Running an ethical trial 60 years after the Nuremberg Code

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The Nuremberg Code has served as a foundation for ethical clinical research since its publication 60 years ago. This landmark document, developed in response to the horrors of human experimentation done by Nazi physicians and investigators, focused crucial attention on the fundamental rights of research participants and on the responsibilities of investigators. Although the Nuremberg Code has provided an important framework for discussions on the requirements of ethical clinical research, and has resulted in the development of other initiatives—eg, the Declaration of Helsinki and the Belmont Report—designed to ensure the rights and safety of human beings taking part in medical research, knowledge of both past events and the current complexity of research suggests further improvements are necessary in the existing approaches to human clinical research.

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A historical perspective

With the horrors of World War II fresh on their minds, the victorious Allies set to work establishing the guilt of, and penalties for, the Nazi physicians and medical administrators (figure 1) who initiated or participated in profoundly degrading, painful, and often lethal experiments on prisoners who were treated as little more than bodies (figure 2). When describing the physicians (figure 3) who took part in these activities, Brigadier General Telford Taylor (figure 4), the chief counsel for the prosecution at the Nuremberg Doctor's Trial, noted:

> "The defendants in the dock are charged with murder, but this is no mere murder trial. We cannot rest content when we have shown that crimes were committed and that certain persons committed them. To kill, to maim, and to torture is criminal under all modern systems of law. These defendants did not kill in hot blood, nor for personal enrichment. Some of them may be sadists who killed and tortured for sport, but they are not all perverts. They are not ignorant men. Most of them are trained physicians and some of them are distinguished scientists. Yet these defendants, all of whom were fully able to comprehend the nature of their acts, and most of whom were exceptionally qualified to form a moral and professional judgment in this respect, are responsible for wholesale murder and unspeakably cruel tortures."[1]

At the end of the written judgment, the judges who oversaw these cases (figure 5) issued a set of principles, known as the Nuremberg Code[2] (panel 1; figure 6), which they, along with their medical advisors, believed should govern the undertaking of ethical clinical research involving human beings.[3]

The first of the ten principles firmly stated that for clinical research to be ethically valid "voluntary consent of the human subject is absolutely essential", a phrase which has become an integral part of all discussions on this topic. The Code also sought to define the responsibilities of those undertaking experiments involving human beings, in terms of the quality of the research (eg, ensuring the study was designed on the basis of "animal experimentation and knowledge of the natural history of the disease"[2]) and the obligations of the investigator to the research participant (eg, "the experiment should be conducted to avoid all unnecessary physical and mental suffering", and "proper preparations should be made…to protect the experimental subject against even remote possibilities of injury, disability or death"[2]). Thus, the Nuremberg Code not only focused on the crucial importance of obtaining fully voluntary informed consent, but also on the importance of research being ethically acceptable before individual consent is allowed to be sought.

Even nowadays, 60 years after the publication of the Nuremberg Code, discussions on ethical human research often begin with the ten components of this landmark document. Although previous attempts had been made to define acceptable behaviour in clinical research—eg, the Reich Health Council guidelines produced in 1930, which resulted from the syphilitic experiments of Neisser[4]—the Nuremberg Code is the only set of principles that has retained its importance up to now. The popularity of this Code is likely to be due to the revulsion surrounding the events that led to the Code's

Figure 1: **The International Military Tribunal trial of war criminals at Nuremberg**
Reproduced with permission from the United States Holocaust Memorial Museum (USHMM).

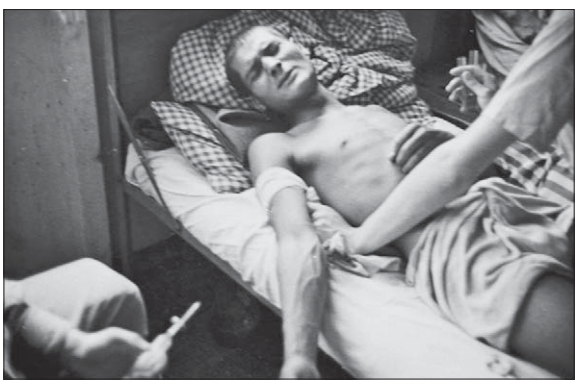

Figure 2: **A romani (gypsy) victim of Nazi medical experiments to make seawater drinkable**
Dachau concentration camp, Germany, 1944. Courtesy of the USHMM.

Figure 3: **View of the defendants standing in the dock during the International Military Tribunal in Nuremberg**
Reproduced with permission from the USHMM.

creation, and the simple, yet authoritative, wording of its profoundly relevant requirements for ethical clinical research.

Despite the fact that its position as the prevailing paradigm of contemporary human-research ethics remains unquestioned, debate still continues on the measurable effect of the Nuremberg Code on human research.

First, the Code does not constitute law, even though it was written by judges (with the assistance of their medical advisers).[1,3] Some have suggested that this absence of legality has severely restricted the effect this Code could have on human research, either within individual countries or the international community as a whole. Second, as will be discussed below, many people believed that the experimentation done in Nazi Germany was so perverse that the Nuremberg Code was not relevant to research involving human beings in other settings. Third, because the Code focuses solely on the obligations of investigators to research participants and the need for routine protection of participants, in terms of the research environment and the manner in which the experiments are undertaken, one might wonder why individuals would ever consider becoming participants in a clinical research project. Furthermore, the question could even be asked as to why society should support such research where so much protection is needed. Finally, the statement that voluntary consent is absolutely essential seems to eliminate the potential for certain research to be undertaken, such as research that involves young children or individuals with serious mental illness. Studies that involve these groups of people can, ultimately, be of great benefit. In fact, the Code provides no guidance on how research involving human beings presumed to be unable to provide fully informed consent might be undertaken in an ethical manner.

After the Nuremberg Code

Ethical conventions

The realistic restrictions of the Nuremberg Code as a practical guide for ethical human research resulted in several subsequent efforts to produce a set of guidelines that would have universal applicability and would deal with issues relevant within the existing research environment, and with future ethical challenges (eg, clinical studies involving participants from developing countries who have unique ethical concerns, such as the risk of exploitation or the inadequacy of informed consent; panel 2).

The Declaration of Helsinki,[5] developed by the World Medical Association, clarified and interpreted the principles of ethical research as outlined by the Nuremberg Code. This international effort, first published in 1964, and updated several times since, acknowledged the crucial relevance of clinical research as an important societal strategy for improving human welfare. Furthermore, this document helped define the actual process of doing ethical research (eg, "each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail."[5]).

Individual national initiatives involving ethicists, investigators, the general public, and governmental agencies have also sought to establish guidelines to ensure appropriate ethics are upheld. In the USA, several clinical research projects—such as the Tuskegee Syphilis Study[7]—resulted in the formation of The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979. This group published the Belmont Report[9] in the same year, one of the most fundamental documents on bioethical research