal and human research: Code of ethics and regulation (Continued)

Hello all, welcome back to this session on module 1, where we were discussing regarding the Regulation of the Biotechnology Research and particularly, we were in the discussion of Ethics in the Animal and the Human Research in the sector of the biomedicine. So, in the previous class we dealt with the issue of why ethics becomes an important issue while considering the research in the area of biotechnology.

As we saw biotechnological research is not only these scientific advancement, but the societal value of the research or the implication of the research towards a greater public health is also taken into consideration when we think of or when we plan some research in the area of the biotechnology.

And some incidences in the past which has revealed that how the animal subjects or human subjects have been subjected to the cruel experimentation that had led to the development of the ethical guidelines or the principles.

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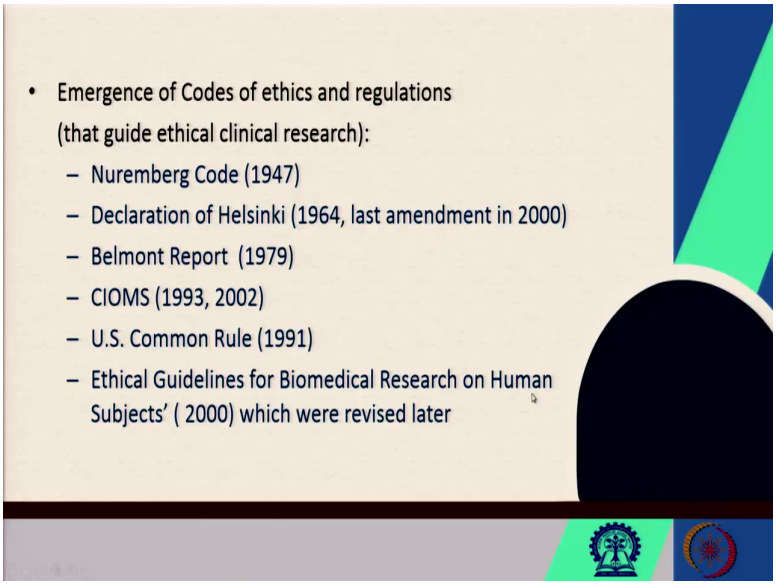

So, continuing the previous discussion we saw that particularly during the Second World War time the treatment of the prisoners in the Nazi camp by the doctors or the physicians had led to the establishment of different regulation in the area of biomedical research or medical research particularly at that point of time. And that led to the genesis of the ethical codes or ethical regulation for the research.

And the Nuremberg Code which was established in the year 1947 was one of the first International Code of Ethics. And after that if you see chronologically there has been many there have been many regulations particularly focusing on the ethics and how the treatment of the subjects during the experimental research or the clinical trials.

So, including the declaration of the Helsinki then the Belmont report of the United States then CIOMS guidelines U.S. common rules and also the modified guidelines of the CIOMS that the ethical guidelines on biomedical research on the human subjects.

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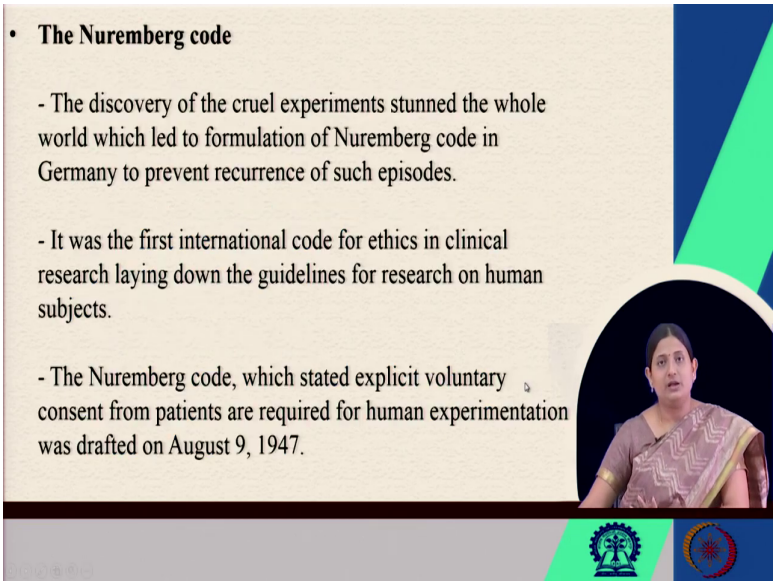

So, I would be just describing a little bit about each of these guidelines, so to understand how the concept of ethics in biomedical research has evolved. So, as we discussed that in the pre–World War 2 time the physician or the patients they themselves were the subject of the clinical trials and during the concentration camps in the Germany during the World War 2 time.

So, the physicians have experimented a number of cruel experiments on the prisoners. So, this discovery of those things shocked the whole world, means how the prisoners were treated inhumanely even without their consent they has been; they have been subjected to various treatment or various experiments which led to the death deliberate death or even if not deliberate death a painful death.

So, after the, this incident when the World War 2 was over this was prosecuted in the US court of war. So, this was a war crime and the physician Karl Brandt and along with the 22 other doctors were prosecuted in the United States courts and during the prosecution itself the court came up with the guidelines how the patients or the human subjects should be treated during the clinical trial process and that lead to different points of consideration during any experimentation on the human subject. So, initially before these things there was no concept

of the voluntary consent means if a patient or a human subject was not aware or was not asked for any kind of permission before any sort of experiment is being tried on him or her.

So, this Nuremberg code was the first international code of ethics which introduced the concept of explicit voluntary consent or consent from the patients. So, the consents from the patient are made as a mandatory requirement before any sort of experimental drug has been utilized on any human subject.

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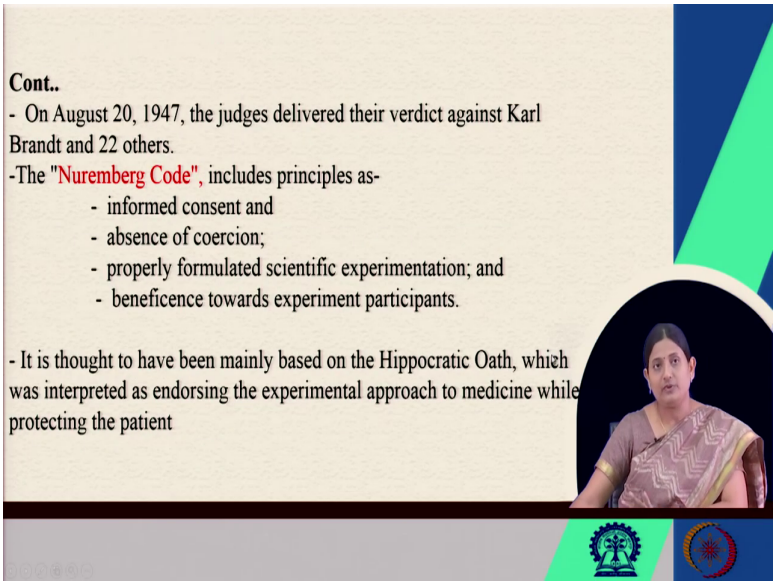

So, during this verdict of Karl Brandt versus united courts there the number of principles has been in enumerated during the judgment and the main principles, which has been laid during this Nuremberg Code was the informed consent, absence of coercion, properly formulated scientific experiments, beneficence towards the experimental participants.

So, before this incident particularly the physicians are mainly avoided by the Hippocratic Oath where the patient's health was almost impotence to a physician. But having said that in many of the cases there has been seen violation when it came to the experimental procedures or when something new has been tried to be developed, so it as these incidents these incidents came into forefront. So, there was a need to understand that the human subjects are not mere experimental animals or an experimental object they are consent. They consent in the terms they should know what is going to happen what are the consequences of the research and is

there any adverse effect on their health or if they are; if they are diseased persons if the disease has is going to be cured or some side effect may occur. So, there may be a number of implications.

So, the patient or the human subject must be made aware of the possible consequences. And if after that the patient agrees then only someone can perform the experimentation on him. Because, in biomedical research you never know and particularly in case of the biotechnology, because this is so much related to biotechnology. We really do not know the effect in some of the experimental processes. So, it is essential that the human subjects must be made aware of the possible consequences.

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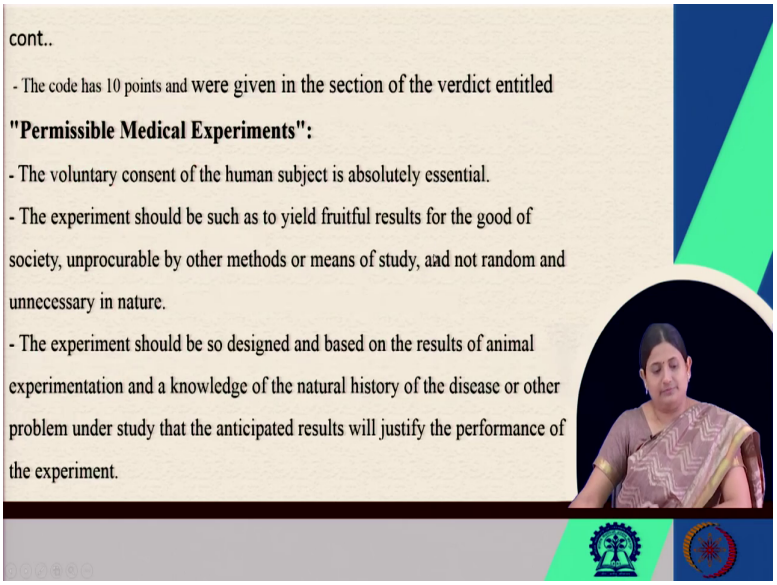

So, in this Nuremberg Code particularly 10 points were given in the verdict sections and they were entitled in the section called the permissible medical experiments. And mainly these permissible medical experiments included the points of voluntary consent from the human subject and the designing of the experiment means the, is it is not that by error and trial method someone can carry out experiment.

So, whenever you are going to carry out some experiments in the field of biomedicine the experiment design must be fruitful and it should result the in the good of the society, the greater benefit has to be achieved by the experiments, which someone is going to perform.

And it should not be random and unnecessary experimentation should not be carried out. And it should be designed on the basis of the animal experimentation.

So, here one issue again comes up. So, first the experimentation has to be carried out on the animal models, because from the very beginning we cannot subject to the human's for the experimental drugs. So, first it has to be performed in the animal models, again that has to be rational and justified as we discussed in the last class.

So, the even the animal experimentation has to be properly formulated, so that undue experimentation or unnecessary numbers of animals should not be used and after that only a properly designed experimentation should be formed and then it should be carried out. So, that it would result in a, result in a positive manner that can be helpful in the; helpful for the society.

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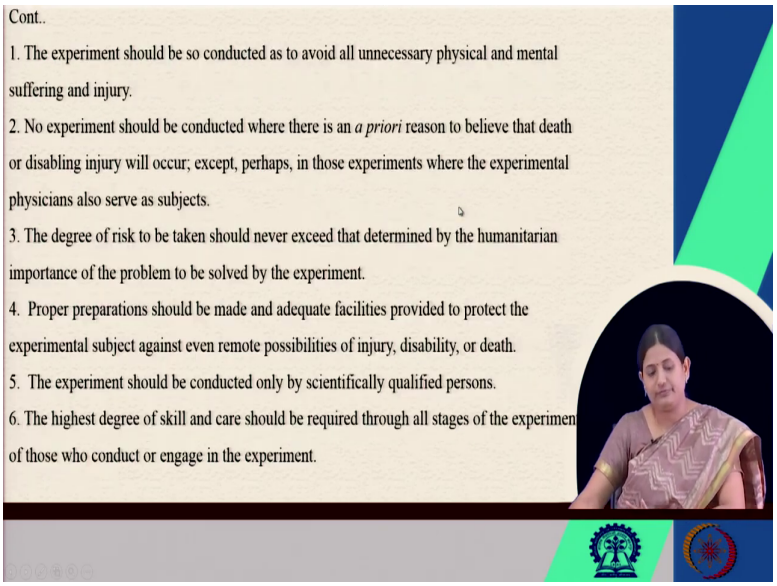

And the experiment should be conducted so as to avoid all unnecessary physical and mental suffering an injury, so because all these points were based on the facts of the Nazi trial. So, there were like these prisoners were subjected to a lot of torture and mental pressure.

So, those things must be avoided during any kind of experimentation and it is also mentioned that no experiment should be carried out when there is a priori reason to believe that death or disabling injury will occur. So, if someone is quite sure that it is going to result in the death or

disability of one patient then that kind of experiment must be avoided and because why to subject anyone to risk which is known already.

And then but again in some cases there is care to be taken where there is no alternative cure. So, in that case the degree of risk to be taken should not exceed the humanitarian importance of that problem, which is solved by that experiment or solved by that population.

So, a risk benefit analysis must be performed. And then wherever the experimentation are being carried out that has to be carried out in a particular adequately provided facility and by properly trained personnel's.

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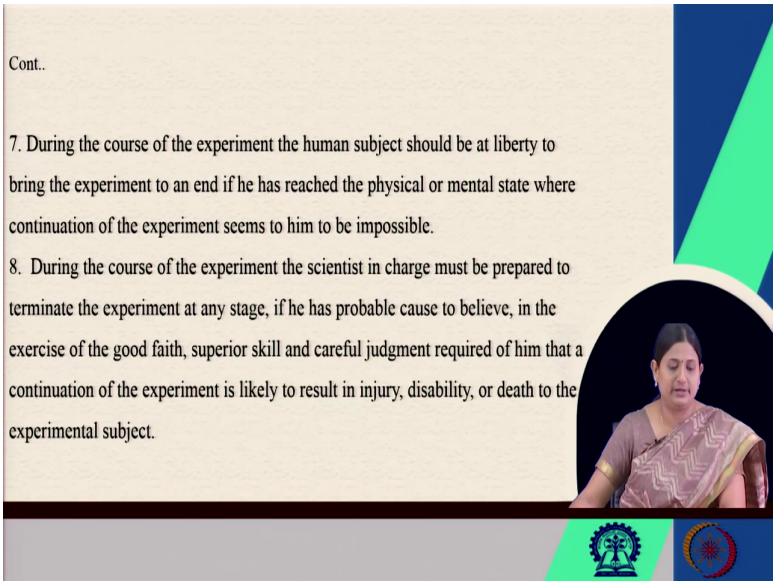

So, that also has been made in that permissible experiments and it also mentioned during the course of the experiments the human subjects should be at the liberty in bringing the experiments to one end, if it has reached the physical or mental state, where the continuation of the experiment seems to him to be impossible.

Means if a patient wants that he no longer wants to be the human subject for that experiment, the then in those cases the experimentation should be stopped at the concern or at the request of that particular patient. It is always that human value of the human subjects in the experiment must be take must be given priority.

And the scientist should not carry out the experiments on to just quench the thirst of their scientific hunger, but they should be mentally prepared to stop the experiment at any stage if it is required. So these are the few of the major points, which was placed during the Nuremberg trial.

And since nothing before that there was no legal or regulatory boundary were given for the experimentation though the physicians were subjected to the Hippocratic Oath. But since the there was no proper legal regulations in that case this became the first court or first kind of a legally binding or kind of a guideline, where all the experimentation should be taking place.

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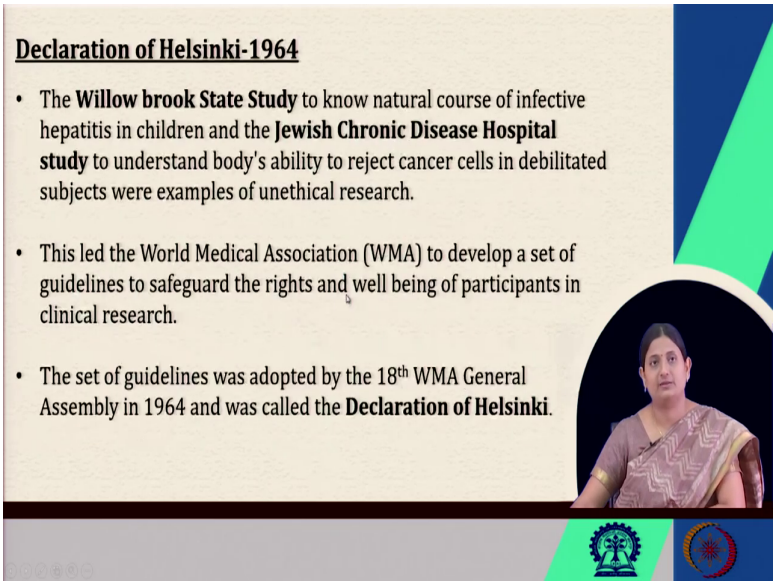

So this was in 1947, after that yes in many of the countries developed nations particularly United States or in the European Union major because most of the new drugs were formulated there. So, those guidelines were taken into consideration, but the unethical practices in the medicine did not stop with that guideline.

There were many other incidents which came to limelight which again raised the question do we have the sufficient guideline for the practices in the biomedicine research. Particularly two incidents like this Willow brook State Study in the New York and Jewish Chronic Disease Hospital study.

So, these two incidences again brought the unethical practices into focus. So, in the first case this Willow brook State Study, where mentally retarded children were subjected to these unethical practices in order to just to study how the hepatitis virus is going to affect the children naturally.

So, the physician there in order to develop a vaccine for the hepatitis B deliberately subjected the mentally retarded children into to the or deliberately introduced the hepatitis B viruses to the children and studied the natural course of action for the hepatitis C virus. And since those children did not understand and it was a long study and so and they were unaware that they are a kind of subject for this kind of experiment.

And in the next case this is a Jewish Chronical disease hospital study, where again patients were subjected to the cancer cells in order to study how the cancerous cells are going to affect the patients and how they are proliferating in a normal human body and all this happened without the knowledge of the participants. And this incident led to the world Medical Association or the WMA to develop a set of guidelines to safeguard the rights and well being of the participants in the clinical research.

So, Nuremberg Code for the first time introduced the concept of the voluntary consent, but again the responsibility of the physician or the rights of the clear human subjects were not properly underlined or properly mentioned in those guidelines. So, after this incidence this World Medical Association they adopted a set of guideline General Assembly in the year 1964, which is known as the Declaration of the Helsinki.

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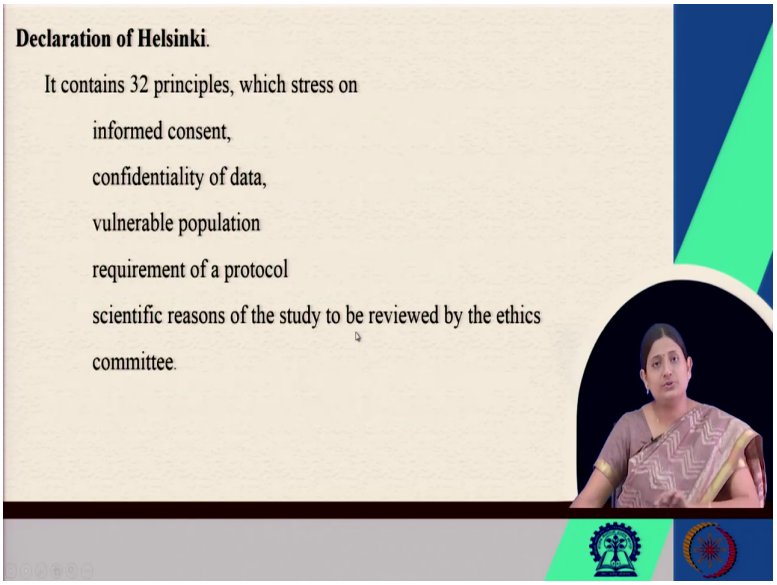

So, this was again one of the major breakthroughs in the area of the biomedical ethical practices and this declaration of the Helsinki basically contains 32 principles, mainly stressing on the factors of informed consent, confidentiality of the data by the patients, vulnerable population treatment of the vulnerable population, requirement of a protocol, scientific reason to study the particular act, which should be reviewed by the ethics committee.

So, this was the first kind of a guideline which led or which emphasize the formation of the ethical committee. So, before that only voluntary consent has been dealt, but nobody thought of about the rationality of the experimental plan and so the physician was at his liberty to carry out certain experiments.

So, but this declaration for the first time brought the concept of the ethical committee, the constitution of the ethical committee on external ethical committee, which should review the plan of action and give a consent before the experiment should be performed. And the rights of the vulnerable population like we saw that in the Willow brook State Study the mentally retarded children.

So, they were not aware so also in there may be any other disable category or any other oppressed category of the people which might be subjected to who might be subjected to such

kind of treatments. So, for that reason the, the vulnerable population must be protected and their rights must be protected. So, these were the few points which has been emphasized in the declaration of the Helsinki.

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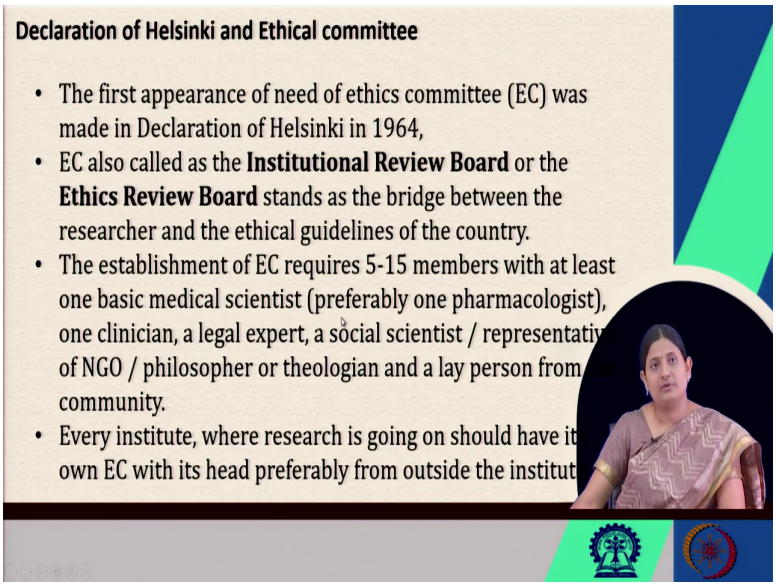

So, the ethical committee was one of the positive points of this declaration and this ethical committee also known as the Institutional Review Board or the Ethics Review Board, it acted like a bridge between the researcher and the ethical guidelines of the country.

So, it mandated that the ethical committee must have 5 to 15 members with at least one medical scientist preferably who may be a pharmacologist, one clinician, one legal expert, one social scientist or the representative of an NGO or the philosopher so or a lay person from the community. So, like it tried to bring different persons from legal community from the society from the scientific community, so that there may be a balance in the plan or the design.

So, that the experimentation which is conducted should not result in undue or should not result in adverse effect to the society. And it mandated that every institute wherever the research is going on should be having the ethical committee and once the ethical committee gives the permission, then only the experiment can be performed.

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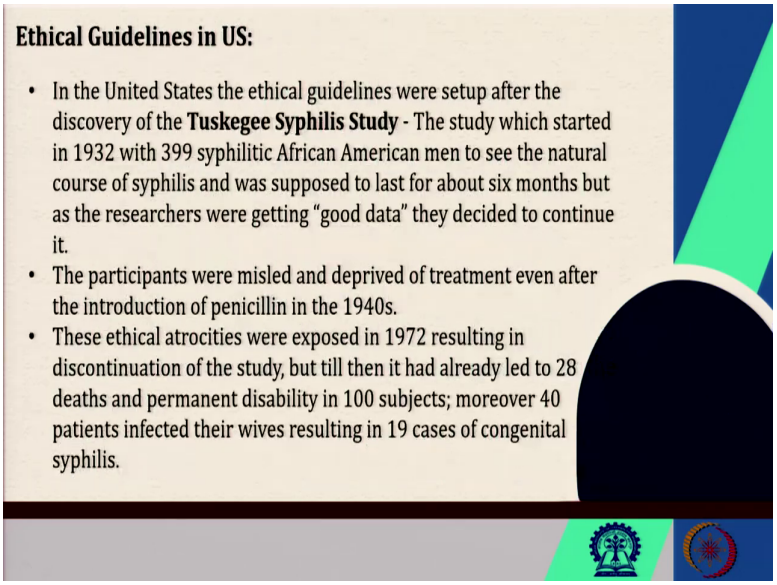

So, this was again the second stage of development, but again the there is still continuation of the unethical practices somewhere or other because of the lack of guideline or lack of proper legal measures the unethical practices kept on continuing. So, another study again, which came to forefront was the again one of the, you may consider as deadliest study which was carried out from 1932.

So, it was carried out for more than 40 years 1932 and this is known as the Tuskegee Syphilis Study. So, here the in this study which started in the year 1932 it had enrolled 399 syphilitic African American Negro population. So, in order to study the natural course of the syphilis and how the patient is doing, in one of the hospitals there they try to enroll the black Negro population who are oppressed from bringing them from one of the states of Atlanta.

And by just giving them hope that they are they will be treated well for the disease syphilis. And with the hope that there will be a free treatment more than nearly 400 persons enrolled in that. But they did not know that they were just subjected to some kind of experimentation, without being given any proper drug for the treatment the doctors kept on studying their natural course of action of the syphilis.

And the thing became more crucial or more bad when even after the discovery of the penicillin, which is a standard antibiotic which is used against such kind of disease it was discovered in 1940 even after that the patients were not given those antibiotics.

In order to just to study how the virus is acting on the body of the population or that Negro persons. So, these atrocities were exposed finally, in the year 1972 and these were again conducted under the CDC of United States and so it raised a number of concerns among the physicians as well as the non general population.

And it was found that this long study 40 years of study had resulted into 28 deaths and permanent disability in more than 100 subjects and the more than 40 patients also infected their wives and 19 cases have congenital syphilis. So, you may you can imagine the by the unethical practices how much suffering the patient has undergone, because of only these unethical practices or unplanned thing.

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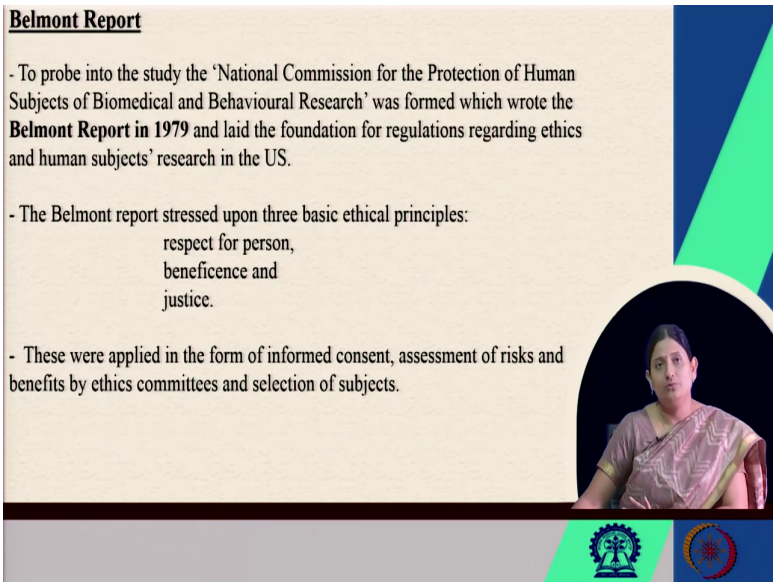

So, after this incident the US government started an investigation to this incident and the national commission for the protection of the human subject of the biomedical and the behavioral research was formed, fine and after looking into this issue they finally released a report in the year 1979 which is known as the Belmont Report.

And this Belmont Report laid the foundation of the regulations regarding the ethics of the human subjects research in the United States and the Belmont Report was again based on the three ethical principles first respect for the person and the concept of beneficence and the concept of justice.

So, because this whole study were carried out only African Negro population or black population, because they are considered to be the oppressed category. So, they were not treated at par with the white persons or other person. So, in the area of biomedical research there should not be any bar or any strata for the patients or the human subjects.

Every person who is enrolled in any clinical studies should be treated equally and the physician must have respect for that person and the concept of the beneficent means all this study, which should be carried out should be carried out for the benefit of the patient, which would lead to the greater benefit of the society. And then the justice and so if any mishap happens or anything bad goes it is and the vulnerable population or the patient must or should get the justice.

So, these three basic principles which were laid down in the Belmont Report were basically applied in the form of the informed consent or the assessment of the risk and benefits by the ethics committee and the selection of the subjects. But somehow the justice on the concept of the beneficence were introduced here along with the need of ethical committee as well as the informed consent.

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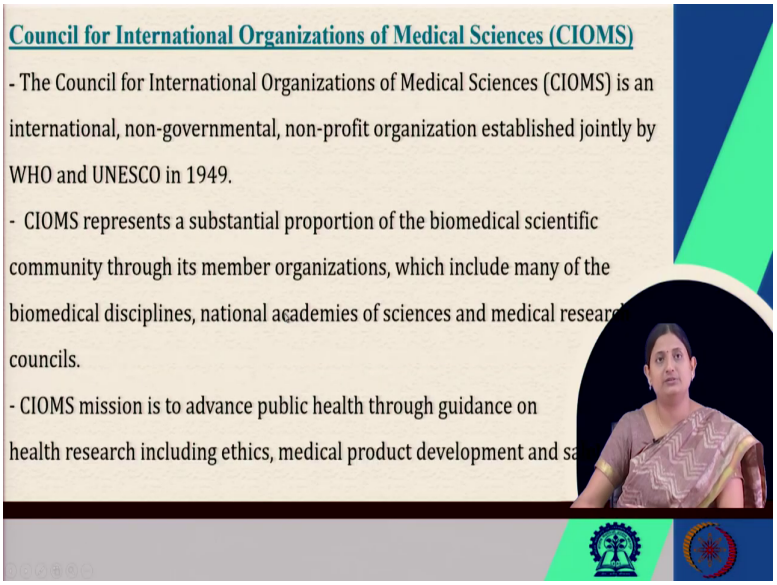

So, this is the third development which happened in the area of the ethics in the biomedical research and after that many changes or alteration has been made to the existing guidelines. Then the Council for the International Organization of the Medical Sciences or the CIOMS which is basically a non government, a nonprofit organization established jointly by the World Health Organization and UNESCO in the year 1949.

So, the CIOM basically represents a substantial proportion of the biomedical scientist community and it has members from both academic as well as the medical research council member. So, it's mission was to advancement or the CIOMS mission is the advancement of the public health through the guidance on the health research including ethics and medical product development and its safety.

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So, in 1982 the CIOMS in associated with in association with the WHO developed the 'International Ethical Guidelines for the Biomedical Research Involving Human Subjects'. And it again stressed upon the ethical issues in the less developed countries like the investigators duty, regarding the consent appropriate inducement, special or vulnerable population, therapeutic misconception and post trial access.

So, all these points and were particularly in the under developed nations all those things were generally not taken into consideration. So, since it is an international body. So, it that all these points must be taken before any biomedical clinical research should begin.

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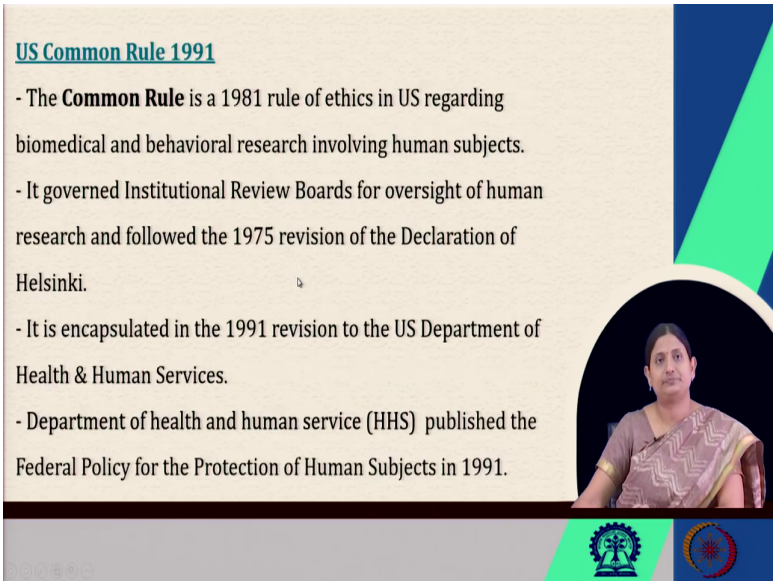

And this CIOM guidelines where again later on modified many times depending on the advancement of the time. So, latest was in 2008 in 2002 also there was substantial amendment and between those again the in the United States there are something called the US Common Rules of 1991.

So, the Common Rule was the rule of ethics regarding the biomedical and the behavioral research involving the human subject. So, it basically governs the institutional review boards for the, which is basically overseeing the human research activity. And it acted as at part with the declaration of the Helsinki.

And finally, in 1991 there was a revision to this rule under the department of the health and human services and it published the guidelines in the Federal Policy for the Protection of the Human Subjects in 1991.

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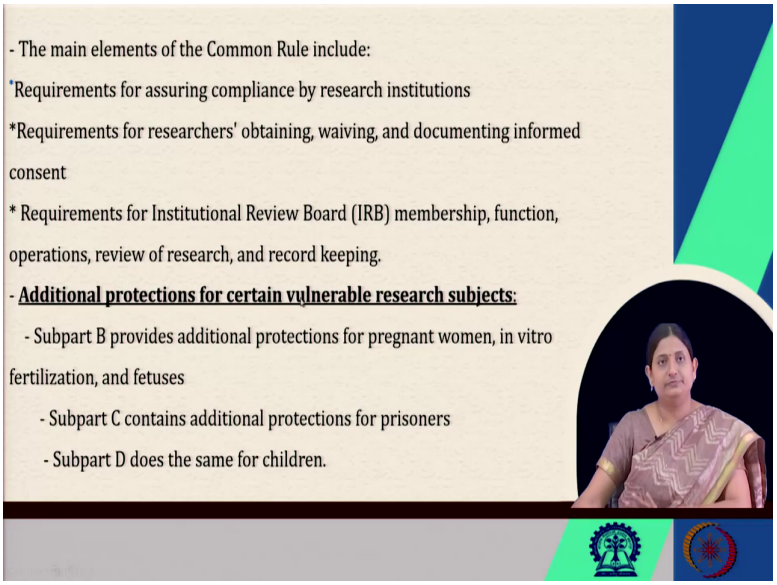

And the main elements of the Common Rule included: The requirements for assuring compliance by the research institute. So, we have a need for ethical committee we have an institutional review committee or the ethical committee. So, the research institute must comply with the mandate of the ethical committee and all these procedures.

Requirements for the researchers obtaining or waiving and documenting the informed consent so, informed consent is required, but there might be ways through which it may not be properly documented. So, it mandated that it must be properly documented and requirements for the Institutional Review Boards for the membership function preparation, review of the research, and record keeping.

And it not only focused on the normal population, but it had also subsections for the additional protection for the pregnant woman or additional protection required during the in vitro fertilization studies or the study on the fetuses and also protection of the prisoners so and then the treatments of the children. So, there might be different consideration while we take this kind of population as a human subject or trial subject. So, those things are also mentioned in the US Common Rule of 1991.

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So far whatever we discussed where the international developments starting from the Nuremberg Code to the Common Rules and CIOM guidelines. So, now, we come to India specific thing in India the first ethical guideline regarding the biomedical studies is released by ICMR Indian Council of Medical Research in the year 1980.

So, the ICMR release the 'Policy Statement on Ethical Consideration involved in the Research of Human Subjects' in the year 1980. And this was the first policy statement which gave the official guidelines for the establishment of the ethics committee. So, we saw in declaration of the Helsinki that it was the first international guideline which mandated the formation of the ethical committee.

But in India the ICMR guidelines are the first which gave in explicit directions how to form an ethical committee in all medical colleges as well as the research centers. But still the same story continues like even though we have a set of guidelines, but somewhere or other the unethical practices kept on coming.

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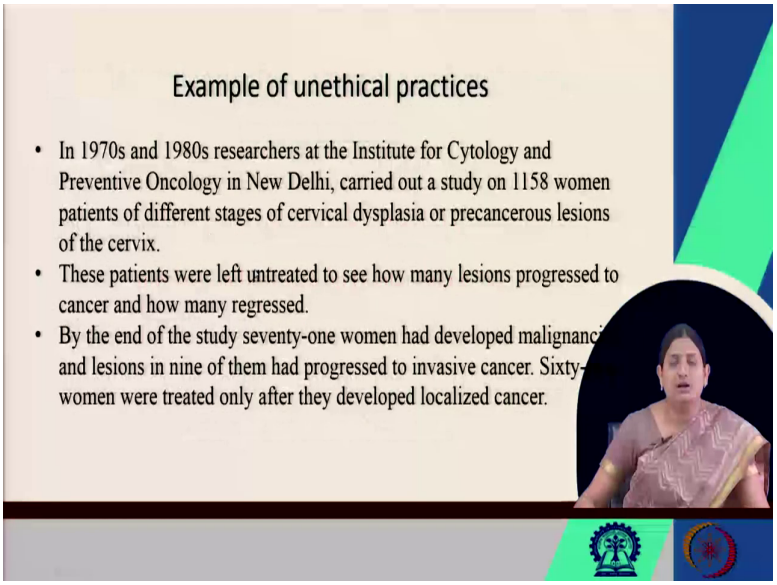

For example, in 1970 as well as in 1980s the researchers at the Institute of Cytology and Preventive Oncology in New Delhi, they carried out a study on nearly 1158-woman patient who were at the different stages of the cervical dysplasia or the precancerous lesions of the cervix.

So the issue here was that they some of the patient at least that the patients were left untreated to see how many lesions are progressing to cancer and how many have regressed without any proper treatment just they were subjected to see what is the natural course of the action.

And at the end of the study seventy-one women had developed malignancy or cancerous cells and nine of them had progress to invasive cancer as well and only some sixty odd women's were treated and after only they developed some localized form of the cancer. So, these were the allegations like without where unethical practices has been adopted during the clinical trials or during the study.

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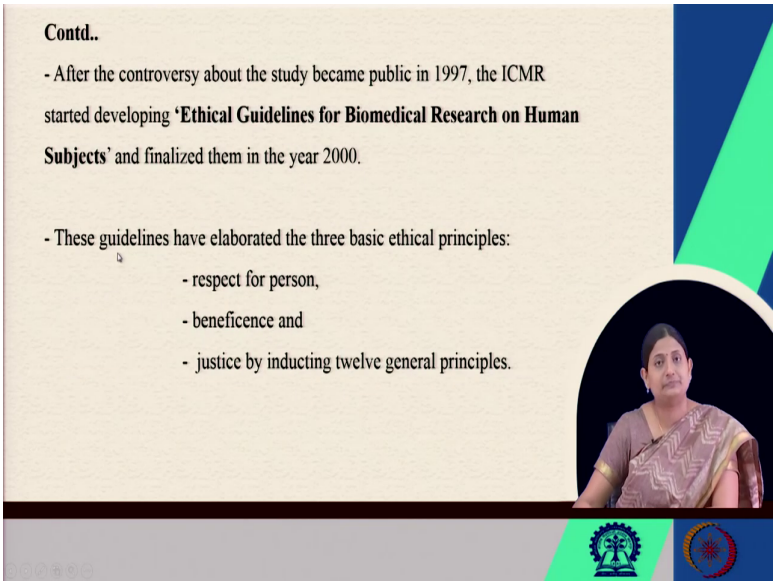

And after this controversial study which is published which is which became public in the year 1997 the ICMR again developed another set of guidelines 'Ethical Guidelines for Biomedical Research on the Human Subjects' and it was finalized in the year 2000. And again, it has also three basic elements that respect of person the concept of beneficence and justice by inducing twelve general principles.

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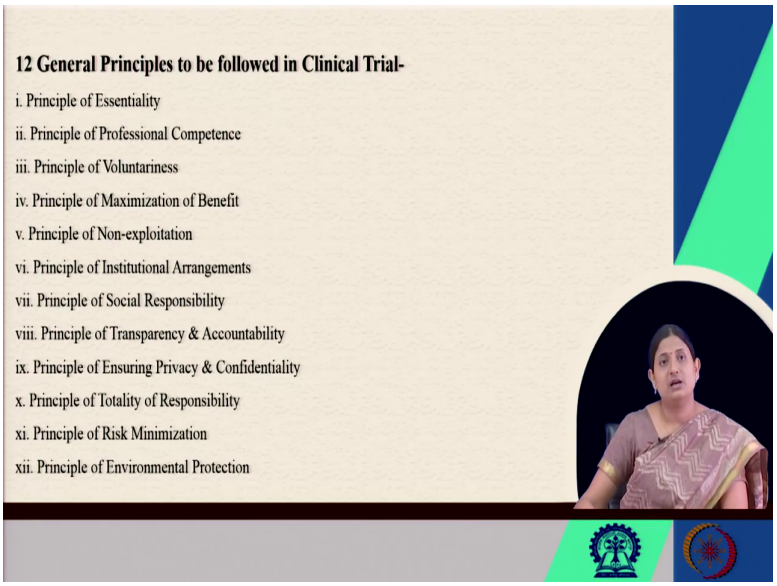

So, basically this ICMR guideline on the ethical guideline on the biomedical research has 12 general principles which must be followed in the clinical trials, they are the principle of essentiality, principle of professional competence, voluntariness maximization of the benefit, a non exploitation, principles of institutional arrangement, principles of social responsibility, principles of transparency and accountability, privacy and confidentiality, totality of the responsibility, risk minimization and environmental protections.

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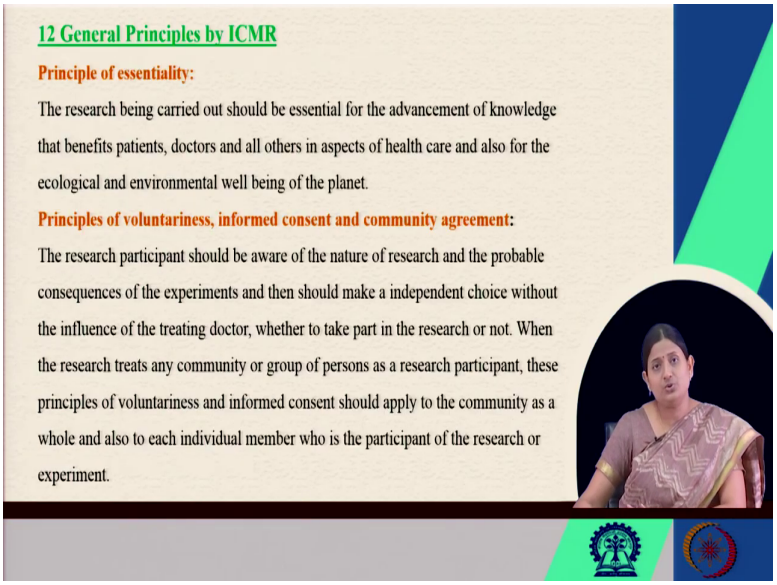

So, briefly, this principle of essentiality: So, it mentions that the research should be essential for the advancement of the knowledge and the benefits of the patient doctors and in all others in all aspects of the healthcare as well as for the ecological and environmental point of view.

Then again, we have gone through we have already been exposed to the principle of voluntariness or informed consent and community agreement, where it mandates that the research participants must be aware of the nature of the research and the probable consequence of the experiments.

And accordingly, they should be allowed to make an informed choice where they know the risk and the benefit associated with them with the study. And this principle of voluntariness and the informed consent must be applying to all the community as a whole as well as to each individual member who is willing to participate in a particular study.

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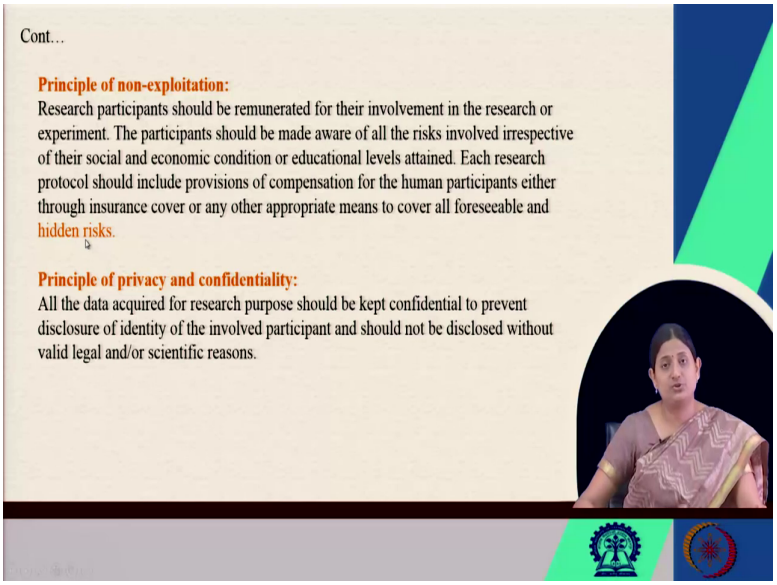

Principle of non exploitation, so when the patient group is belonging to vulnerable group or any other category where you know in India the, we have different strata of the people who one uneducated or really do not have much idea regarding the medical sciences. So, in those cases the research protocol the compensation mechanism and the post trial measures like the insurance mechanism and appropriate means should be there to cover all the foreseeable and the hidden risk associated with the study.

And principles of privacy and confidentiality dealt with basically the confidentiality of information regarding the patient, regarding their disease and regarding their, what you called their belongings a bit in the sense from which strata of the society they belong. So, the identity of the patient if like if the patient wants that should be protected and this privacy and confidentiality must be allowed for each of the patients enrolled in any kind of the study.

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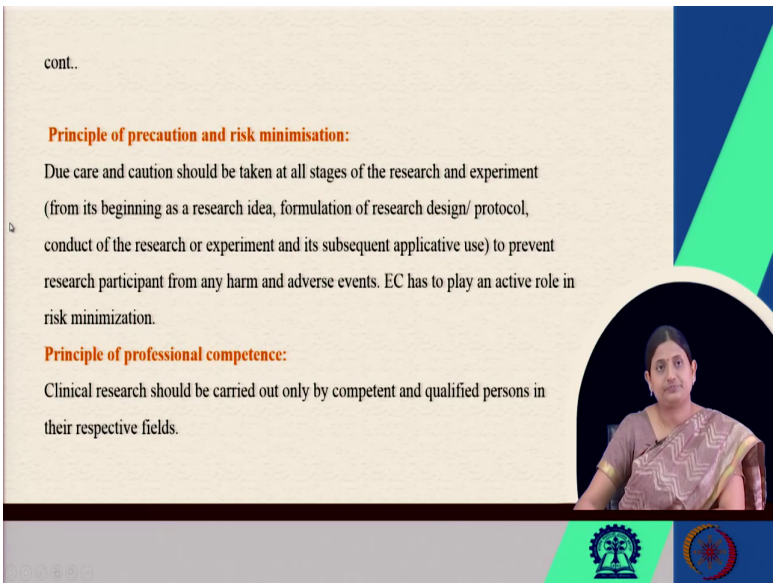

And principle of precaution and risk minimization aware due care and caution must be taken at the all stage of the research and experiments, so that there should be minimal risk. And here the ethical committee should play an important role while undergoing the research planned by before approving any sort of research, they should see whether the risk assessment has been properly done and the preventive measures or the other measures are available if something happens.

So, those things must be taken care of. Principle of professional competency where the clinical research should be carried out by the qualified persons in India one of the issue is issue raised in one of the committee report that we do not have adequate competent personnel in the area of the clinical research, so that was one of the issue.

So, because they should the persons who are engaged in the clinical research or in assisting the clinical research apart from the physician should also be aware of the nature of the study and different protocols.

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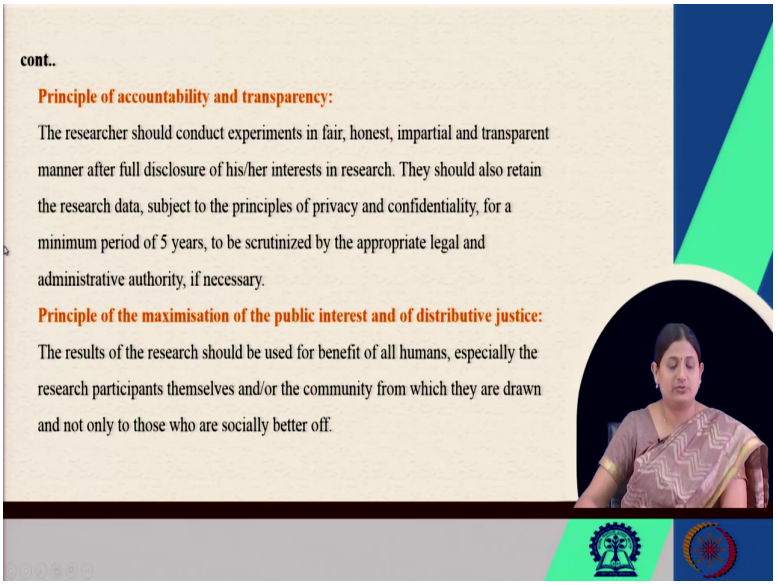

So, there is one of the other requirements, accountability and transparency like the researcher should conduct the experiments in the fair, honest and impartial manner and the disclosure should be a disclosure about the research interest must be made fully and like the data privacy and confidentiality must be maintained whole time, so those things are mentioned in this principle.

And then principle of maximization of the public interest and disruptive justice, where it says that any interest any research which has been carried out should focus on the benefit of all humans and especially the research participant themselves or the community to which they belong.

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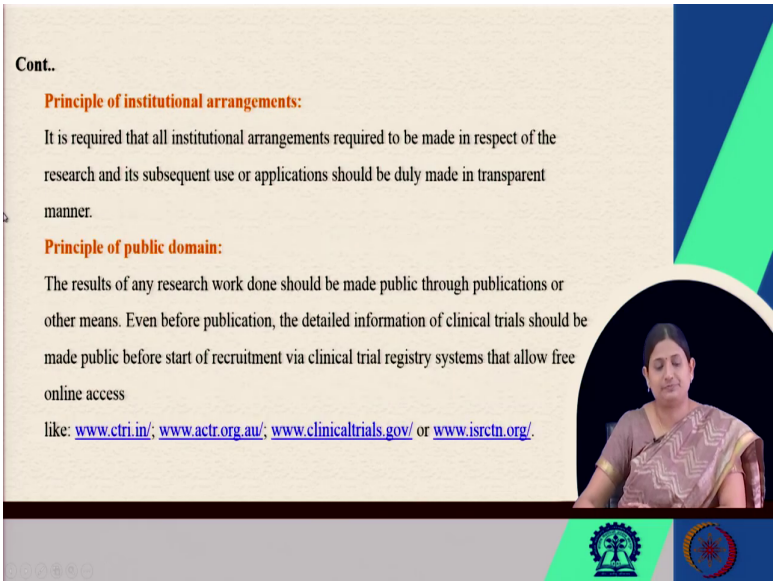

So, the social implication of the research must be taken into account. And institutional agreement were arrangements, where it should be made with respect to the research and subsequent views of the application should be made in the transparent manner. And principles of public domain: So, here this is one of the interesting steps, where the result of any research walk should be made public to the publication of the publication or by any other means.

And the detailed information of the clinical trial must be available to the public and before the start of the recruitment of the patients or the human subjects and it led to the establishment of the clinical trial registry. So, these are the website where website for the clinical trial registry of the India, where the ongoing clinical studies are listed and if the patient wants, they can enroll by knowing the nature of the study.

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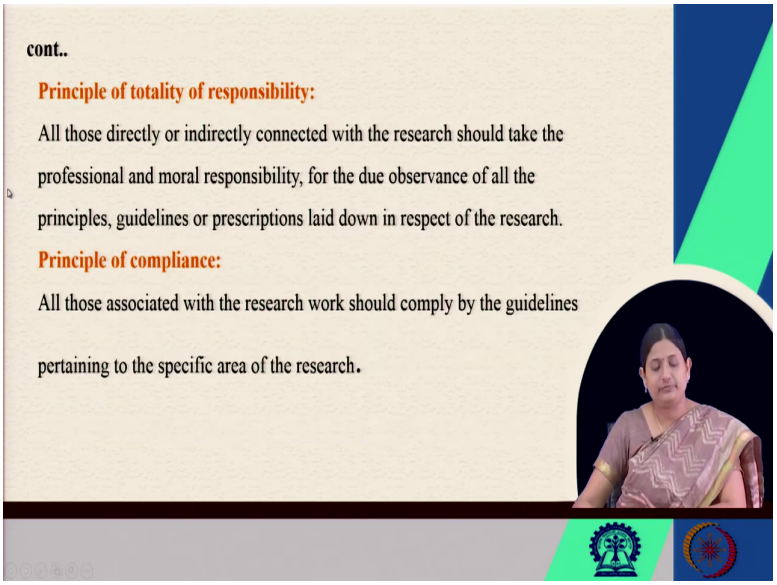

Then principle of total responsibility where all those who are directly or indirectly connected with the research should take the professional and the moral responsibility at for the due observance of all the principles, guidelines and the prescription as laid down in the research plan. And principle of compliance so all those who are associated with the research work should comply the guidelines pertaining to the specific area of the research.

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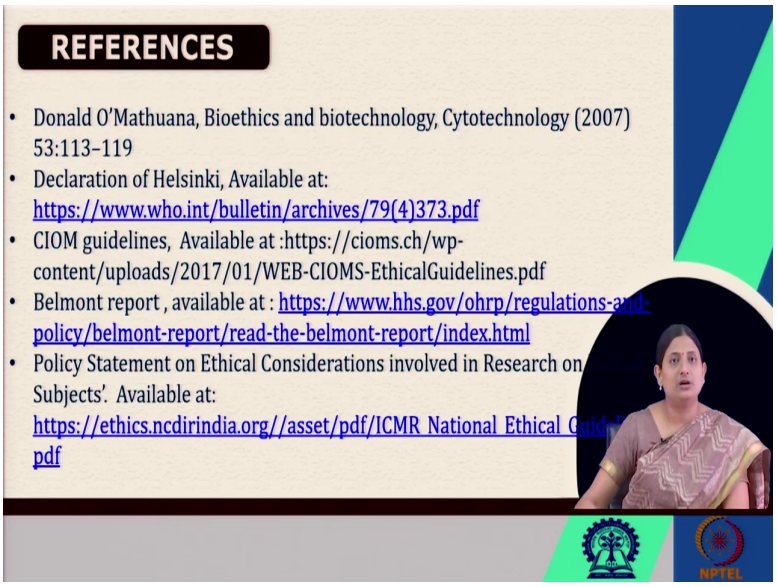

So, these are the few guidelines which are laid by the ICMR I have just given few references if you want, please, you can read more about the reports which are available in the public domain. So, whatever we have discussed so far is all about the genesis of the code of ethics and regulations in the area of the biomedical research. And we just had a brief outlook to the Indian system of ethics in biomedical science.

In the upcoming classes we will see more about this clinical trials and ethical issues maybe with respect to stem cells and other embryonic cells. So, please stay tuned.

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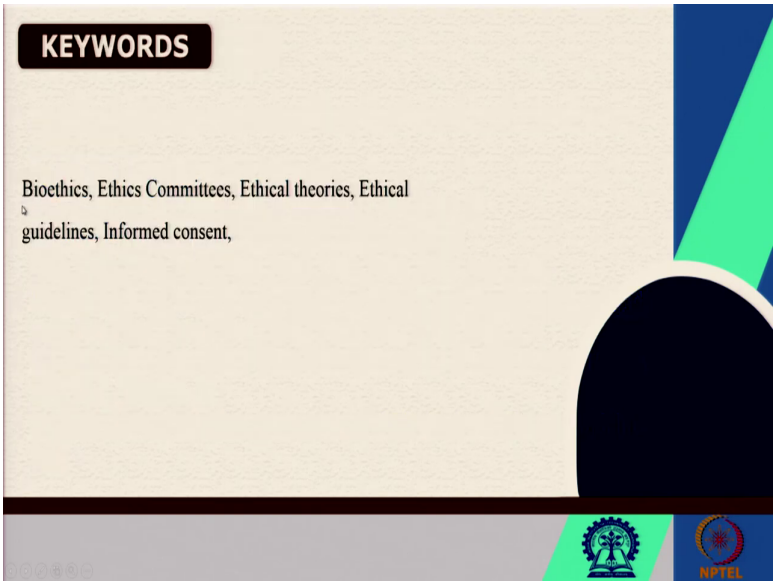

Thank you, thank you very much for attending the session.

Thank you.