



Volunteers for clinical trials: from the history of abuses and exploitation to the inclusion movement, and to an income resource

Voluntários para ensaios clínicos: de uma de história de abusos e exploração até o movimento de inclusão e fonte de renda

Voluntarios para ensayos clínicos: de una historia de abusos y explotación hasta el movimiento de inclusión y fuente de renta

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Abstract

Medical research is essential to develop new and better therapies, increase social standards and a better life for all of us. Scientific curiosity has helped to achieve many successful innovations, but history also demonstrates that research can lead to abuses of individuals neglecting autonomy and integrity of the human being. Since the 1960ies we have witnessed a continuous development of international regulations and ethics guidelines (*soft law*) in medical research, leading to a higher quality of scientific results. An important focus lies on recognizing human vulnerability and a therefore adapted informed consent procedure. Our modern clinical trials structure requires the inclusion of healthy volunteers in the first phases of the development of a new medicinal product, leading to new ethical questions and challenges. The Corona-Pandemic has accelerated vaccine development in a successful way also leading to a new importance of healthy volunteers in the medical research landscape.

Keywords

COVID-19. Medical research. Ethics. Healthy volunteers. Informed consent.

Resumo

A pesquisa médica é essencial para desenvolver novas e melhores terapias, aumentar os padrões sociais e uma vida melhor para todos nós. A curiosidade científica ajudou a alcançar muitas inovações bem-sucedidas, mas a história também demonstra que a pesquisa pode conduzir a abusos de indivíduos, negligenciando a autonomia e a integridade do ser humano. Desde a década de 1960, temos testemunhado um desenvolvimento contínuo de regulamentos internacionais e de diretrizes éticas (*soft law*) em pesquisa médica, levando a resultados científicos de maior qualidade. Um foco importante está no reconhecimento da vulnerabilidade humana e, conseqüentemente, num procedimento de consentimento informado adaptado. A nossa estrutura moderna de ensaios clínicos requer a inclusão de voluntários saudáveis nas primeiras fases do desenvolvimento de um novo medicamento, suscitando novas questões e desafios éticos. A pandemia de coronavírus acelerou o desenvolvimento de vacinas de uma forma bem-sucedida, contribuindo também para uma maior importância de voluntários saudáveis no cenário da pesquisa médica.

Palavras-chave

COVID-19. Pesquisa médica. Ética. Voluntários saudáveis. Consentimento informado.

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Resumen

La investigación médica es esencial para desarrollar terapias nuevas y mejores, aumentar los estándares sociales y una vida mejor para todos nosotros. La curiosidad científica ha ayudado a lograr muchas innovaciones exitosas, pero la historia también demuestra que la investigación puede conducir a abusos de individuos que descuidan la autonomía y la integridad del ser humano. Desde la década de 1960 hemos sido testigos de un desarrollo continuo de las regulaciones internacionales y de las directrices éticas (*soft law*) en la investigación médica, lo que ha llevado a una mayor calidad de los resultados científicos. Un enfoque importante radica en el reconocimiento de la vulnerabilidad humana y, por lo tanto, en un procedimiento de consentimiento informado adaptado. Nuestra moderna estructura de ensayos clínicos requiere la inclusión de voluntarios sanos en las primeras fases del desarrollo de un nuevo medicamento, lo que genera nuevas cuestiones y desafíos éticos. La pandemia de coronavirus ha acelerado el desarrollo de vacunas de una manera exitosa, lo que también ha dado lugar a una nueva importancia de los voluntarios sanos en el panorama de la investigación médica.

Palabras clave

COVID-19. Investigación médica. Ética. Voluntarios sanos. Consentimiento informado.

Historical background and the development of laws and guidelines

Although there have been already as early as 1900 regulations for medical research in the German Empire, and renewed regulations in the *Reichsrichtlinien* from 1931 (1), the starting point in the history of clinical research in regard to our current standards has been the Nuremberg Doctors Trial of 1946/47 with the Nuremberg Code. The Code emphasized explicitly the importance of the autonomy of the individual and his freely given *informed consent* for the participation in a medical experiment. This document, with its ten principal rules, is seen as the starting point of standardization of clinical research. However, autonomy, as prerequisite for any clinical experiment, is not only timely because of the Nuremberg Code, but also sign of an all comprising paradigm change from paternalism to self-determination of the human being. From the early 1960ies on, the Code was seen as a “fundamental document on research procedure” (2).

Right after World War II, the World Medical Association (WMA) (3), was founded as an international organization of medical associations with the goal to improve international relations between the national associations of medical doctors in order to – last but not least – further *peace on earth*.

The WMA (3) developed from early on an *International Code of Medical Ethics*, as well as an intense engagement with the development of ethics and human experiments (4). Out of this engagement originated the *Declaration of Helsinki*, which was published at the WMAs General Assembly, in Helsinki in 1964, and turned out to be the most important procedure for

clinical research. The Declaration is not a binding law; it is a guideline, representing *soft law* and it is the basic document for clinical research worldwide. The significance of such a guideline is, that it represents a harmonized standard and thus makes it possible that (multicentric) research projects can be conducted in various countries and regions of the world. The Declaration defined rules for therapeutic and non-therapeutic research and, in the tradition of the Nuremberg Code, required informed consent of the person to be enrolled.

After 1964, the *Declaration of Helsinki* was amended many times. One of the most important amendments in the history of the Declaration was the amendment of Tokyo in 1978, where the requirement for the establishment of *Ethics Committees* was introduced. From then on, Ethics Committees were responsible for approving the research protocol in human experimentation. It was required that members were composed of doctors and lay persons, men and women, independent from the investigator and the institution. Ethics Committees play a crucial role in the evaluation of the documents submitted for the research project. They have to assess if the risk/benefit ratio is acceptable and they have to examine the procedure for obtaining informed consent.

However, the history of ethical violations of medical research has not ended with World War II. In later years and in other areas of the world, serious transgressions have happened. A particular repulsive human experiment – without proper information of the participants and with intentional withholding of information about a proven therapy, Penicillin, which was available in the 1940ies – was the *Study of Untreated Syphilis in the Negro Male*, also called Tuskegee Experiment after the site of the study in rural Alabama (5). The study, conducted by the U.S. Public Health Service started in 1932. Its goal was to observe untreated Syphilis, and continued long after Penicillin was available as effective treatment. Public pressure ended it in 1972. It was much later when President Clinton apologized publicly to the victims and families of the study (6).

In 1966 the Harvard anesthesiologist Henry K. Beecher (7) published an article, in the *New England Journal of Medicine*, reporting on 22 studies with deficiencies in the study design and especially in the informed consent procedure. This article was very influential and speeded up a broad discussion regarding ethical aspects of medical research. From then on, ethical aspects were increasingly in the center of discussion, national laws were progressively established governing medical research and a great number of guidelines (*soft law*), by various scientific organizations, was published. In the center of all these laws and guidelines

was the preservation of the autonomy of the potential participant describing elements of the information procedure and consent prerequisites.

In the United States, the so called *Belmont Report* was presented by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1978, and is seen as the *cornerstone* of federal research in the United States (8).

Another concept which signifies an important milestone in the area of ethical and scientific quality standards is *Good Clinical Practice*: The International Conference on Harmonization (ICH), composed of expert working groups from industry and regulatory bodies representing the European Union, the United States and Japan published guidelines for Good Clinical Practice (GCP). These guidelines were insofar important, as – in a world of many different legal systems – they guaranteed a harmonized scientific and ethical standard which made it possible for the industry to conduct multicentric clinical trials internationally in order to develop new drugs for marketing approval (9). Good Clinical Practice was furthermore the foundation of European Laws beginning from 2002 on and governing clinical drug research.

The Council of the International Organization of Medical Sciences² (CIOMS), an international, non-governmental and non-profit organization established jointly by the World Health Organization (WHO) and the United Educational, Scientific and Cultural Organization (UNESCO) in 1949, published also ethics guidelines, in 1982, which were intended at advancing cross-cultural research. In the 1980ies, international research became more important, and the HIV/AIDS epidemic increased the need for international cooperation in the field of medical research.

All these guidelines and laws have in common, that they describe in detail the pre-conditions of the ethical and legal principles and norms that govern the inclusion of a patient or healthy volunteer in a medical research project. Since then, the level of protection for research participants has been continuously improved.

In order to include a person and to obtain his or her consent – patient or healthy volunteer – the following has to apply:

- the person has to be legally and mentally competent,
- the person has to be able to thoroughly understand the information,
- the person has to give his or her informed consent.

² <https://cioms.ch/>.

Special situations – vulnerability

The term *vulnerability* is essential in the field of bioethics. Its notion derives from the field of human experimentation and represents the characteristic of single individuals, and specific populations “most exposed and poorly defended against the maltreatment and abuse of others” (10). Therefore, the procedure to give informed consent protects the fundamental rights of a person to execute his or her autonomy.

Special provisions exist for persons who are not capable of giving informed consent, either legally like children and minors, or incapacitated adults like those with dementia and temporarily incapacitated persons like those with sepsis, or heart attack or an accident. For all of those groups of persons, a substitute consent or assent has to be given. National laws usually provide a regulation about such a procedure.

Further groups require also special consideration as their autonomy is limited, which means that they cannot participate freely in the consent procedure. Those are persons who are in a hierarchical situation with the responsible investigator of the research project as they might hope for advantages if they comply, or fear retaliations if not. This applies to students, employees, nurses and other technical personnel etc. in a hospital.

Prisoners are a vulnerable group because of the potential of coercion, also subordinate populations (military, armed forces). But there are also other persons and groups who are considered vulnerable like migrants, refugees, the homeless etc.

Participant recruitment in clinical trials

In the past years, we witnessed that people have increased interest in and knowledge about the body and its functions, their curiosity in medicine has been woken up. People have gained much more *health literacy* than they had before. And it is clear that in order to provide a functioning informed consent procedure, it is necessary to assess the health literacy capacity, the reading level and also the comprehension via adequate tools (11).

One obvious reason is the internet and its possibilities in generating knowledge. Through the internet and its various websites people do also learn more about medical research. There are many informative websites about general health issues, but there are also databases like www.clinicaltrials.gov. This is an important registry where clinical trials from around the world are listed and thus provides transparent information to the public. This registry has been created through an initiative of the Committee of the Medical Journal Editors

(ICMJE) from the most important journals to avoid selective reporting and the withholding of clinical trials results (12).

Patient support groups or patient representatives are following medical research in their specific field of disease and in many cases are eager to participate in a clinical trial in order to benefit early on from a new and potentially efficient therapy. These volunteers are recruited often via advertisements and they are subjected to an extensive information procedure about the clinical trial before they are asked to give their informed consent. There needs to be a whole array of aspects included in the information. The required aspects are listed in the various guidelines describing the informed consent process.

Healthy volunteers and their role in clinical research

Clinical trial registries not only provide transparent information in order to guarantee later publication of results, but also information about the possibility of participation in a clinical research project as patient suffering from the respective disease or healthy volunteer. Healthy volunteers are essential participants in the early phases of a clinical trial. When a medicinal product is new in the pipeline of development and enters the phases of clinical trials, healthy volunteers are needed to study how the drug is interacting with the human body. Here safety and dosage of a new drug are assessed. However, (cancer-) patients, suffering from this specific type of cancer are needed if the trial is testing a cancer drug, as the potent medicinal product will not be applicable for healthy individuals.

One important content, which also needs to be actively addressed, is the *therapeutic misconception*, which means that in a first phase of clinical research, there is no direct benefit to be expected, as the intention of the clinical trial is to obtain information about the safety and the participation in a trial may not be mistaken for a treatment (13).

All other trials than cancer-trials are looking for healthy volunteers in phase I, and out of safety concerns – normally for young healthy adult males. It took a long time to lift the ban against women of childbearing potential to be included in phase I trials (14). A ban in the early phases of a clinical trial would only postpone the risks to a later stage of clinical research. There need to be other safeguards to protect women of childbearing potential and also pregnant women (15). Exclusion from the participation in a clinical research project is no solution because women take medicinal products as much as men, therefore there is an urgent need to include women in the clinical trials and to investigate efficacy and safety.

Clinical trials are important. They are necessary to obtain information and data of the efficacy and safety of new drugs, medical devices and therapies. Only carefully designed clinical trials can lead to correct data and a successful licensing of the drug or medical device. In the past 50 years, pharmaceutical companies and academic institutions organized very efficiently the development of new drugs in early phases of clinical trials with healthy volunteers.

The need for healthy volunteers is great and, as they cannot benefit medically from their participation in the research project, it is accepted that they receive a financial compensation for the time they invest. While in Northern countries young university students enroll in clinical trials and have preferences regarding the level of risks they would accept (16), in resource limited areas of the world they are often people who might not understand the complex situation of a medical research project and therefore accept risks they do not fully understand because of their lack of health literacy. Furthermore, another reason for accepting a risk is the participation might be a source of income, with all dangers this encompasses, especially that they might be enrolling in several clinical trials in parallel which can lead to drug interactions. Some countries even set up registries for healthy volunteers in order to avoid their participation in several trials at the same time and in order to guarantee adequate financial compensation (17). Healthy volunteers, even if they are not in a hierarchical order with the responsible investigator of this project, are vulnerable persons, as they might agree to accept risks, which they cannot foresee.

Vaccine trials

The Corona-pandemic with its urgent need to develop quickly efficient vaccines, has involved thousands of healthy volunteers in vaccine trials. A specific type of vaccine trial is the *human challenge trial*. Those are tests, where healthy volunteers are intentional and under clinical conditions infected with the investigated pathogen to learn more about the disease it causes and to test vaccines quickly. In regard of the specific burdens like being confined to the trial unit and bearing the risk of suffering from the disease under investigation, a fair compensation is accepted and sometimes even encouraged. However, it needs to be ruled out, that the payment presents an undue inducement (18). Healthy volunteers are more likely to focus on being altruistic and on the risk and not on the amount of money offered when asked about their decisions (19). Human challenge trials have been conducted for other diseases like Malaria to develop a vaccine quicker, as one needs less participants than in

field trials to achieve viable results. But unlike as for Malaria, for COVID-19, there is no specific treatment, and no *magic bullet* in the sense of an efficient rescue therapy, which poses a potential danger (20) leading to a controversy regarding the permissibility. The healthy volunteers are young and therefore not as susceptible for severe disease. Some groups however, including Black, Asian, and minority ethnic groups, are at higher risk, which has to be considered when recruiting for such trials without forgetting that those groups are disproportionately affected and therefore need to be included in the research.

Conclusion

Consent expresses the appreciation of the dignity and the rights of human beings. Therefore, the procedure of clear and understandable information about risks and benefits, burdens and obligations as well as informed consent is crucial. We should be aware that this applies not only to medical treatment in general, but especially to the many circumstances of medical research as stated in Article 6 of the Universal Declaration on Bioethics and Human Rights of UNESCO (21).

References

1. Ruisinger MM. Geschichte des Humanexperiments, Zur Entwicklung der Forschung am Menschen. Standards der Forschung, Historische Entwicklung und ethische Grundlagen klinischer Studien. Bern: Peter Lang D; 2007. p.19-35.
2. Czech H, Druml C, Weindling P.(eds). Medical Ethics in the 70 Years after the Nuremberg Code, 1947 to the Present. Wiener klinische Wochenschrift. 2018 Jun;130(3):159-253.
3. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053.
4. Wiesing U, Ehni H-J. The Declaration of Helsinki of the World Medical Association: its history, meaning and future. In: Wiesing U, Parsa-Parsi RW, Kloiber O (eds): The World Medical Association Declaration of Helsinki: 1964-2014, 50 Years of Evolution of Medical Research Ethics. Cologne: Deutscher Ärzte-Verlag GmbH; 2014. P. 18-35.
5. Rockwell DH, Yobs AR, Brittain Moore M. The Tuskegee study of untreated syphilis: the 30th year of observation. Archives of Internal Medicine. 1964;114(6):792-798.
6. Clinton WJ. Remarks by the President in apology for study done in Tuskegee [video]. 1997.

7. Beecher HK. Ethics and clinical research. Biomedical ethics and the law. Boston, MA: Springer; 1966. p. 215-227.
8. Beauchamp TL. The origins and evolution of the Belmont Report. In: Childress JF, Meslin EM, Shapiro H (eds.). Belmont revisited: ethical principles for research with human subjects. Washington D.C: Georgetown University Press; 2005. S 12–25.
9. European Medicines Agency. ICH E6 (R2) Good clinical practice. Available from: <https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice>
10. Patrão Neves M. Respect for Human Vulnerability and Personal Integrity. In: Ten Have H, Jean MS (eds). The UNESCO Universal Declaration on Bioethics and Human Rights. Paris: UNESCO Publishing; 2009. 370 p.
11. Montalvo W, Larson E. Participant comprehension of research for which they volunteer: a systematic review. *Journal of Nursing Scholarship*. 2014;46(6):423-431.
12. Laine C, Horton R, DeAngelis CD, Drazen JM, Frizelle FA, Godlee F, Haug C, Hébert PC, Kotzin S, Marusic A, Sahni P. Clinical trial registration: looking back and moving ahead. *JAMA*. 2007 Jul 4;298(1):93-4.
13. McCormick J. How Should a Research Ethicist Combat False Beliefs and Therapeutic Misconception Risk in Biomedical Research? *AMA J Ethics*. 2018;20(11):E1100-1106. doi: 10.1001/amajethics.2018.1100.
14. Sherman LA, Temple R, Merkatz RB. Women in clinical trials: an FDA perspective. *Science*. 1995 Aug 11;269(5225):793.
15. Macklin R. Enrolling pregnant women in biomedical research. *The Lancet*. 2010 Feb 20;375(9715):632-3.
16. Chen SC, Sinaii N, Bedarida G, Gregorio MA, Emanuel E, Grady C. Phase 1 healthy volunteer willingness to participate and enrollment preferences. *Clinical Trials*. 2017 Oct;14(5):537-46.
17. Leisinger KM, Schmitt KM, Bompert F. Healthy Volunteers in Clinical Studies. In: Schroeder D, Cook J, Hirsch F, Fenet S, Muthuswamy V. (eds). *Ethics Dumping. SpringerBriefs in Research and Innovation Governance*. Springer, Cham; 2018. https://doi.org/10.1007/978-3-319-64731-9_8
18. Blumenthal-Barby J, Ubel P. Payment of COVID-19 challenge trials: underpayment is a bigger worry than overpayment. *J Med Ethics*. 2020;0:1–2. doi:10.1136/medethics-2020-106901
19. Grady C et al. Motivations, enrollment decisions, and socio-demographic characteristics of healthy volunteers in phase 1 research. *Clinical Trials*. 2017;14(5):526-536.



20. O'Neill McPartlin S. Covid-19 vaccines: Should we allow human challenge studies to infect healthy volunteers with SARS-CoV-2? *BMJ*. 2020;371:m4258. doi: <https://doi.org/10.1136/bmj.m4258>

21. UNESCO. Universal Declaration on Bioethics and Human Rights. Available from: <https://en.unesco.org/themes/ethics-science-and-technology/bioethics-and-human-rights>

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