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An Overview of the Nuremburg Code, Declaration of Helsinki and Belmont Report in the Context of Promoting Ethical Global Clinical Trial Conduct

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Abstract

Globally, clinical trials are widely accepted as the gold standard for determining the safety and efficacy of clinical interventions. As laws and regulations vary by country and by region, standardized guidelines have been developed to promote global adherence to a set of ethical values and benchmarks with the goal of protecting research-subjects from both physical and non-physical harm. Three critical guidelines are: The Nuremburg Code, The Declaration of Helsinki and The Belmont Report. Observance of these guidelines is critical for the successful conduct of a clinical trial not only in terms of ensuring subject safety but also as it relates to promoting data integrity. However, further considerations need to be taken as it relates to artificial intelligence, wearable technologies, social media clinical trial recruitment and other 21st century solutions that are not addressed by the guidelines.

Keywords: Regulations • Guidelines • Nuremburg • Belmont • DoH • Ethics

Abbreviations

DoH: Declaration of Helsinki; NC: Nuremberg Code; PISs: Patient Information Sheets; ICFs: Informed Consent Forms; NHS: National Health Service; WHO: World Health Organization; GCP: Good Clinical Practice; AI: Artificial Intelligence; WMA: World Medical Association.

Introduction

The historical advancement in the field of medicine witnessed in the 20th and 21st centuries is in large part characterized by a wide range of carefully planned clinical trial efforts. These clinical trials were carried out by researchers from a variety of medical specialties as they sought to achieve unique goals across various therapeutic areas [1-3]. Despite the differences in clinical interventions, most clinical trials of the past 50+ years have been managed in accordance with a universal set of ethical principles that are widely accepted by virtually all scientists, clinician-researchers, industry representatives, Contract Research Organization professionals and others involved in today's clinical trial efforts. A careful review of three key ethical principles is presented and includes The Nuremburg Code, The Declaration of Helsinki and The Belmont Report.

Literature Review

Nuremberg code

Perhaps the best-known ethical research principle, The Nuremberg Code, refers to a set of guidelines created as a result of the dreadful human subject experimentation carried out by Nazi Germany and its allies. Throughout the war, Nazi doctors inflicted widespread atrocities on their patients by unwillingly subjecting them to clinical trials that amounted to little more than torture experiments. This included grotesque 'high-altitude' experiments in which concentration camp inmates were forced, without oxygen, into high-altitude chambers that duplicated conditions at up to 68,000 feet (nearly 21 kilometers); removal of sections of bone, muscle, and nerves, including whole legs removed at the hips to transplant to other victims; artificial wounding and exposure to mustard gas; wounding of two limbs and treatment of one but not the other with sulfonamide antibiotics and intramuscular injection with fresh typhus [4].

On 19 November 1945, roughly six months following the end of World War II in Europe, the Allied Powers enacted an International Tribunal [5]. This Tribunal culminated in a series of trials being held against suspected major war criminals and Nazi sympathizers who held various political appointments, military assignments and other high-profile positions before and during the war [6]. Charges levelled in the trials included the abovementioned torturous activities that were conducted under the guise of medical/clinical research. Nuremberg was symbolically selected as it was the ceremonial birthplace of the Nazi Party [5].

The first trial proceedings conducted by the Nuremberg Military Tribunals took place in 1947. It was popularly referred to as 'The Doctors' Trial' [7,5]. A total of 23 physicians (all members of the German Nazi Party) were tried for crimes against humanity following the atrocious experiments they conducted on groups of unwilling war prisoners who doubled as their patients [7]. Fischer explains that the interventions ranged from the dehumanizing tattooing of Jewish prisoners with identification codes to the previously described barbaric high-altitude torture. As noted by [3], of the 23 accused, 16 were found guilty. Their jail sentences ranged from 10 years to life imprisonment. Seven of the 16 received death sentences.

The court rulings in Nuremberg Trials also led to the establishment of Nuremberg Code, which consists of ten ethical principles that must be strictly followed when carrying out human subject research. The first principle in the Code requires researchers to obtain the voluntary consent of each participant before carrying out an experiment. Today, this is widely interpreted as requiring the voluntary written consent of participants, unless the patient is unable to provide written consent. In practice, this is collected on what are known as Patient Information Sheets (PISs) or Informed Consent Forms (ICFs). Electronic versions of the same are also available and acceptable according to various regulatory agencies such as the United Kingdom's National Health Service, commonly known as "the NHS" (National Health Service, 2018). The second principle stipulates that the results obtained from any human-based experimentation must be of benefit to society, not attainable by other means and that the trials are done for a purpose other than unnecessary curiosity

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[8,5]. Thirdly, the court advised that all human experiments need to be based on previously conducted experiments on animals and that the anticipated results justify the performance of the human trial. Fourthly, all experiments must be framed in a way that avoids physical or mental harm or suffering to the participants. The fifth ethical principle prevents all researchers from carrying out any form of the experiment that is believed to result in the death or disability of the subject [9]. Sixthly, the risks associated with the experiment in question should never exceed the anticipated benefits. The seventh principle requires researchers to use adequate facilities and cautionary procedures to ensure the maximum protection of the subjects. The eighth principle calls for all human-based experiments to be carried out exclusively by highly qualified scientists. The ninth point of the Code states that all subjects must have the opportunity to withdraw their participation from an experiment at any time of their choice [6,2]. Lastly, the tenth point of the Nuremburg Code states that the scientist in charge of the experiment must be ready to terminate the process in the event that an injury, disability, or death of a participant occurs or there is probable cause to believe that such events are likely.

The Nuremberg Code has had a far-reaching impact on clinical trials despite the fact that it has never been officially accepted as a binding law by any nation, nor did any government implement it as its official ethical guideline for clinical research [10,11]. That being said, the idea of ethical human subject research as described by the Nuremburg Code was so widely accepted that it led to the development of a set of even more detailed principles that today are the basis for clinical trial conduct. These principles are known as Good Clinical Practice (GCP). GCP is an approach that offers a unique standard for studying, implementing, conducting, and analyzing clinical trials [8]. Today, GCP is globally considered to be a combination of numerous thoughts, precedents, as well as lessons learned throughout the history of clinical research on the topic of what is ethical and justifiable in terms of human subject trials. The Nuremberg Code is, without doubt, the foundation stone for GCP. It can therefore be said that a clinical trial must be deeply rooted in the specifics of the Nuremberg Code if it is to be successful.

Unfortunately, even today, some clinical trials fail on this basic premise of human dignity. In 2019, a French professor was accused by the Ministry of Health of performing an unauthorized clinical trial for a skin patch to treat Alzheimer's, Parkinson's and other neurological diseases. The trial was not conducted in a medical facility but rather in a monastery and it is being suggested that the patients were not adequately informed of the risks [12]. Fortunately, these situations are far and few between and widely condemned by the research community. That being said, it should also be noted that Germany had clinical trial rules in place as early as 1931, including laws which stated that "The Deutsche Reich forbids innovative therapy unless the subject or his legal representative has unambiguously consented to the procedure in the light of relevant information provided in advance…" though we know that those rules sadly did not apply to all humans equally [13].

Declaration of Helsinki

Abbreviated as DoH and developed by the World Medical Association (WMA) [14], the Declaration of Helsinki is a crucial milestone in the field of clinical research as it unifies and summarizes a set of ethical principles to be followed when carrying out human subject trials. As with the Nuremburg Code, the DoH has not been recognized under international law. Instead, the document owes its legal powers to the extent to which it has been acknowledged, accepted, and codified in national and regional directives and legislation. Historically, the implementation of DoH began in 1975. Since then, it has been revised several times with both minor and major updates all occurring during WMA annual meetings. It was most recently revised at the 64th WMA General Assembly in Fortaleza, Brazil in October 2013. Significant changes accepted in 2013 include stating that physicians cannot participate in clinical trials unless they are confident that the benefits of the research outweigh the risks, and that the presented risks have been adequately assessed. This is a higher threshold than previous versions which only required physicians to protect the life, dignity, self-determination, health, privacy, confidentiality and integrity of the participants [15]. It also places a greater burden on clinicians to ensure that the risks have been properly identified. The overarching previous themes of the DoH have remained intact despite numerous updates over the years. For example, the 2013 DoH [16] is addressed primarily to physicians though others "involved in medical research involving human subjects" (para. 6) are encouraged to adopt the principles. The same audience was targeted in the 2008 version. Considerations for the wellbeing of human subjects and careful consideration of the risks and benefits to the subject have been basic DoH principles since the 1964 version which specified that "every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others" (WMA, 1964, p.1) which echoes the 2013 version's instructions that "Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects" (WMA, 2013, para.12). Structurally, the sections continue to cover the same topics as in previous versions, but with more pertinent information for today's researchers.

The first section (i.e., Section A) of the 2013 DoH emphasizes the physician-researcher's responsibilities as it relates to protecting the health and wellbeing of the research participants. This section reminds each medical practitioner that vulnerable populations engaged in any form of research must be closely monitored and fully protected from all forms of physical or psychological injuries. Fischer [7] identified people who are economically and medically disadvantaged as the main examples of these special populations. Additional examples include people who lack basic reading and writing skills or individuals who may be compelled to give the consent under duress. Furthermore, subjects who may not necessarily benefit from the study on a personal basis and those for whom the research intervention is combined with their standard of care treatment(s) are protected by the DoH special populations principles.

Section B of the DoH provides a comprehensive discussion on the basic principles that must be strictly observed when planning and executing all forms of medical research [1,3]. This section emphasizes the need for strictly following the points outlined in the Nuremberg Code, such as the inherent need to ensure that all human trials are rationally based on the available evidence. However, it is important to note the fact that the DoH significantly widens the principle of voluntarism as spelled out in the Nuremberg Code. The DoH asserts that study respondents need to give their written consent for participation in any form of medical research after being fully informed and educated on the setup, goals, and sources of funding for the impending study. Participants should also have an adequate understanding of the anticipated study's risks and benefits, and they must be made aware of the sources and implications of potential conflicts of interest, their inherent moral right to be excluded from the research voluntarily, and the affiliations of the researchers before obtaining their informed consent [7,14,17] Further, only populations with a higher probability of benefiting from the study in question should be recruited to the clinical trial.

Per DoH, people regarded as members of vulnerable populations should be excluded from the trial if qualified non-vulnerable populations available for the research [17]. Further, populations that require a third party to provide consent on their behalf (e.g. patients who are temporarily paralyzed) are required to give assent as a proof that they have agreed to take part in the study. Researchers are morally and ethically obliged to look for signs of undue influence in the study enrollment process. The last section of DoH, Section C, provides a comprehensive discussion on all forms of research interventions integrated with medical care and affirms that this combination can only take place if it has the inherent capacity to diagnose, reduce the severity of the condition under study, or treat it [7]. In such cases, the study participants must have a comprehensive understanding of the specific aspects of their healthcare that are being combined with investigational treatments [14]. assert that it is appropriate to use experimental treatments for conditions in which ordinary care has proved to be ineffective for the patient's condition.

Clause 30 of the DoH calls for all study participants to be assured of continued access to the best "proven prophylactic, diagnostic and therapeutic methods identified by the study" (WHO 2001 p. 373) [18]. This must be considered by researchers and industry as it relates to the long-term costs of the clinical development program. It is also a potentially significant barrier to conducting research, especially for small companies that may not have the

needed resources to continue funding patient care post study conclusion. Similar to the Nuremberg Code, the DoH has had a major impact on clinical trials since its adoption in the field of medical research. The DoH is a direct indication of the commitment demonstrated by researchers, the WMA and the regulatory agencies in the ongoing efforts to promote evidence-based and ethical research. It will be interesting to note if subsequent versions of the DoH adapt to the changing research landscape that has been brought about by, for example, the introduction of subject recruitment *via* social media or mobile applications.

The Belmont report

The Belmont Report was formulated after an agreement was reached during the 1978 Conference on Clinical Research in Belmont, Ireland. The report, published in the United States Federal Register on 18 April 1979, sought to provide a summary of the ethical principles as well as guidelines for research targeting and involving human subjects [1,19,3,20]. Despite the fact that the conference proceedings underscored the inherent existence of other previous codes governing and guiding the field of human research, its participants had a strong belief that these various codes had resulted in a formation of regulations that could not effectively address the broad range of highly complicated issues in clinical research. In simpler terms, the codes that were in place were too complex and a shortened and unified global guideline was needed. The implementation of the Belmont Report led to the identification of three core principles associated with research involving humans. [19,21] These principles include an inherent respect for all humans that serve as study participants, justice, and beneficence. Also included in the Belmont Report are the three primary areas of application. These areas include the informed consent process, an inherent evaluation of research-based risks as well as the anticipated advantages, and appropriate selection of study subjects.

Discussion and Conclusion

In today's clinical research environment, significant deviations from well-established ethical guidelines, such as the Nuremburg Code, Belmont Report, and Declaration of Helsinki would undoubtedly result in discrediting of the trial results. It may even have legal consequences for the researchers and trial sponsors. Adherence to these guidelines is critical in the context of both promoting the well-being of research participants from a patient-safety standpoint, and appropriate clinical trial conduct from a regulatory position. This is particularly true for trials that involve vulnerable patient populations who are at greater risk. Revisions to these ethical principles may be warranted as 21st century technologies such as Artificial Intelligence (AI), wearable technologies and social media recruitment become more prevalent in clinical trials. In the absence of such updates, clinical researchers should use the frameworks provided by the available guidelines and adapt them, as appropriate, to promote high ethical standards in the use of 21st century technologies in their clinical trials.

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