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The Declaration of Helsinki on Medical Research involving Human Subjects: A Review of Seventh Revision

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ABSTRACT

The pinnacle of success achieved by the medical science and the benefits accrued to the patients have become possible through the medical research where human participants in the research are exposed to hazards inherent to the experiments. To protect the human subjects and to maintain high ethical standards, the World Medical Association has adopted "The Declaration of Helsinki" in 1964. After two years of consultation with the experts throughout the world, the seventh revision of the Declaration was adopted on 19th October 2013 in Brazil. The aim of this article is to review the seventh revision of the Declaration of Helsinki in relation to medical research involving human subjects and highlight the amendments made in the latest revision which are relevant to clinical research in human subjects. The latest revision has made four substantial changes on the existing Declaration, whch include dealing with the compensation of the trial-related injuries, approval of use of placebos in the clinical trials, protection of vulnerable groups and the post-trial provisions. The implications of these amendments in the clinical research are highlighted.

Keywords: Consent; Declaration of Helsinki; ethics; experimental medicine; research; seventh revision.

INTRODUCTION

Extensive medical research is being conducted throughout the world with an intention to understand the aetiology, natural history, diagnosis, prevention and treatment of diseases; and evaluate the safety, efficacy, and outcomes of best proven interventions through strategically designed clinical trials.[1,2] This involves human subjects for experimentation, whose participation is vital and dependent on the their trust on the researchers. For the protection of the participants, and to draw reliable conclusions, it is paramount to maintain high ethical standards and clinical governance for protection of the participants in the research.[3] To achieve this objective, the World Medical Association (WMA) has adopted the Declaration of Helsinki, as a set of ethical principles intended to protect the human subjects, which has been the cornerstone document of human research ethics.[4,5] After a worldwide consultation process lasting for over two years and following extensive deliberation by the experts at the WMA meeting held in Brazil, the WMA has adopted and published the seventh revised version of the Declaration in medical research on 19th October 2013. In order to address the shortcomings those existed in the previous edition of the Declaration, the latest revision has made four substantial changes, whch include dealing with the compensation of the trial-related injuries, approval of use of placebos in the clinical trials, protection of vulnerable groups and the post-trial provisions. The aim of this paper is to review the updates on the seventh revision of the Declaration of Helsinki and highlight their relevance to clinical application in medical research on human subjects.

LITERATURE SEARCH

The literature searches were carried out in PubMed using the MeSH words "medical research", "Helsinki Declaration", "ethics", "revision", "World Medical Association" and "research". One hundred and one publications thus retrieved were compiled in the EndNote software (Version X 7.7.1; BLD10036; Thomson Reuters, Philadelphia, PA, USA) and relevant references, agreed by both authors, were included in the narrative synthesis of the review.

THE DECLARATION OF HELSINKI

The historical perspectives of the Declaration of Helsinki has been published previously.[6] To summarise, the

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World Medical association was founded in Paris on 18th September 1947 for the maintenance highest standard of medical care, which currently represents over 10 million doctor in 112 countries worldwide.[7] After the Second World War, (1939-1945), in 1946, the "Doctors' Trials" of Nazi crimes against humanity were carried out in Nuremberg in Germany, which 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. The Nuremberg Code was introduced in 1947 consisting of ten points which defined the codes for conducting legitimate research, which emphasised the need of voluntary consent and legal capacity to consent on the part of the human taking part in 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.[8] In 1948, the WMA adopted the Declaration of Geneva, which was essentially the revision of the Oath of Hippocrates emphasising the humanitarian goals of medicine.[9]

The Declaration of Helsinki is a statement of ethical principles directed to the medical community conducting medical research involving human subjects, including research on identifiable human material and data. This was recommended by the WMA in its 18th General Assembly held in June 1964 in Helsinki, Finland, to maintain a high global ethical standards.[4] This was amalgamation of the Nuremberg code and the Declaration of Geneva intended to address the issues of clinical research. Since the first Declaration in 1964, seven revisions have been carried out by the General Assembly of the WMA (Table 1).

The first revision carried out in 1975 elaborated the document to twice its original length where the concept of an "independent committee", "informed consent" and "publication ethics" were introduced.[10] Subsequent revisions between 1975 and 2000 were relatively minor. In the 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 sixth revision was made in 2008 after the incorporation of inputs received from a wide range of sources, which emphasised that the well-being of the individual research subject must take precedence over all other interests.[13]

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 Meeting, 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
2013: Seventh revision. 64th Meeting, Brazil

SEVENTH REVISION OF THE DECLARATION OF HELSINKI

The general assembly of the WMA had set up a workgroup to consider potential revisions to the Declaration of Helsinki and present to the WMA Ethics Committee, which aimed not at changing core ethical principles but at determining whether additional guidance was needed. The WMA invited all experts and stakeholders to submit comments in the draft version via emails to the WMA secretariate no later than 15th June 2013.

At the conclusion of the public consultation period on 15th June 2013, the work group met in Washington DC in August 2013 and incorporated the public input into the revised draft document. The workgroup finally presented the revised Declaration of Helsinki to the WMA's Ethics Committee and council meetings held in Brazil on 19th October 2013 and obtained approval, which has been adopted and published now as the Seventh revised version of the Declaration of Helsinki. The full version of the Declaration is available elsewhere, however, the main sections and their articles are summarised below.[14,15]

GENERAL PRINCIPLES

Although the declaration is addressed primarily to the physicians, the WMA encourages others, who are involved in medical research involving human subjects, to adopt these principles. It is the duty of the physicians to promote and safeguard the health, well-being and rights of the patients and those involved in research and the physicians should dedicate their knowledge and conscience to achive this goal. It is expected to consider the ethical, legal and regulatory norms and standards for research involving human subjects for their protection. Medical research involving human subjects must be

conducted only by individuals with appropriate ethics and scientific education, training and qualification. Provision must be made for appropriate compensation and treatment for subjects who are harmed as a result of participating in research.

RISKS, BURDENS AND BENEFITS

Most interventions in medical practice and research involves risks and burden, therefore, research should only be conducted if the importance of the objective outweighs the risks and burdens to the subject. Minimisation of the risk and continuous monitoring, assessment and documentation by the researcher must be implemented. During the course of research, when the risks outweigh the benefits, assessment with regards to further continuation of the intervention must be carried out and stopped, if necessary.

VULNERABLE GROUPS AND INDIVIDUALS

Protection of vulnerable groups and individuals from incurring additional harms must be put in place. If research has to be done in this group for health benefits and no alternatives are available, safety measures must be guaranteed, otherwise they should be avoided in the research participation.

SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

Based on the scientific evidence, a protocol for the research must be developed, which should be approved by a designated ethics committee. The protocol must clearly define the objectives and methodology to achieve the objectives. The post-trial provisions must be clearly stated.

RESEARCH ETHICS COMMITTEE

The research committee has the right to review the protocol, monitor the progress of the research, modify the protocol if necessary and investigate any serious adverse events. On completion of the study, the final report must be submitted to the committee containing a summary of the findings and conclusions.

PRIVACY AND CONFIDENTIALITY

During course of research, every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information. No information of the research subject should be divulged to a third party without written permission of the participant.

INFORMED CONSENT

The requirement of obtaining informed consent before participating in the research is strongly emphasised. Involvement of family members in the consenting process is advised if appropriate. During the consenting process, a detailed discussion about the methodolgy, potential risks and anticipated benefits, conflicts of interest, source of funding, institutional affiliation must be done. The person has right to refuse from participation or withdraw from the study at any time without reprisal. The physician must seek advice from a legally authorised representative if the subjects are physically or mentally incapable of giving consents. For the use of identifiable human tissue or data, informed consent must be taken for collection, storage and /or reuse.

USE OF PLACEBO

In this revision, the use of placebo, while testing the benefits, risks, burden and effectiveness of the new intervention, is allowed, but after consideration of specific indications. The use of placebo is permitted only when no proven interventions exists to compare with the new intervention or when no intervention will not subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

POST-TRIAL PROVISIONS

Subjects participating the trial must have provisions made by the trial sponsors for post-trial access for the treatment that have shown benefits during the study. This information must also be disclosed to the participants during the consent process.

RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

All research projects must be registered in the publicly accessible database. On completion of the study, the results must be published for dissemination of the new knowledge. Negative, positive or inconclusive results must be published. Any report not in concordance with the Declaration of Helsinki should not be accepted for publication.

UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

Application of unproven interventions in clinical practice, when a proven intervention exists in the treatment of an individual patient, the physician, after seeking expert advice, with informed consent of the patient or legally authorised representative, may use

the unproven intervention for the benefit of the patient. However, this intervention should be made aware to the participant and the recorded new information should be made publicly available.

DISCUSSION

The seventh revision of the Declaration of Helsinki has made four substantial changes on the previous sixth revision, which include dealing with the compensation of the trial-related injuries, use of placebos, protection of vulnerable groups and the post-trial provisions. The changes also place more obligations on sponsors of research, on the researchers themselves and on host governments to protect research subjects.

With increasing number of research trials being conducted to address complex clinical questions, there is always a potential for adverse events affecting the participants of the trial, who may require recompensing for the losses incurred. The severity of adverse events may range from trivial to life-theatning damages which may affect the qualty of life of the participant and dependent family, in both short- and long-terms. Provision for compensation to the participants in these situation is an amemdment on the seventh revision of the Declaration of Helsinki.

Assessment of the effects of a new interventional strategy for the treatment of medical conditions by comparing the new intervetion with a placebo is an addition to the seventh revision of the Declaration of Helsinki, where specific indications and precautions those need to be taken into consideration are clearly defined. In the previoius (sixth) revision of declaration, the demand to use “the best treatment” excluded the use of placebo in the control group and had presented an obstacle to the scientific evaluation of a number of drugs in general. It is justificble to use placebo if the use of placebo does not cause ireversible damage or considerable suffering to the well-informed patient. Therefore, the current seventh revision will allow the use of placebo in controlled clinical trials of treatment of number of diseases, especially those which have tendency to s spontanous improvement or have a pronounced psychological component rather than physical component.[16-18] In these cicumstances, informed consent of the participants after thorough discussion on the advantages and disadvantages of the use of placebo is paramount. A recent international prospective randomised controlled phase-3 superiority trial has compared the effects of tranexamic acid and placebo in hyperacute primary intracerebral haemorrhage and assessed their outcomes, exemplifies the current research practice permitted by the revision.[19]

Autonomy of the patients on particiation in any research is paramount. On the other hand distributive justice and beneficience are impotant motivating forces while instituting any treatment. Under these circumstances, it becomes imperative to protect the vulnerable group of individuals, such as the children and individuals with lack of mental capacity to comprehend the subject and consent for participation. Several practical difficulties may have to be overcome to protect these individuals.[20] The impact of clinical trials in low-income community and the interaction between their life-styles structures and the efficiency of risk-minimising procedures has been a subject of controversy.[21] The seventh revision of the Declaration emphasises the need to have appropriate arrangements in place to protect this group of invividuals. It is recommended to avoid research on these individuals, if additional harm is anticipated and alternative strategies for research are available.[22]

At the end of several research trials, beneficial effects of new treatment are observed and reported. The new form of treatment may not be readily available for public use after completion of the trial or may have limited accessibility for logistic reasons, including their costs.[23] However, the seventh revision emphasises that the trial sponsors must ensure that the participants of the trial have post-trial access for the treatment that has shown benefits during the study. This information must be disclosed to the participants during the consent process.[24]

CONCLUSIONS

This review has highlighted the changes incorporated in the seventh revision of the Declaration of Helsinki. In the future, it is anticipated that additional issues will emerge as more complex researches are being undertaken, which will necessitate further revision of the Declaration of Helsinki. It is mandatory that the researchers, who undertake 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. It must be appreciated that the present state of advancements in medical science, which has benefitted human illnesses, have become possible through the contributions made by patients and human volunteers and it the foremost duty of all researchers to adopt the Declaration of Helsinki for their protection and benefits.

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