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The Declaration of Helsinki in relation to Medical Research: Historical and Current Perspectives

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ABSTRACT

Medical research aims at improving diagnostic, therapeutic and prophylactic measures and understanding of the aetiology and pathogenesis of diseases in humans, and their application to improve the quality of life and survival. The subjects involved are exposed to hazards inherent to the experiments. In order to protect the human subjects and to maintain high ethical standards, the World Medical Association had adopted the "Declaration of Helsinki" in 1964. The aim of this article is to provide a comprehensive review on the historical and current perspectives on the Declaration of Helsinki in relation to medical research on human subjects.

Keywords: ethical issues; Helsinki declaration; human experimentation; therapy; world medical association.

INTRODUCTION

Medical research is conducted either to evaluate new treatments or to contribute to the development of new treatments. For the protections of the participants of the research and to draw reliable conclusions, it is paramount that the research is conducted by maintaining high ethical standards and clinical governance.[1] In order to maintain a high standard of medical research, the World Medical Association (WMA) developed the **Declaration of Helsinki** in Finland, as a set of ethical principles for the medical community in relation to experimental research in humans, which is intended for the protection of human subjects. This is widely regarded as the cornerstone document of human research ethics.[2,3] The aim of this article is to provide a comprehensive review on the historical and current perspectives on the Declaration of Helsinki in relation to medical research on human subjects.

LITERATURE SEARCH

The literature searches were carried out in PubMed and relevant Websites using the words "medical research", "Helsinki declaration", "ethics" and "world medical association". Relevant references were compiled using the EndNote software (Version 4.0.2).

HISTORICAL PERSPECTIVES

World Medical Association (WMA)

The WMA was established on 17th September 1947 in Paris, France, which aimed to serve humanity by making endeavours to achieve highest international standards in medical care, science, ethics, education and health-related human rights for all people of the world.[4] The WMA represents all doctors regardless of their specialty, location or practice settings. To co-ordinate and develop policies on the medical ethics, the WMA Ethics Unit was established in 2003, which liaises with other international units via conferences and websites and develops a robust ethics document.

Nuremberg Code

After the Second World War (1939-1945), in 1946, the "Doctors' Trials" of Nazi crimes against humanity were carried out in Nuremberg in Germany.[5] These trials exposed the horrific and deadly experiments conducted by the Nazi physicians on prisoners in the concentration camps against their free will to take part in various experiments.[6] This resulted in the adoption of "Nuremberg Code" in 1947, which consisted of ten

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points defining legitimate medical research.[7] The Code emphasised on the need of the voluntary consent and legal capacity to consent on the part of the human taking part on the experiment. It stated that the experiments should be carried out for the benefits of the human beings in a scientifically designed manner done by qualified personnel; the experiments should be based on the results of animal experiments and natural history of the disease; and the experiments should be terminated at any stage if this resulted in injury, disability or death of the experimental subjects.

The Declaration of Geneva

The Declaration of Geneva was adopted by the General Assembly of the World Medical Association at Geneva in September 1948 and amended in 1968, 1984, 1994, 2005 and 2006.The declaration was a revision of the Oath of Hippocrates, which emphasized the dedication to the humanitarian goals of medicine.[8]

The Declaration of Helsinki

In order to maintain high global ethical standards in medical research involving human subjects, the WMA in its 18th General Assembly held in June 1964 in Helsinki, Finland, recommended a set of ethical principles to the medical community conducting medical research which involved human subjects, which is known as the **"Declaration of Helsinki"**.[3] The declaration had amalgamated the Nuremberg code and the Declaration of Geneva, and specifically addressed clinical research.[9] It is one of the most influential documents in research ethics and is considered as the "property of all humanity".

The full document on the Declaration can be found online.[2] There are 35 articles grouped in three sections; introduction, principles for all medical research and additional principles for medical research combined with professional care (clinical research). In summary, it is emphasised that the well-being of the individual research subject must take precedence over all other interests. The primary purpose of medical research is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions. Even the best current interventions must be evaluated continually through research for their safety, effectiveness, accessibility and quality.

Medical research must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature related to animal and human experimentations. They must be conducted by individuals with appropriate scientific training and qualifications. A research protocol must be designed and approved by ethics committee. Each potential subject participating must be adequately informed about the risk and benefit of the intervention and an informed voluntary consent must be obtained. It is the duty of the doctors to maintain the safety of the life and health of the subject and discontinue the research if the research is considered to be harmful to the individual. The interest of the science and society should not take precedence over considerations related to the well-being of the subject. Ethical obligation with regards to publication of the results of the research and responsibilities of the investigators is well-described.

Since the first Declaration in 1964, six revisions have been carried out in the General Assemblies of the WMA (Table 1). The first revision carried out in 1975 elaborated the document to twice its original length where the concept of "independent committee", "informed consent" and "publication ethics" were introduced.[10] Subsequent revisions between 1975 and 2000 were relatively minor. In 2002 and 2004 meetings, clarifications of the articles 29 and 30 with regards to use of placebo in trial, particularly in the developing world and post-trial care, respectively were endorsed.[11,12] The last revision was made in 2008 after incorporation of inputs received from wide range of sources.[2]

Table 1. Timelines of WMA meetings and revisions of the Declaration of Helsinki

1964: Original version. 18th Meeting, Helsinki, Finland
1975: First revision. 29th meeting; Tokyo, Japan
1983: Second revision. 35th Meting, Venice
1989: Third revision. 41st Meeting, Hong Kong
1996: Fourth revision. 48th Meeting, Somerset West (SA)
2000: Fifth revision. 52nd meeting, Edinburgh
2002: Note of Clarification. 53rd Meeting, Washington
2004: Note of clarification. 55th Meeting, Tokyo
2008: Sixth revision. 59th Meeting, Seoul

CURRENT PERSPECTIVES

At present, new treatments are evaluated through scientifically designed *clinical trials*, whereas knowledge for new therapeutic strategies is elaborated through *preclinical research*.[13] A new paradigm of medical research, termed *translational research*, adopts bench-to-bedside approach by translating a basic research done at the molecular and cellular levels (bench) to clinical application in patients (bedside).[14] These involve human subjects for experimentation, where protection of the subjects through adherence to the Declaration of Helsinki becomes paramount.

The Declaration of Helsinki, although morally binding, is not a legally binding tool in international law, but is used to influence the regional or national legislation and

regulations. However, countries have their own laws governing the criminal, civil and ethical responsibilities.[15] Today, most countries use declaration of Helsinki as the cornerstone document for human research ethics, an ethical template, regulatory or legal document.

In order for the medical science to advance, for new drugs and treatments to be studied and approved, the participation of human beings in research studies is absolutely necessary. On the other hand protection of the rights of the human research subjects cannot be overemphasised. The risk to human subject exists in most types of research extending beyond drug and interventional studies, such as observational studies, surveys, genetic analysis and so on. Therefore the Declaration of Helsinki has become the foundation of research ethics and of the protection of human subjects. All researchers are expected to conform to its mandates.[16]

In recent years, research ethics have become more complex as recruitment of human subjects and nature of researches have been extended to wider range of criteria thereby leading to emergence of additional complexities, which are represented below.

1. Research on incompetent subjects

When incompetent subjects, such as a minor or those with learning difficulties, need to be involved in the research, the Declaration of Helsinki has endorsed this provided consent is obtained from legally authorised representative. The main emphasis is clearly on protecting these subjects. In more recent years, in the process of protection of these vulnerable subjects, their needs for research are not met, hence are excluded. This is true with children as they are often excluded from research on new drugs that are studied on and approved for adult population, the results of which are extrapolated for the children.[17] It has to be appreciated that the Declaration of Helsinki does not take into account of the wishes of the incompetent subjects, hence it is mandatory that both researchers and authorised representatives need to pay attention to the wishes of the incompetent subjects.[17,18] This does not undercut the Declaration of the Helsinki.

Current UK guidelines regarding clinical research on children permit research that is non-therapeutic from the perspective of that particular child. Research interventions that cause temporary pain, bruises or scars are permitted in the guidelines. It is argued here that such research conflicts with the Declaration of Helsinki according to which the interests of the research subject outweigh all other interests.[19] Clinical research on Alzheimer's disease poses significant challenges to research ethics. In fact, the development of the disease progressively reduces the patient's ability to make choices, although they are not totally incapacitated. Several solutions are offered for a "proxy" consent or authorisation. French Law protects mostly three categories of vulnerable people: minors, adults with a legal representative, and the people living in sanitary and social establishments. Specific protection is given as well to pregnant women, detainees and persons with psychiatric disorders in involuntary commitment.[20]

2. Research without advance consent

It is being increasingly recognised that under special circumstances, it is not possible to obtain advance consent; hence the research should be allowed to continue. This is particularly applicable to an emergency situation where intervention is required, the subject is unable to give consent and surrogates are not available in the relevant time frame. Such research may be necessary, for example, to improve therapy in an unconscious patient with head injury, or use of anonymised tissues obtained in the past when it is not possible to gain consent from the subject at this time.[21] Not allowing such research, valuable information will be lost and at the same time rights and interest of the individual will not be protected. Allowing such research to proceed will not undermine the Declaration of Helsinki demanding informed consent to be obtained in advance, as this is not feasible under the circumstances.[22]

3. The role of independent research committee

The Declaration of Helsinki insists that all research protocols must be submitted and approved by the independent research committee to ensure the rights and interests of the subjects are protected.[23] This may not be possible in a situation like multi-centre research protocols where the research is carried out at several centres and obtaining ethical approval from several centres often results in serious delays and conflicting demands.[24] Furthermore, expertise may not be available in every institution, particularly in the emerging fields such gene and stem cell research. This calls for a move towards an establishment of centralised review committee, which is compatible with the declaration of Helsinki.

4. International research

Several researches are being conducted at international levels across many countries with participations of subjects from diverse cultural and ethnic backgrounds, such as in multicentre trials.[25] There can be differences in the cultural understandings about the researcher-patient relationships and informed consent, which is not indicated in the Declaration of the Helsinki. Clearly,

individual countries and communities may have their own requirements, which need to be incorporated in their local guidelines.[26,27]

WAY FORWARDS

In the future, it is anticipated that additional issues will emerge as more complex researches are being undertaken, which will necessitate revision of the Declaration of Helsinki. It is mandatory that the researchers, who participate in studies involving human subjects, tissues, or medical records, should be intimately familiar with the contents of the Declaration of Helsinki, as well as their local and national research standards and regulations. If any doubt or confusion arises, the local research ethics committees should be contacted for clarification and guidance. It is the responsibility of everyone involved in research to ensure that human subjects, their tissues and their personal and medical information are protected and respected at all times, without exception. We must appreciate that it is their contributions, which has led to the present state of advanced medical science, the benefit of which we are enjoying today.

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