

EDITORIALS

Revising the Declaration of Helsinki: a work in progress

Ruth Macklin

Professor of Bioethics, Department of Epidemiology and Population Health, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461 USA
e-mail: macklin@aecom.yu.edu

The World Medical Association (WMA), the organisation that issues the Declaration of Helsinki (DoH), is planning another revision of this influential ethics guidance document. The last revision in 2008 (1) strengthened the guidelines in some respects and weakened them in others. I described some of the changes from the previous version in these pages early in 2009(2). The 2008 revision strengthened the paragraph that addresses the control group in a randomised controlled trial by significantly limiting the circumstances in which a placebo control is acceptable. The most critical weakening from the previous version is the paragraph that describes post-trial benefits. To this day, these two paragraphs remain contentious, with supporters and critics on both sides.

The 2008 version states: "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" (paragraph 33). The previous version was stronger in that it specified the benefits more precisely: "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study" (paragraph 30).

Some people may prefer the current version on the grounds that it allows for a wider range of benefits. There is some merit to this in cases where trial participants contributed to a trial but did not benefit. For example, if neither the control nor experimental group receives a proven, effective medication during the trial, then provision of another health-related benefit could be appropriate. Arguably, nothing further is owed to participants who enter a clinical trial and are helped by a medication which they receive during the study but no longer need when their participation ends. However, they are still entitled to be informed about the outcome of the study.

The weakness of the revised guideline is that it does not *guarantee* provision of the beneficial method to participants who still need it after their participation in the study ends. In a clinical trial of a new treatment for HIV, for example, participants will still need the experimental product or the current therapy provided in the control arm, since HIV is a chronic disease and fatal if left untreated. This is especially problematic in resource-poor countries or communities where HIV therapy is not available to all who need it. Furthermore, it is not at all clear what "other appropriate care or benefits" might be, and how those would be determined.

To its credit, the WMA has been holding a series of conferences to gather a wide range of opinions as the Association embarks on the process of revising the DoH once again. The most recent conference was a satellite held in conjunction with the World Congress of the International Association of Bioethics in Rotterdam in June 2012 (the agenda for that meeting and copies of the presentations are on the WMA website)(3). Speakers were invited to present their views on a range of topics, including whether the DoH should be more "risk-based"; how to address the ongoing controversy over the use of placebo controls; whether an obligation exists to provide ancillary care to research participants; and what the requirements should be for informed consent in biobanking, among others. No decisions are taken at these consultations. The purpose is to open up discussion and provide arguments and positions for the WMA DoH workgroup, which is ultimately responsible for drafting the next version. A future conference is scheduled for early December 2012 in Cape Town, South Africa.

In introducing the Rotterdam conference, Dr Urban Wiesing, a member of the WMA DoH Scientific Board, issued a number of caveats (3a). After describing the increasing length of the document from its inception in 1964 through the series of revisions up to the present, he presented a consensus of the working group on the following points: the character of the DoH is unique and should not be changed; the DoH must remain distinct from other guidelines; and the DoH should not become much longer. Dr Wiesing emphasised this last point a number of times. The prohibition on lengthening the document is problematic because it does not allow for elucidation of vague or ambiguous wording. In the example of Paragraph 33 discussed above, without further specification the determination of what constitutes "other appropriate care or benefits" is left wide open. Without the possibility of saying more, the distinction cannot be made between research participants who still need the intervention and those who do not.

Another example of uncertainty in how to interpret key words or phrases has been ongoing since controversy over the paragraph on control groups first erupted back in the late 1990s. The 2008 version states: "The benefits, risks, burdens and effectiveness

of a new intervention must be tested against those of the best current proven intervention..." (paragraph 32). Those who seek to ensure that placebos will not be used in control groups in resource-poor countries when they could not ethically be used in industrialised countries interpret "the best current proven intervention" to mean "anywhere in the world." In contrast, those who contend that the design of clinical trials should reflect what is available to the population where the research is conducted interpret "the best current proven intervention" as "what is locally available" or "what is provided by the ministry of health in the country." It is clear that these are very different standards and without some guidance from the DoH, double standards may persist: one for countries in which the best current proven intervention is available outside a clinical trial, and another for countries in which it is not.

The WMA satellite conference in Rotterdam took place on one day only. The forthcoming meeting in Cape Town will be held over a three-day period. Short presentations are scheduled on the following topics: vulnerable groups, post-trial arrangements, biobanks, and ethics committees. A session devoted to "positions of the international organizations" includes proposed speakers from the World Health Organization (WHO), the European Medicines Agency (EMA), the US National Institutes of Health (NIH) and Food and Drug Administration (FDA), the Council for International Organizations of Medical Sciences (CIOMS), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), and several others. The only proposed speaker from a low or middle-income country is from the Medicines Control Council of South Africa. The inclusion of South Africa is understandable as the meeting is being held in that country. Nevertheless, the roster of organisations has a distinct imbalance in the absence of representatives from, for example, Brazil and India, countries in which a large amount of research is conducted and where increasing numbers of generic drugs are manufactured.

Regarding the most controversial paragraphs in the DoH (placebo controls and post-trial benefits), the positions of several of the organisations on this list are already well known. The US FDA has been among the strongest proponents of clinical trial designs with placebo controls. In studies in which a new medication is being tested and a current effective treatment exists, the EMA prefers a placebo control in a third arm of the trial (4). When the controversy over using placebo controls in resource-poor countries first erupted in 1997, the then Director of the NIH, Harold Varmus, co-authored a paper in the *New England Journal of Medicine* (5) defending the placebo-controlled, mother-to-child HIV transmission study the NIH was sponsoring in developing countries. The IFPMA naturally supports the FDA position; it also bemoans the production of generic drugs by Brazil and India, which takes away market share from the big, profitable, pharmaceutical companies. The only international organisation that has positions on these two controversial areas that mirror the relevant DoH paragraphs is CIOMS. Historically, CIOMS intended to apply and expand the provisions of the DoH with specific reference to developing countries. This year CIOMS is embarking on revisions of its own 2002 ethics guidelines (6), and it is not known whether the organisation will attempt to continue to follow the DoH. What is clear, however, from Dr Urban Wiesing's presentation in Rotterdam (3a), is the WMA consensus that "the DoH must remain distinct from other guidelines." He referred to these others as "competing" guidelines. In explicating this point, Dr Wiesing noted that all other documents on medical research are younger than the DoH, and longer. The apparent implications of this point are that the DoH should not adopt new guidelines or the wording of existing guidelines based on what is in the other documents.

It is understandable that the WMA wants its premier guidance document to retain its character. However, it is not at all clear why the DoH should not incorporate missing elements that exist in other guidelines. Interestingly, the revision in 2000 did just that. The 2000 revision of the Declaration contains a provision about benefit to the population that was not included in the earlier versions. Paragraph 19 stated: "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research." That point was made in an earlier version of the CIOMS ethical guidelines back in 1993. The 2008 revision of the DoH expands the point further and adds the same wording that appears in the 2002 CIOMS Guideline 10: "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 and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research" (Paragraph 17, italics added). This is known as the "responsiveness requirement," and is yet another point that has been a source of controversy. It does appear that in drafting the 2008 revision, the WMA saw fit to draw on one of the CIOMS guidelines in order to improve a similar point in the DoH. There is no good reason why it should not do so in the forthcoming revision if doing so would further improve the DoH.

I was invited to deliver a keynote address at the Rotterdam satellite conference. In my presentation (3b), I mentioned several points that are missing from the current DoH. Chief among these is a guideline that addresses women in biomedical research, including pregnant women. That appears to be a glaring omission, especially since until fairly recently women were routinely excluded from clinical trials. Even today, although the general picture has improved, pregnancy remains an exclusion criterion for virtually all biomedical research, and if women become pregnant during a trial in which they are enrolled they are immediately withdrawn. One paragraph in the 2008 revision could be interpreted to refer to women (among others) but there is no specific mention of any group. Paragraph 5 says: "Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are under-represented in medical research should be provided appropriate access to participation in research."

Although it would add words and therefore increase the length of the DoH, the guideline should identify such under-represented populations, with explicit mention of women.

In 2008, the US FDA abandoned adherence to the Declaration of Helsinki for foreign studies (7). But the rest of the world still looks to the DoH as the leading ethical guidance for research involving human beings. The WHO's ethics review committee is guided in its work by the DoH, in addition to the CIOMS international ethical guidelines. In my keynote address at the satellite conference, I noted that to continue to be timely and relevant, the Declaration of Helsinki should remain at the forefront of international ethical guidance for research involving human beings. In so doing, it can help to promote global justice in human subjects research.

References

1. World Medical Association. WMA Declaration of Helsinki- Ethical principles for medical research involving human subjects [Internet]. WMA;2008Oct [cited 2012 Sep 05].5p. Available from: <http://www.wma.net/en/30publications/10policies/b3/>
2. Macklin R. The Declaration of Helsinki: another revision. *Indian J Med Ethics*. 2009 Jan-Mar;6(1):2-4.
3. World Medical Association. WMA satellite meeting during the 11th World Congress of Bioethics: Thinking ahead – the future of the Declaration of Helsinki[Internet]. Rotterdam: WMA;2012 Jun 26[cited 2012 Sep 05]. Available from: <http://www.wma.net/en/50events/20otherevents/10doh1/index.html>.
- 3a. Wiesing U. The future of the Declaration of Helsinki: Introduction – remarks about the next revision[Internet]. Rotterdam: WMA;2012 Jun 26[cited 2012 Aug 27]. Available from: <http://www.wma.net/en/50events/20otherevents/10doh1/Wiesing.pdf>
- 3b. Macklin R. The future of the Declaration of Helsinki: Maintaining a leadership role in global health research ethics[Internet]. Rotterdam: WMA;2012 Jun 26[cited 2012 Aug 27]. Available from: <http://www.wma.net/es/50events/20otherevents/10doh1/Macklin.pdf>
4. European Medicines Agency. EMEA/CPMP position statement on the use of placebo in clinical trials with regard to the revised Declaration of Helsinki. [Internet]. London:EMEA;2001 Jun 28[cited 2012 Sep 05];EMEA/17424/01:[Available from: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500017646
5. Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. *N Engl J Med*. 1997Oct 2;337(14):1003-5.
6. CIOMS in collaboration with the WHO. *International ethical guidelines for biomedical research involving human subjects* [Internet]. Geneva: CIOMS;2002 [cited 2012 Sep 05].113p. Available from: http://www.cioms.ch/publications/layout_guide2002.pdf
7. Kimmelman J, Weijer C, Meslin EM. Helsinki discords: FDA, ethics, and international drug trials. *Lancet*. 2009 Jan 3;373(9657):13-4.

IMA strike: need for public debate

B Ekbal

Consultant Neurosurgeon, Former Professor of Neurosurgery and Former Vice Chancellor, University of Kerala, Thiruvananthapuram 695 034 INDIA e-mail: ekbal@gmail.com

The Indian Medical Association (IMA) called for a nationwide strike on June 25, 2012 to protest against the formation of the National Council for Human Resources in Health and the promulgation of the Clinical Establishments (Registration and Regulation) Act, 2010 The strike call raises two issues that need to be examined in detail: whether the opposition to the government legislation is justified from a professional and societal point of view, and whether it is ethically justifiable for doctors to go on strike.

The National Commission for Human Resources for Health Bill, 2011, was introduced in the Rajya Sabha on December 22, 2011, by the Minister for Health and Family Welfare, Ghulam Nabi Azad(1). It was referred to the Department Related Standing Committee on Health and Family Welfare under the chairpersonship of Brajesh Pathak, which is scheduled to submit its report.

Regulation of health education

The Bill seeks to establish a mechanism to determine and regulate the standard of health education in the country. It will repeal the Indian Nursing Council Act, 1947, the Pharmacy Act, 1948, the Dentists Act, 1948, and the Indian Medical Council Act, 1956, on such date as decided by the central government. It seeks to set up the National Commission for Human Resources for Health (NCHRH), the National Board for Health Education, and the National Evaluation and Assessment Council. It also establishes various professional councils at the national and state level and an NCHRH Fund to meet expenses.

The IMA feels that the decision to dissolve the Medical Council of India (MCI) and other paramedical bodies like the Nursing Council of India and the Dental Council of India and replace them with the NCHRH will be deleterious to the best interests of the medical profession. It argues that the NCHRH will be governed by bureaucrats instead of members of the medical profession; and that this will lead to vested interests controlling such bodies, and is also likely increase red tapism and lead to harassment of doctors (2, 3).

The IMA also argues that the formation of the NCHRH will lead to the centralisation of decision making in matters concerning medical education and the medical profession. Though there is a provision for the formation of medical, nursing and other