REVIEW ARTICLE

RESEARCH STUDY OF MEDICINES USING THE HUMAN BODY AFTER HIS/HER DEATH

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ABSTRACT

The aim of this paper is to determine the legal nature and basis for the research of medicines using the human body after establishing the fact of his/her biological death.

Materials and methods: This research study is based on an analysis of the norms of international law and legislation of some states on the admissibility of the research of medicines using the human body after establishing the fact of his/her biological death. The research was carried out using the methods of dialectical and formal logic, general scientific and special legal research methods.

Conclusions: The possibility of organizing and conducting research using the human body after ascertaining the fact of his/her biological death as a scientific study distinguishes such studies from related types of medicines research, proposed standardization of these studies within the preclinical research of medicines, and examination of materials funds.

KEY WORDS: scientific research of medicines, clinical trials, preclinical trials, human body, statement of death

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INTRODUCTION

The study of the effect of new medicines on the human body is carried out within the medicines' clinical trials, which are preceded by preclinical studies, during which the information necessary to address the possibility of continuing and study features of the medicines in humans.

However, the importance of preclinical studies, mainly in cell cultures and animals, for predicting the safety and efficacy of therapy in human trials remains limited. Attempts to improve the predictability of human test results with animal data are not accompanied by a reduction in a high incidence of clinical medicines failure. In addition, poor interpretation of information obtained in animal studies for use in clinical trials of medicines in humans leads to a significant loss of resources [1; 2].

One of the most common errors observed in preclinical studies concerns dose determination for humans (phase I trials) based on animal studies. There is a misleading trend regarding linear transposition based on a simple conversion of the dose calculation used in small animals (mg/kg) extrapolated to a patient with average body weight [3].

Approximately 12% of medicines that undergo preclinical studies are subsequently placed in human clinical trials. Only 60% of them successfully complete the first phase of testing. Overall, almost 89% of the medicines studied are unsuccessful in human clinical trials, and about half of these failures are due to unforeseen human toxicity [2].

Carrying out preclinical studies in animals poses many challenges in terms of their ability to ensure the safety of clinical trials in humans. Therefore, proposals are made to reduce them through using other, potentially more reliable methods. More often scientific organizations and government regulators are recognizing that alternative methods can replace animal testing and improve the safety of new therapeutic medicines for human use [4]. For example, the US FDA published in 2006 "Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies", which called for greater use of the so-called Phase 0 clinical trials [5]. The time and cost savings for the development of new therapeutic medicines can be significant if the safety of preclinical trials without the involvement of animals is proven [4].

In research of alternatives for some pharmaceutical companies for certain medicines, there is interest in their preclinical study using the human body after establishing the fact of his/her death.

Studies of medicines using the human body with artificially supported life support systems after establishing the fact of his/her death (hereinafter – the Research), as well as clinical trials of such medicines, could provide data on the effects on the human body of the study medicines but would have an undeniable advantage because the data are obtained in the human body, but without safety risks using in healthy volunteers or patients.

As stated in the preambular paragraph of Regulation (EC) №536 / 2014 [6], the safety risk of the subject of clinical trials is based mainly on two sources: investigational medicinal product and maneuver.

Because of the use of the deceased's body in the Research, the functioning of which is maintained artificially, such a study is safer than a clinical trial and does not contain risks of adverse effects on humans. In this context, the Latin expression "mortui vivos docent" (dead teach the living) is relevant.

It should be noted that in medical education (in particular, surgical training) the corpse has always been used for the purpose of direct study of the human body, surgical practice, and new scientific methods [7].

At the same time, the Research is closer to a clinical trial, compared to other common types of preclinical studies performed with animals.

Thus carrying out Research does not replace clinical trials, and allows solving a question of expediency of carrying out a clinical trial of medicines.

During the organization and conducting of Research, first of all, the question of the legitimacy of such activities arises. It should be noted that the relevant legal relations have not found special regulation, they are regulated in fragments at the level of various normative acts. In addition, these issues have not been addressed in research. The issues of medicines trials have been studied mainly in the context of medical trials in general and clinical trials in particular.

This state of regulation and scientific development, of course, negatively affects the legal relations that arise during such activities and necessitates a separate scientific study of the organization and conduct of Research.

THE AIM

This paper aims to determine the legal nature and research basis of medicines using the human body after establishing the fact of his/her biological death.

MATERIALS AND METHODS

To achieve the research's objectives the features of normative regulation, different types of medicines' research in different countries, including considered international regulations, as well as regulations of some states on the research topic are analyzed.

The methods of theoretical analysis and synthesis were used during the study of the legal norms' content and concepts contained in normative legal acts and ethical norms. The method of systematic analysis was used, in particular, in clarifying the legal nature of the research. Formal-legal analysis of regulations on the use of the deceased's body allowed to conclude on the research legitimacy and to formulate proposals for their regulation in the preclinical medicines' research study. The comparative legal method was used in the analysis of the peculiarities of the regulation in different states of the use of the body of a deceased person in scientific research. Methods such as formal-logical (to highlight the differences between the research and clinical trials, clinical trials of tissue and cell grafts) and some others were also used in solving the problems of the study.

REVIEW AND DISCUSSION

To clarify the legal basis for conducting research using the human body, it is first necessary to establish the relationship between the study and clinical medicines 'trials. A clinical trial of medicine is defined as research conducted on ***a human being as a research's subject***, designed to evaluate the efficacy and safety of medicinal products (Part 2 of Article 2 of Regulation (EC) №536 / 2014, paragraph 1.12 of ICH GCP E6 (R2) [8]).

Analysis of the legal provisions for clinical trials allows us to conclude that the latter are conducted: 1) in order to establish or confirm the effectiveness and safety of the drug; 2) after mandatory assessments and official approval. In this case, the decision on clinical trials is made in the presence of positive conclusions of examination of the materials of the preclinical study on the effectiveness of medicines and their safety; convincing evidence that ***the risk of medicines side effects will be significantly lower than the expected positive effect.***

These requirements are due to the fact that clinical trials of medicinal products are performed on humans (paragraphs 14, 15 of the preamble, paragraph 1 of part 2 of Article 2 of Regulation (EC) №536 / 2014) – both on a patient and a healthy volunteer (paragraph 17 of part two) Article 2 of Regulation (EU) №536 / 2014). Human research is referred to in Article 16 of the Convention for the Protection of Human Rights and Dignity of Biology and Medicine: Convention on Human Rights and Biomedicine [9]. At the same time, one of the conditions for conducting human research is the absence of an alternative whose effectiveness would be similar to the effectiveness of human research (paragraph 16 of Article 16 of the Convention and Article 5 of the Additional Protocol to the Convention on Human Rights and Biomedicine in Biomedical Research) № 195) [10]).

According to paragraph 1.57 of the ICH GCP E6 (R2), the research's subject is defined as a person who participates in a clinical trial in the group receiving the test product or in the control group.

It should be noted that the term "person" is used to denote a physical party as a participant in a legal relationship. In this case, the person's death terminates his existence as a participant in legal relations.

The above provisions have legal significance and indicate that the terms "a person", "physical party", "law subject", "research subject", "a patient", "a healthy volunteer" are the terms used to denote a living person.

These features are reflected in the terminology used, in particular, in the legislation on transplantation of anatomical materials to humans, which distinguishes between the concepts of ***"living donor" and "corpse donor" ("dead person").***

For example, the Additional Protocol to the Convention on Human Rights and Biomedicine on Transplantation of Human Organs and Tissues (ETS № 186) [11] separately regulates the removal of organs and tissues from a living person – a living donor (Chapter III) and a deceased person (Chapter IV). It is stipulated that doctors who testify

to the person's death may not be those persons who are directly involved in the removal of organs or tissues from the deceased body or in subsequent transplant procedures or are responsible for potential recipients of organs or tissues (part two of Article 16 specified Additional Protocol).

Participation in the research of human medicines (living person) is a qualifying feature of medicines' clinical trial and one of the conditions. However, this is not a shortcoming of legal techniques and does not mean that there is a gap that must be eliminated by analogy with the law, applying to the Research conducted on the dead bodies, regulations on clinical trials, because it corresponds to a well-established international approach to understanding the nature of clinical trials.

The use of the body in the Study will take place after the person's death, i.e. after the termination of a person's right to life. Obviously, the deceased body cannot be examined by the patient and have the status of a research subject. In this case, it is the research object.

These findings and the content of clinical trial regulations indicate that they regulate only those researches that are performed on living people (including patients who are in critical and emergency conditions) but do not regulate the medicines' research on the deceased bodies.

Thus, the Research cannot be considered to be conducted with the participation of patients or healthy volunteers, and therefore, it does not belong to medicines' clinical trials.

Given the above, it can also be argued that the recording of information necessary for the Research of manipulation and test results should not be done using the patient's primary medical records used in medicines' clinical trials, as the last subject (patient or healthy volunteer) is no longer available due to death.

In addition, the procedure for obtaining permission from the regulatory body to conduct medicines' clinical trial, control over its conduct, its suspension's bases are aimed primarily at ensuring the protection of the rights, safety, and well-being of patients. This is stated in particular in the provision of ICH GCP E6 (R2), which is defined as an international ethical and scientific standard for planning and conducting research involving ***a human as a subje***ct, as well as documenting and presenting the results of such research.

However, since the Research of medicines is administered exclusively to the deceased body, which does not meet the definition of a patient (healthy volunteer), there is no need to assess the potential risk of the study for the subject in relation to his/her benefits.

This means that the legislative provisions determining the procedure for organizing, approving, conducting medicines clinical trials of drugs do not apply to the Research, because the latter does not meet the qualifying feature of the clinical trial, namely – has no subject, but will be conducted on the corpse, which is no longer a subject of legal relations, but is an object, but with a special legal regime, unless otherwise expressly provided.

For example, Guide 11 "Collection, storage and use of biological materials and related data" contained in the International Ethics Guidelines for Human Health Research, developed by CIOMS in collaboration with WHO, provides that the person whose biological materials and relevant data are used in the Research is the research participant and the ethical guidelines that apply to the study participants are applied in this situation. In addition, it indicates ***the use of samples and data of deceased bodies in the research*** **[12, p. 42].**

Thus, these International Ethical Guidelines distinguish between two types of research – with human participation and with the samples' and the corpse' data using.

The Research does not apply to the regulations on clinical trials of tissue and cell transplants (including cord (stem) cord blood stem cells) and examination of clinical trial materials. The last type of research is also carried out with the participation of a person and during its conduct, the use of the deceased as a body of the deceased is not regulated. In such studies, the deceased may only be a donor of anatomical material for transplantation or manufacture of bioimplants.

It is also necessary to dwell on the comparison of research and medicines' preclinical studies. Standards for the planning and conduct of preclinical studies of medicinal products in the EU are set out in Guidance EMA / CPMP / ICH / 286/1995 (ICH M3 (R2)) [13].

Medicines' preclinical Research **is a set of chemical, physical, biological, microbiological, pharmacological, toxicological, and other scientific studies that are conducted *before the start of clinical trials***. Preclinical studies of the medicinal product include laboratory preclinical studies and/or experiments on laboratory animals to determine the specific activity and safety of the medicinal product.

Animal models as well as *ex vivo* **and** *in vitro* **preparations can be used as test systems in preclinical studies of drug safety pharmacology.** *Ex vivo* **and** *in vitro* **systems may include but are not limited to, such systems as isolated organs and tissues, cell cultures, cell fragments, subcellular organelles, receptors, ion channels, transporters, and enzymes [14, p. 11].**

Thus, pre-clinical researches under current regulations do not cover studies performed on deceased bodies.

However, the Research has the same purpose as a preclinical study, namely: to predict the human response to the medicine and to minimize the risk of adverse reactions in humans to such medicines.

Normative prescriptions for preclinical research can be extended to research conducted on the deceased bodies only by standardizing the specifics of their organization and conduct.

Differences between these types of medicines' research do not mean that the study should be prohibited as different from other types of Research, the order of which is standardized.

Research is a type of scientific study in the field of health care, so it is subject to legal regulation of scientific research in general and scientific research in the field of health care in particular, including conducted by scientific, educational

institutions, or scientists. The Research is aimed at obtaining new scientific knowledge about the studied medicine, which will be recorded in documentary form.

However, the Research is possible only if the legality of using the corpse after his/her death.

In some countries, the relevant issues are regulated by law, which enshrines the right of an individual to order the transfer after his death of not only organs and other anatomical materials, but also bodies in general to scientific, medical, or educational institutions. Thus, these regulations create a legal basis for research using the deceased body by the relevant institutions.

However, like any medicines' study, the Research has its own specifics and the relevant features require a separate regulatory framework, as insufficient regulation of the use of the deceased body in research can cause not only legal but also ethical and psychological problems related, in particular, concerning the deceased.

For example, the Civil Code of the French Republic was supplemented by provisions on the inviolability of the human body by the Law of 29 July 1994 on the Inviolability of the Human Body. Thus, it was provided that the human body is inviolable and cannot be the subject of property law (Articles 16-1). In addition, it is provided that any agreements aimed at giving the human body property value are null and void (Article 16-5) [15, p. 24-25].

These regulations meet the requirements of Article 21 of the Convention for the Protection of Human Rights and Dignity of Biology and Medicine: the Convention on Human Rights and Biomedicine, according to which the human body and its parts as such should not be a source of financial gain.

The Trans-European Pedagogical Research Group on Anatomical Sciences has highlighted the fact that in Europe there are significant differences in legal and ethical requirements for using the body for anatomical research. Such differences reflect cultural and religious differences, as well as different legal and constitutional boundaries. There are different views on "ownership" of the body and on the need to develop special legislation in this regard. In addition, there are differing views on the acceptability of using unclaimed bodies by persons who have not given informed consent. For example, in the Italian Republic, according to the law, an unclaimed body can be transferred for educational purposes and research. In this case, the voluntary consent of the deceased is not required. In addition, the question of the possibility of ordering a person to transfer his/her body for scientific purposes is not regulated by law. However, there is no legal prohibition in this regard, so a person can use the tools by which the last will of the person, in particular, the will, to make such an order [7].

In the Netherlands, a person can transfer his/her body for use by the anatomical institute in medical science. To do this, it is necessary to write and sign a declaration by own hand that the person wants his/her body to be transferred to medical science after his/her death. The declaration is stored in the institute's documents, and copies are issued to the person and his/her family doctor. If a person is registered as a donor, priority is given to donation [16].

The current state of normative regulation of relevant issues, characterized by insufficient attention in the legislation of many states to the conditions and procedure of disposal of a human body in case of death, violates the principle of legal certainty and puts in uncertain legal position participants in such Researches, significantly reducing the protection of their rights and does not provide an adequate level of protection for the data obtained from such Researches.

Of course, it should be agreed that a person should be able to order the transfer of his/her body for research or educational purposes, as well as to limit the examination and dissection of the body [7], with certain statutory exceptions (for example, to determine the cause of death) law enforcement agencies).

It is considered that the right to consent to the use of the body after death should be granted only to an able-bodied adult without the use of the institution of informed consent of the legal representative used in clinical trials of medicinal products.

In this case, Researches on the content and purpose are close to the medicines' pre-clinical study, given that, in the process of regulatory regulation of their conduct may also take into account the normative developments in this type of medicines research.

CONCLUSIONS

Research using the human body (after establishing the fact of his/her biological death) can be organized and conducted as a scientific study, in particular by scientific institutions, educational institutions, or with the participation of individual scientists. The study is subject to regulations governing scientific activities, including in the field of health care.

Provisions using the human body are not subject to the provisions of the legislation on:1) medicines' clinical trials, 2) preclinical study of medicines and examination of materials of a preclinical study of medicines; 3) clinical trials of tissue and cell grafts and examination of relevant materials.

The state of normative regulation of medicines' research using the deceased body is unsatisfactory, because apart from the general norms on the scientific activity there are no special normative regulations, while other types of research of medical measures are sufficiently regulated at the legislative level.

However, given the nature and purpose of this research, which aims to obtain data on the medicines' effectiveness and safety, it is close to preclinical studies of such medicines, so the regulation of the latter can be supplemented by provisions on organization and conduct of medicines' research using of the corpse.

Normative regulation requires resolving the following issues: 1) granting a person for life, as well as revoking his/her consent to use his/her body after death in medical examinations (determination of the entity entitled to such an order or consent to a deceased person, form of order, circumstances that exclude the use of the body in medical

research); 2) the possibility of a relevant order from the close relatives of the deceased, if it does not contradict his/her order; 3) the right of the said persons to give appropriate consent to receive information regarding the use of the body in research; 4) approval of the Research by the ethics committee of the institution in which it will be conducted, and further ethical supervision of the Research; 5) prohibition of participation in the fact statement of the person's death of medical specialists who will carry out Research on a deceased body; 6) confidentiality of information on the use of the deceased body in the Research; 7) the subsequent corpse's fate after the Research's end.

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