

EDITORIALS

The new 2013 seventh version of the Declaration of Helsinki – more old wine in a new bottle?

VASANTHA MUTHUSWAMY

**President, Forum for Ethics Review Committees in India, Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai 400012 INDIA
e-mail: vasanthamuthuswamy@yahoo.co.uk**

The eagerly awaited seventh version of the Declaration of Helsinki (DoH) was released by the World Medical Assembly (WMA) on October 19, 2013 at the 64th General Assembly (1). It has been 13 years since the most debated version of the DoH, the fifth one, was released in 2000, followed by two related notifications in 2002 and 2004 and the less debated sixth version of 2008. The decade following the fifth version has witnessed many conceptual changes and debates all over the world. Of special note is the fact that most research participants are drawn from the developing countries and are considered to have a higher degree of vulnerability than their counterparts in the developed countries. Since 2000, a landmark year from many perspectives, national and international ethical guidelines have been updated or new ones developed to address the current and emerging issues facing the research community.

In India, the Indian Council of Medical Research (ICMR) released its 2000 version of the 1980 ethical guidelines and subsequently updated it in 2006. Further revision is under way now. The operational guidelines of the World Health Organization (WHO) for ethics committees that review biomedical research (2000) were updated in 2011. The Council for International Organizations of Medical Sciences is currently busy revising its 2002 version. UNAIDS revised its 2000 guidelines for HIV vaccine research in 2007, while the HIV Prevention Trial Network of the United States modified its 2004 version in 2009. UNESCO announced its landmark Universal Declaration on Bioethics and Human Rights in 2005. This is a list of only some of the recent updates and many other guidelines have been updated around the world. The Presidential Commission for the Study of Bioethical Issues, set up to examine the US Public Health Service studies conducted in Guatemala in the 1940s, came out with a candid report in December 2011 and recommended that research participants be protected in domestic as well as international research. Hence, with the proliferation of guidelines from all quarters, the research community has been waiting with bated breath for the past two years for the WMA's new version of the DoH, which is considered the gold standard for research ethics to guide physicians all over the world. The brand new seventh version is definitely a better guidance document than the last, though it contains more of the old wine in a new bottle. It also sets forth some direct guidance points pertaining to vulnerable groups from developing and resource-poor countries, besides dealing with a few new areas that have not been mentioned so far.

It is interesting to take stock of the evolution of the DoH over the years. The first version was released by the WMA in 1964 at Helsinki in Finland, following the crisis in research ethics during World War II. The first revision was made in Tokyo, Japan in 1975. This was twice the length of the original, which had 11 articles and 713 words. It was this version which first introduced the concept of an independent committee to review research proposals.

Researchers continued to be governed by the 1975 version for the next 25 years, till the fifth version was released in Scotland in 2000. The second, third and fourth versions released in the intervening 25 years were of relatively minor importance. The revision of 2000 was the most debated, challenged and controversial version, and formed the subject of seminars and conferences all over the world. The three major newly introduced topics which were the cause of all these deliberations were the use of placebos, best proven current therapeutic interventions in the control arm, and post-trial access to proven interventions. The 2000 revision had been the most contentious and far-reaching one till then, both structure-wise and content-wise. The following are some of the salient features of this version:

- i) The distinction between therapeutic and non-therapeutic research in the original document was removed. Instead, Article 16 clearly spelt out that ethical principles must be applied both in the case of healthy volunteers and all others referred to as human subjects.
- ii) The scope of ethical review by the ethical committees (ECs) was expanded to human material and data.
- iii) The concept of publication ethics was expanded to include the necessity of disclosing conflict of interest (Articles 14 and 30)
- iv) The most controversial revisions were placed under "Additional Principles," in Articles 31, 32 and 33. Clarifications were issued on these matters during 2002 and 2004. The United States Food and Drug Administration (USFDA) rejected the 2000 version and the subsequent clarifications. It issued a final rule in April 2008 that resulted in the replacement of the DoH with good clinical practice in October 2008. The European Commission, on its part, recognises only the 1996 version, but the European Council refers to the 2000 version.

The latest in the series is the newly announced seventh version. Although this version contains no radical changes, it is definitely more readable. For the first time, the vital principles are placed under separate sub-headings, emphasising the importance of these issues. Compared to the original 11 articles in the 1964 version, this version has 37, just two more than the number in the 2008 version. There are 13 articles under the General Principles (3–15), eight under informed consent (25–32), three under risk, burden and benefits (16–18), two each under the preamble (1–2), vulnerable groups and individuals (19–20), and scientific requirements and research protocol (21–22). One article each is devoted to research ethics committees, privacy and confidentiality, the use of placebo, post-trial provisions and unproven therapies.

In the latest version, the following areas have received greater emphasis than in the preceding versions.

1. Under-represented groups should have better access to research and greater protection should be provided to vulnerable groups (2)
2. Research can be undertaken only if the importance of the objective outweighs the inherent risks and burden.
3. The requirements for post-study provisions have been expanded.
4. The version calls for a more systematic approach to the use of placebos.
5. Clarifications have been made on the role of ECs in monitoring.

The provisions that have been introduced for the first time are as follows.

1. Appropriate compensation and treatment must be ensured for those harmed in research (Articles 15 and 22)(3)
2. The researchers should undertake monitoring of the risks, assessment and documentation (Article 17).
3. After the study has been concluded, the researchers must submit to the committee a final report that contains a summary of the findings and conclusions (Article 23).
4. All study subjects involved in medical research should be given the option of being informed about the general outcome and results of the study (Article 27).
5. Every research study involving human subjects must be registered in a publicly accessible database (Article 35).

In addition, there are many changes in terminology(4). Whether these have been made to place greater emphasis on specific issues or are simply reflective of the different writing styles of different authors is not clear. For example, “treatment” has been replaced by “interventions;”, “best proven current treatment” by “best proven intervention;”, “clinical trial” by “research study;”, and “should” by “must”.

In some articles, changes have been made on conceptual issues, as shown below.

2008	2013
Researchers must provide monitoring information to the Committee, especially about SAEs (15).	The risks must be continuously monitored, assessed and documented by the researchers (17).
Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community (17).	Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group (20).
Every clinical trial must be registered in a publicly accessible database before the recruitment of the first subject (19).	Every research study involving human subjects must be registered in a publicly accessible database before the recruitment of the first subject (35).
At the conclusion of the study , patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits (33).	In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process (34).
It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of the personal information of research subjects (11). The responsibility for the protection of research subjects must always rest with the physician or other healthcare professional and never the research subjects, even though they have given consent (16).	It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research (4). It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of the personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other healthcare professionals and never with the research subjects, even though they have given consent (9).

<p>Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries, as well as the applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration (10).</p> <p>This committee [research ethics committee] must be independent of the researcher, the sponsor and any other undue influence (15).</p>	<p>Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries, as well as the applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration (10).</p> <p>This committee (REC) must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified (23).</p>
--	---

Note: The numbers within parentheses indicate the article number of DoH.

In addition to the issues above, there are many others which require greater clarity and explanation to avoid confusion among researchers and the members of ethics committees. These are as follows:

1. The term “best proven intervention” remains ambiguous. Where is it applicable – locally or globally? Who decides on this? If countries make their own interpretation of this concept, will it result in a dilution of the principles of the DoH regarding the protection of participants?
2. According to the latest version, the post-trial provisions consist of the interventions identified as beneficial in the trial. This definition has diluted the provision in the 2008 version, according to which post-trial provisions signified “access to interventions identified as beneficial in the study **or to other appropriate care or benefits.**” Some guidelines on the mechanisms for achieving this would have been useful to the countries, although the new version does place a responsibility on the sponsors, researchers and government of the host country.
3. The requirement for appropriate compensation and treatment for those harmed in research is a welcome introduction. India has been insisting on this for the past few years and the provision has been accepted by the country’s regulator, although there have been debates on its implementation. It is a positive sign that the WMA has accepted the need for appropriate compensation and treatment, although there is still no mention of ancillary care.
4. More clarity is needed on issues related to biobanking. No mention has been made of sharing genomic data, which is a complicated issue. Article 32 still talks about a broad consent for storage and reuse. The different options for consent that can be offered to research participants do not seem to have been considered, unlike the ICMR guidelines of 2006, which provide various options.
5. The following statement needs elaboration: “Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.” What does this imply? Which group does it refer to? Does it include autonomous adults whose autonomy has been reduced due to various reasons, or is it that some vulnerable groups are more vulnerable than others?
6. What is meant by duly qualified EC members? – those who are professionally qualified or those with ethics-related qualifications? What would be the qualification for non-technical and lay members? “Well-trained EC members” would probably be a better term
7. Registration of clinical trials in a database has been replaced by registration of all research studies in a database prior to the recruitment of subjects. This is a major change involving each and every research study concerning human participants, human material and data. The implementation of this is an enormous task. The Clinical Trial Registry - India can be considered a trendsetter in this area as it already registers all types of research, in addition to intervention trials
8. As for the term “medical research,” it might be useful to elaborate what it encompasses since many individuals are unclear about whether behavioural and operational studies fall in its domain.
9. In the latest version of the Declaration, the terms “human subjects,” “patients,” “research subjects” and “research participants” are used interchangeably. Since the word “subject” has ethical ramifications and confers an inferior status on an individual participating in research, the term “research participant” may be a better alternative and should be used consistently.

Thus, a critical review of the seventh version of the DoH indicates that it is a welcome version that has greater clarity than its predecessor, both in terms of presentation as well as content. However, it cannot be considered a perfect document as many of the pending issues could have been clarified further and new issues elaborated. The DoH is a living document and further revisions are bound to attempt to make it a more complete and authoritative document to ensure the protection of human participants in biomedical and behavioural research.

References

1. World Medical Association Declaration of Helsinki – Ethical principles for medical research involving human subjects. WMA General Assembly, Fortaleza, Brazil; October 2013. *World Med J.* 2013 Oct;59(5):199–202
2. Ndebele P. The Declaration of Helsinki, 50 years later. *JAMA.* 2013 Nov 27;310(20):2145–6. doi: 10.1001/jama.2013.281316.
3. Millum J, Wendler D, Emanuel EJ. The 50th anniversary of the Declaration of Helsinki – progress but many remaining challenges [viewpoint]. *JAMA.* 2013;310(20):2143–4. doi: 10.1001/jama.2013.281632
4. Meslin EM. If perfect isn’t possible, is the good “good enough?”—placebos, post-trial provisions and the politics of Helsinki. *World Med J.* 2013 Oct;59:185–7