REVIEW

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Patient's informed consent in clinical trials

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Abstract: The doctrine of informed consent is fundamental to all medical personnel involved in investigational research. Informed consent arose from the Helsinki Declaration that stated, 'concern for the interests of the subject must always prevail over the interests of science and society'. As clinical research is a part of medical practice, it is reasonable to assume that exceptions to fully informed consent that are defendable in medical practice can also be applied to clinical research. The exceptions to fully informed consent are waiver, incompetence, therapeutic privilege, emergency, or proxy.

Key words: ethic, informed consent, ICH-GCP

INTRODUCTION

What is Informed Consent? Patient information and informed consent is the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is also a continuing process throughout the study to provide information for participants. To help someone decide whether or not to participate, the medical staff involved in the trial explain the details of the study. It is obvious that consent should be provided in the local language and the research team can then provide an informed consent. The research team provides an informed consent document that includes details about the study, such as its purpose, duration, required procedures, and key contacts; risks and potential benefits are also explained, and the participant then decides whether or not to sign the document. Informed consent is not a contract, and the participant may withdraw from the trial at any time. The process of obtaining informed consent from a subjects is a critical point of entry for research participants. Patients learn about clinical trials in numerous ways, and there are also several factors affecting their decision-making capacity. Educational materials for patients and informed-consent documents present highly complex information that must be understood by the patients [1, 2]. Kuczewski and Marshall recommend adopting the approach that consent is an interactive and dynamic process, and many factors can influence the study participant's willingness to sign the document. These factors include: socio-economic background, cultural traditions, literacy and language ability, and interactions with physicians and other healthcare professionals [1].

Informed consent is designed to protect the individuals participating in clinical research trials. The participant should be able to review the document with doctors and ask questions about anything they do not understand. Official consent to participate in the trial is given when this document is signed, with the researcher and the participant retaining a copy each. However, the process of informed consent should not end there. The researchers are obligated to keep the participant updated and answer any questions the participant may have. Informed consent does not obligate the participant to finish the trial. A participant has the right to leave the trial at any time during the study [3, 4].

The manner and context in which information is conveyed is as important as the information itself. The ability to understand is dependent upon the patients' intelligence, rationality, maturity, and language, and it is necessary to present information in a way suitable for the subject's capacity to understand. The informed consent process presents some major challenges for study participants and research staff, e.g.

- Subject's hesitation to ask detailed questions,
- Variable presentation of the content,
- Difficulty verifying the subject's comprehension [1, 3].

Informed Consent in History. During World War II, doctors in Nazi Germany conducted horrifying research on prisoners in concentration camps. This research was carried out on involuntary participants who often died as a result of the experiments. After the war, many of these doctors were tried at Nuremberg for their crimes (US *vs.* Karl Brandt et al., Case I [Medical Case]. The International community was shocked by the revelations of their research. As a result of the trial, the Nuremberg Code was created in 1948. This international document was one of the earliest to address ethics in medical research. It stated that voluntary consent was mandatory before any clinical research could be undertaken. Voluntary consent meant that the participants were able to agree, were not being coerced to do the study, and understood the risks and benefits involved. The Code was adopted by the United Nations in 1948 [4, 5].

The Nuremberg Code. Sitting in judgment of Nazi doctors accused of committing barbarous acts in the name of research on human subjects during World War II, the judicial officials not only prosecuted the Nazis' actions, but also developed the Nuremberg Code to help prevent their recurrence. The Code combined the Hippocratic obligation of physicians to 'do no harm' to their patients, with their responsibility to obtain informed consent, which is not addressed in the Hippocratic Oath [5].

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> The first principle of the Nuremberg Code is as follows: The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision [5].

The Helsinki Declaration. Following publication of the Nuremberg Code, the World Medical Association published its own Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, which are better known as the Helsinki Declaration. Adopted at the 18th World Medical Assembly in Helsinki, Finland, in 1964, and amended at other assemblies thereafter, the Declaration has as its first and second principles the necessity of scientific validity of research and committee review of experimental protocols [6].

The World Medical Association was accused of trying to subvert the Nuremberg Code and distance physicians from Nazi medical crimes by attempting to have peer review supplant informed consent as a first principle in clinical research. Nevertheless, the Helsinki Declaration acknowledges the authority of the Nuremberg Code regarding consent and does not undermine it. Moreover, the documents together serve as models for US federal research regulations, which require both the consent of subjects and peer review of proposed research by Institutional Review Boards (IRBs) before such research can be performed [4, 7].

However, there were many unethical clinical research trials conducted during World War II in America and Britain. President Franklin Roosevelt created an Office of Scientific Research and Development to combat diseases such as dysentery, influenza and malaria, diseases that commonly affect soldiers. One of the research teams created a potential vaccine for dysentery, and to test it the researchers used institutionalised orphans and mentally retarded individuals. The orphans developed dangerously high fevers, thus proving that the vaccine did not work. Another research team deliberately infected psychotic patients at the Illinois State Hospital with malaria in order to test a cure. Penicillin, the wonder drug of the century, was tested on prisoners to find the most effective dosage. At the time, the attitude prevailed that it was necessary for some sacrifices to be made to benefit the whole of society. This was same premise used by the Nazi doctors in their research. After the war and the creation of the Nuremberg Code, many American medical researchers still felt the same and continued with unethical medical research [6, 8].

Many medical advancements came from World War II and the US government sought to continue this trend by creating the National Institutes of Health, which provided funds for experimentation. These funds were provided with no stipulations about the rights of the participants in the experiments. In the period between 1945-1966, the NIH funded 2,000 research projects, none of which used informed consent [6]. During this same period, a drug called thalidomide was being developed, a drug that was supposed to prevent miscarriages. The head of the Food and Drug Administration did not want to approve use of the drug because of dissatisfaction with test results. However, 200,000 American women were given the drug without knowing that it had not been approved – they were essentially taking part in a drug trial without their knowledge [6]. They were not warned of the risks, with the result that many babies of women taking this drug were born with extreme birth defects. Congress passed an amendment to the Food, Drug and Cosmetic Act that required doctors to inform patients if they were taking a trial drug. The mindset at that time, that these types of unethical trials were permissible because they benefited the whole of society, was slowly changing. One major event that brought this about was an article written by Henry Beecher that appeared in the June 16 1966 issue of the *New England Journal of Medicine* [9]. This article exposed many clinical research trials that had been funded by the government that were highly unethical. He gave 22 examples of such unethical research. One of the examples was that mentally retarded children at a state school were infected with hepatitis virus. The researcher who carried out this experiment eventual became head of the paediatrics department at New York University. He felt that he was justified because a cure for hepatitis would benefit many more people. In each of Beechers examples, clinical trials were conducted on marginal members of society, such as the poor, the developmentally disabled, and the senile. These marginalized members of society were incapable of making a decision to participate in these trials. The NIH had already been endeavouring to make clinical research more ethical, and in July 1966 a set of standards was issued that called for an independent Institutional Review Board to review all research conducted by an institution. The Review Boards examined the risks and benefits of research, and how the researcher intended to obtain informed consent. Shortly afterwards the FDA, in its investigations of new medicines, also created rules for obtaining informed consent [8].

One of the major events that brought the issue of obtaining informed consent to the public notice was the revelation of the Tuskegee Syphilis Study [10]. The study was conducted by the United States Public Health Service between 1932 and 1972, when it was finally revealed to the public. The purpose of the study was to examine the long term effects of syphilis and was carried out on 400 African American males, who were primarily poor sharecroppers. These men all had syphilis, but were unaware of it. They were also unaware of the true nature of the experiment. The most horrifying aspect of the experiment was that in the 1950s penicillin was proved to be effective cure for syphilis, but the researchers did not treat the men syphilis, and even prevented other doctors who saw the participants from treating the syphilis. As many as 100 men may have died from complications as a result of their untreated syphilis [10]. The study was revealed in 1972 by a researcher who had worked on the project, and his newspaper article shocked the country and caused the project to be shut down. In 1997, President Clinton formally apologized for the study [11].

The patient who is incapable of giving informed consent: the requirements of the Directive. The Directive points out that special protection should be given to patients who are incapable of giving legal consent to clinical trials. It elaborates further that, in the case of persons incapable of giving informed consent, other than children, 'such as persons with dementia, psychiatric patients etc.' [12], inclusion should be on an even more restrictive basis. Article 5 requires furthermore that such persons must receive information according to their

capacity of understanding regarding the trial, the risks, and the benefits. In addition, the explicit wish of the subjects who are capable of forming an opinion and assessing the information must also be taken into consideration by the investigator [12]. To increase patient protection, the Directive requires the written consent of the patient's legal representative, and further states that the notion of a legal representative should refer back to existing national law. The Directive does not expressly refer to the emergency patient or the patient in an Intensive Care Unit (ICU).

The process by which the patient/subject shows his/her willingness to accept medical treatment suggested by a physician, after being informed about all aspects (including risk and benefit) of the particular treatment, is called 'Informed Consent'.

In general, in medical science the term 'informed consent' can be used in routine medical practice as well as in ethical clinical research. However, informed consent in routine medical practice differs from that in clinical research. In routine medical practice, the primary goal of the physician is to treat the patient, where the patient rightly assumes that the physician's motives are well-intended. In routine medical practice, therefore, a patient's consent is not the mandatory requirement, except for potentially hazardous treatments or surgical processes. In clinical research, the primary goal of the clinical researcher is to test a scientific hypothesis for safety and efficacy of the new drug under investigation. The researcher faces a conflict of interest between what is good for the current patient, the future patient, the sponsor, and the researcher himself. This conflict of interest may influence the safety of the subject. To protect and ensure the subject's safety in the clinical trial, the documentation of an effective and efficient consent process is the mandatory requirement for regulatory approval [13].

Written informed consent has to be obtained voluntarily from each and every subject participating in a trial. The investigator, the medically qualified person under whose supervision the trial has to be conducted, is responsible for obtaining efficient informed consent. Written informed consent must be documented on an informed consent form preapproved by an Ethics Committee, or other regulatory authority. If the subject is unable to give consent, it may then be obtained from the subject's legally acceptable representative, who can be a blood relative (father/ mother/ son/ daughter), spouse, or anyone who has a close association and is legally authorized. If the legal representative is also unable to read and understand the consent form, an impartial witness must be present during the informed consent discussion and read the consent form or any other written information provided to the subject. An impartial witness is a person who is independent of the trial, and who could not be unfairly influenced by the investigator or other people involved in trial [14].

The investigator or his delegate must discuss all pertinent aspects of the study with the subject (and legally acceptable representative or impartial witness, if applicable). The summary of the consent form should include (but not be limited to) information that the trial involves research, the purpose of trial, treatment options, potential risk(s), reasonably expected benefits, alternatives available for treatment of the subject's health problem, expected duration of the study, and any other relevant information. It must also clearly state that the participation of the subject in the trial is voluntary, and that the subject may withdraw from the trial any time. All queries or doubts of the subject regarding a new drug under investigation, or any other aspect of the conduct of the trial, must be resolved. Once all such queries have been resolved and the subject has shown his/her willingness to participate in the trial, informed consent must be documented [14].

The consent form must be signed and dated by the subject (and legally acceptable representative or impartial witness, if applicable), and also by the person conducting the informed consent discussion. For non-English speaking subjects, the summary and consent form must be in the local vernacular language. The written translated version of the consent form must be approved by an Ethics Committee in accordance with local regulatory requirements. The method by which the informed consent was obtained must also be documented. For paediatric clinical trials, consent is required from the parents as well as from the child to show the willingness to participate in the trial.

If any new safety information on the product under investigation becomes available during the course of the study, or any change in the conduct of the trial has been implemented which may affect the subject's decision to continue with the trial, re-consent must be obtained on an updated version of informed consent form.

The concept of informed consent is supported by the right of consent and refusal contained within common law.

However, ethical clinical research is based on the Helsinki Declaration and the guidelines for ethical clinical research, known as the International Conference of Harmonization and Good Clinical Practice Guidelines (ICH GCP Guidelines). The main objective of ICH GCP guidelines is to protect the safety and well-being of the subjects participating in clinical trials. This objective has been ensured with the process called 'Informed Consent'. The reliability and accuracy of clinical trial data depend on the reliability of the informed consent process, which is considered the backbone of all ethical clinical research [12, 15, 16].

Conclusion. Research involving human subjects and biological sciences poses complex ethical issues, and requires careful thought and consideration on the part of both researcher and research participants. The goal of this paper is to assist all those involved in the informed consent process as it occurs in everyday clinical practice (i.e., not in the research setting) in order to improve the patient-physician communication that is so crucial in creating truly informed patient decision-making about major treatment options.

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