PROTECTION OF THE RIGHTS OF THE EXAMINEE IN CLINICAL RESEARCHES

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Abstract: Issues of the trial subjects' rights protection rose sharply after World War II, when Nazis researchers conducted inhuman and cruel experiments on people. XXI century is the time when person's freedom and rights became primary treasure in all spheres of the life, and medical science was not an exception. This article covers crucial historical stages of development of subjects' rights protection and its main implementation tools.

Keywords: Human rights, Clinical tests, Science, Health and life of citizens.

Before discussing specialties of the clinical trial process, we would like to draw your attention to development and sign of the following important cornerstone acts and codes, such as Nuremberg code (1947) [1], Declaration of Helsinki (1964) [2], Good Clinical Practice (1996) [3]. What was the trigger for the development of those documents? Twentieth century appears to be a century of famous achievements and discoveries; it is the century when human life became primary treasure. Many international organizations such as UN, UNESCO, and UNISEF have been organized to protect human rights and freedoms in all spheres, and medicine science was not an exception.

There are many examples of inhuman experiments from the past. For instance, in 1932 FDA approved clinical trial in Tuskegee, the purpose of which was to find cure against syphilis [4]. The researchers, from one side, had been studying pathogenesis and disease progress on patient for 30 years. From the other side, there was no available effective treatment at the moment of the trial initiation. In 1942 the penicillin became widely spread and was considered standard of treatment. However, the researchers continued the trial without any treatments applied, leaving people suffer from the disease. In 1972 FDA officially closed Tuskegee trial. The official apologizes and compensations for jeopardizing rights were given to the trial victims. Though whatever money was given trial participants' soul wounds could never be cured.

However, there two sides of the coin. Tuskegee trial gave results which played significant role in further infectious medicine understanding of such important social disease as syphilis. On the contrary, there are serious ethical concerns about using such information, taking into consideration the way it was obtained. What about human rights? This is the example when scientific interest was placed beyond the human rights. As researchers we should remember such crucial experience and do our best to prevent such experiments in the future.

Another important page in the history of clinical trials was inhuman experiments conducted by Nazi's investigators during World War II. Terrible examples would be investigating human body metabolism executed in extremely low temperatures, exposing human extremities to liquid nitrogen, or performing experiments with biological and chemical weapons on humans. The subjects participated in those trials without any form of consent; moreover, usually outcome of such studies for healthy volunteers was the death. Those events led to Nuremberg lawsuit when 12 investigators were put either under the death penalty or under the long-term imprisonment. As result of that suite international community developed Nuremberg code, which included basic principles of clinical trials, and issues of human rights protection such as: free will for participation in the clinical trial, free will to withdraw from trial, appropriate conditions of facilities, scientifically sound researches and benefits for the subjects and the community at whole. That document became one of the first documents, which protected human rights in clinical trials.

The next step was an international conference organized by World Medical Association, which took place in Finland Helsinki 1964. The outcome of the conference was the Declaration of Helsinki, developed and spread among scientific community; it was edited 6 times in the future. The document covers main principles of medical experiments conducting on human being; it includes 11 paragraphs in first version and 35 paragraphs in the last one

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The important points of the declaration are protection of health, rights and wellbeing of human subjects; protection shall be over interest of science; trial participants shall give their written informed consent, and withdraw from the trial whenever they wish, without loss of follow-up health services; researches shall have scientific base, and the clinical trial shall be based on pre-clinical studies carried out on animals; clinical trials shall bear benefit for the participants and the society.

In the second half of XX century, several disastrous events were highlighted by media, such as Thalidomide which appeared in 1957 in several countries’ markets, as a result of its usage thousands of children were born with malformed extremities and were left incapacitated for whole life.[6]

Improper and low quality preclinical and clinical trials could lead to deaths of thousands people and there are many examples from history of drug development; thus, high quality trials is a significant step in protection of subjects’ rights. The study of new transgenic agent investigation, which aimed to cure ornithine transcarbamylase deficiency, could serve as an example of misconducts during pre- and clinical studies and breach of human rights. Jesse Gelsinger, a young man 18 years old died as a result of participation in this trial[7]. In this particular trial chief investigator was financially interested in the results of clinical trial; he withheld doubtful results of preclinical trials conducted on primates, and it was discovered he did not stop the treatment when the first symptoms of serious adverse event appeared. Discrepancies that took place during preclinical studies were the reason of human death during the clinical trial; the brave man who acted in sake of altruism to contribute to the science development became dead.

As a result of such disasters, the medical and pharmaceutical scientific community recognized that all stages of drug development should be systematized to prevent fatal cases in the future. Unfortunately such amendments and new standards are implementing as a consequence of tragedies that already had taken place and thousands lives.

From this point, it is become clear that primary purpose of Good Clinical Practice is human rights protection, rather than science. Study participant is free of choice to participate or withdraw if further participation put subject under uncomfortable conditions [2, 3]. Subjects have rights to know all available information regarding safety, toxicology and efficacy of drug under the investigation, based on such information s/he could assess the risk of participation in the trial, though subjectively on data presented.

By taking into account, that pharmaceutical field is one of the most profitable and R&D of new drugs is impossible without conducting clinical trials; each country should develop law base to protect citizens from unfair researchers. The regulatory legal base should maximally cover all aspects of the clinical trials; moreover, it should be followed by new achievements in the field by harmonization and actualization. It could be done by them or by the following of developed countries’ experience; the latter is more convenient for developing countries due to absence of experience. The last mentioned strategy is useful for Kazakhstan due to incomplete regulations in this important part of human rights protection.

There were three major pharmaceutical markets before 1996, which were: the USA, Western Europe and Japan. The representatives of industry, who was supposed to spread new drugs, were obligated to repeat trials in each region because of differences in regulatory frameworks. Practically, it was replication of the clinical trials, which was already conducted in another region. It means that excessive number of people was exposed to unjustified risk, which was the breach of people’s rights. Documental bureaucracy was diverse, and it slowed down the drug development process and made new effective treatments unavailable. Additionally there was persistent controversy between commercial pharmaceutical industry and regulatory authorities. From one hand, the state funds were not able to finance important and costly R&D projects, which could have helped million of people. On the other hand the industry was able to conduct such important and costly R&D projects but it was difficult to pass the regulatory barriers and required additional monetary expenses.

In 1996 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use brought together regulatory authorities and industry representatives from three major pharmaceutical regions, the USA, Europe, and Japan, to create universally acceptable framework of standards. As a result of hard work they came to the decision, which was agreed by all parties, and released guidelines to regulate and provide roadmap for R&D of new drugs from the idea to the market release. The part regulating efficacy, by the other word clinical trials, is often used interchangeably with Good clinical practice guideline (ICH, GCP E6R1), though, there are 16 guidelines covering and providing description of the clinical trial process. [8]

From this point, it should be clear that GCP guideline by itself is just a part of the ICH efficacy guidelines. It is an inaccurate perception that by implementing GCP E6R1 in the regulatory framework regulatory authorities would fulfill its obligation to its citizens in terms of protection of their rights. Additionally, it is important that GCP E6R1 is an overall instruction without detailed explanation and description; it should be considered together with other guidelines covering safety (E2A), statistics (E9), control group selection (E10), and other aspects.

Since the regulatory framework in developed countries nowadays becomes more complicated and conduct of clinical trials becomes an expensive enterprise; many commercial pharmaceutical companies start the clinical trials in developing counties. Developing countries with poor legislation of clinical trials present comfortable place to conduct inexpensive and fast clinical trials due to the low literacy and poverty of trial subjects and the absence of good rights protection mechanisms.[9]

Currently, Kazakhstan is on its first steps to enter the huge market of pharmaceutical R&D. Thus, it is time to think about protection of our citizens through implementation and harmonization of regulations as it was done in the developed countries.

Conclusion:

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Implementation of the Good Clinical Practice should be done with respect to all new aspects of conducting clinical trials. Special attention should be paid to: requirements for the clinical bases, qualification, education and definition of responsibilities of the researchers, robust requirements for monitoring, audit and inspections, and penalties for improper attitude of investigators to the study participants.

References:

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