doi: 10.3325/cmj.2009.50.105

7th Revision of the Declaration of Helsinki: Good News for the Transparency of Clinical Trials

Karmela Krleža-Jerić, Trudo Lemmens

Otawa Group
karmela.krleza-jeric@cihr-irsc.gc.ca

In October 2008, the 59th World Medical Association (WMA) General Assembly in Seoul adopted the 7th revision of the Declaration of Helsinki: "Ethical Principles for Medical Research Involving Human Subjects." This new version is the result of an extensive review process which started in 2007 and which received contributions by various national medical associations, researchers, and medical journal editors (1). The 7th revision of Declaration contains important new requirements related to the registration of clinical trials and reporting of their results.

Both requirements are indeed appropriately situated among the core principles of contemporary research ethics (Paragraphs 19 and 30). The main purpose of trial registration is to reduce publication and reporting bias and thus provide reliable evidence for decision making, but it can only achieve this if complemented by public reporting of results.

Various controversies over the last decades have confirmed the need to firmly reiterate that medical research involving humans has a clear public purpose and that transparency is a crucial requirement to ensure that this public purpose is respected (2,3).

A firm commitment of the medical community to transparency should help rebuild trust in medical research, which has been seriously damaged by these controversies. Ensuring transparency and integrity of data also reflects an ethical commitment to respect for research subjects. Indeed, using research subjects (or as we prefer to call them, participants) for research that remains hidden because of corporate or other interests amounts to using human beings as instruments of marketing and undermines their dignity. Finally, transparency in research on humans is also a core component of promoting the physical well-being of research participants and of patients who will end up consuming the products that result from research. Knowing about trials that have already taken place is crucial in preventing unnecessary exposure to potential harms in research and in promoting safe prescription behavior. Changes made to the Declaration, particularly those related to the need for the registration of clinical trials and results reporting, are a clear sign that the medical community is taking the issue of transparency, and public accountability of research seriously.

Here we shall briefly present the background to these provisions and address their implications and some of the remaining challenges.

HISTORY OF THE DECLARATION

As is well known, the Helsinki Declaration grew out of physicians' international initiatives which promoted general ethical standards for the medical profession after World War II. The first initiative of the World Medical Association in that context was to update the Hippocratic Oath with the Declaration of Geneva (1948), which focused on the basic ethical obligations of physicians toward their patients (4,5). The WMA subsequently embarked on a process to develop ethical principles for physicians involved in medical research on humans. It was developed in direct response to the International War Crimes Tribunal's condemnation of several prominent German physicians for their involvement in horrific medical experimentation on prisoners. The Nüremberg Court's decision contained a statement of core ethical principles that had to be respected in medical experimentation, the so-called Nüremberg Code (6,7).

Even though these principles were thought to be "generally accepted" and widely shared by the medical community, it took the WMA a substantial amount of time to reach a consensus on its own ethical principles for medical research. This was in part due to the fact that many delegations, particularly the US and Canadian, felt that the Nüremberg Code was too restrictive, particularly with respect to research involving children and people in mental health institutions and prisons (5). The version that was finally adopted in 1964 as the Declaration was clearly more flexible in that respect, providing a weaker informed consent, and allowed, for example, research on incompetent

patients. It also made a clear distinction between so-called therapeutic and non-therapeutic research, providing for weaker informed consent requirements in the context of research involving patients, ie therapeutic research.

Over time, the Declaration has undergone important changes, many of which were in line with the growing recognition of the need for fully informed consent in the context of medical practice, not just medical research. It was also revised to address new scientific and technological developments (8). According to Williams (1), the Declaration's evolution addressed the balance between general and individual interests, while continuing to emphasize that individual interests are primary and cannot be overridden for the sake of society or science. In the major revision of the Declaration in 2000, the distinction between so-called "therapeutic" and "non-therapeutic" research was abolished. At the same time, the Declaration forbade the use of placebo when there was an existing therapy, and added a public health component by requesting researchers to seek benefit for populations in their research (9).

7TH REVISION OF THE DECLARATION AND PROMOTION OF TRANSPARENCY

The 7th revision of the Declaration continues on this path of adapting to a changed research environment and a growing awareness of newly emerging ethical issues. We want to draw attention here to two important paragraphs and highlight their significance. The first is Paragraph 19 (Box 1) which introduces prospective registration of trials as a strict requirement. The second is Paragraph 30 (Box 2), which emphasizes the importance of the disclosure of research results.

Box 1.

Declaration of Helsinki, Paragraph No 19

Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

The inclusion of these two paragraphs in the Declaration has a long history. As early as the 1980s, commentators argued that there was a need to introduce a registration system for clinical research, as an important step to promote transparency (10-12). This call for registration and reporting of results has become louder in recent years, in the context of growing concerns over the incomplete disclosure of clinical trials data and bias in reporting research results (13-17).

Box 2.

Declaration of Helsinki, Paragraph No 30

Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Frustrated with the frequent publication and outcome reporting bias, the International Committee of Medical Journal Editors (ICMJE) made trial registration a mandatory prerequisite to consider trial results for publication, thus creating significant pressure and adding a very important motivation for clinical trials registration (14). Following the recommendations of the Mexico Summit on Health Research in November 2004, the 58th World Health Assembly adopted a resolution in 2005 which called for the development of a voluntary clinical trials registry platform (18). In the summer of 2005, the World Health Organization set up a working group to develop uniform criteria for trial registration and an international trial platform. This started an intensive international movement that contributed significantly to the development of the international standards, which were launched in 2006, and supported by the ICMJE and many others (15).

The Ottawa Group (to which we belong) has also been a vocal advocate for transparency. At its October 2004 meeting, this independent international group of stakeholders adopted a statement on the principles of trial registration, the so-called Ottawa Statement (13,19). In 2007, the Ottawa Group recommended to the WMA that the new version of the Declaration should include: (a) the need for performing systematic reviews in medicine, (b) prospective registration of trials, in line with the international standards launched by the WHO in 2006, and (c) public disclosure of results (20).

Not all of these proposed changes have been fully implemented. The need for systematic reviews is not explicitly listed and registration is included but without defining the registries. Ideally, the Declaration could have provided more clarity around registration and results reporting. For example, the Ottawa group thought that using the term "freely" accessible (meaning no payment at the moment of use), not just accessible, would be extremely important, as it would particularly promote access to research results for resource-poor countries. Furthermore, it was felt that there should have been a clear definition of the necessary public ownership of registries, which should have excluded registries set up by entities with a potential conflict of interest associated with the results (eg, industry-owned registries). Still, the fact that the Declaration does include a clear and undeniable reference to the need for public accountability of research is laudable. The Declaration explicitly requires that results are made publicly available (Paragraph 30), which includes not only publications in peer-reviewed journals, but also results posted on the Internet (21).

DECLARATION AND REMAINING CHALLENGES IN PROMOTING TRANSPARENCY OF RESEARCH ON HUMANS

The Declaration aims at setting generally acceptable principles and cannot provide all the details, which have to be worked out by regulatory bodies and organizations. While this international declaration of principles is a beginning, there is a need for further initiatives at national and international levels. These initiatives must address two ongoing challenges. First, there is a need to develop standards for results disclosure on a global level. This has been recommended by the participants of the international meeting on Public Reporting of Clinical Trials Outcomes and Results (PROCTOR), organized by the Canadian Institutes of Health Research (CIHR) in March 2008 (22). In June 2008, the WHO Working Group on reporting of findings of clinical trials proposed that findings of all clinical trials be made publicly available. WHO also started a public consultation process (23), which we can expect to lead to the development of international standards. Second, there is a need to ensure national implementation and enforceability of the Declaration requirements and of the WHO/ICMJE international standards for trial registration. In Canada, for example, the Declaration principles are reflected and further developed in the research ethics policy developed by the major federal funding agencies, the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (24). This Policy Statement defines ethical standards in research involving humans that is undertaken in federally funded institutions. The Tri-Council Policy Statement is currently being revised and the new draft, which has been made publicly available for commentary, contains explicit provisions related to trial registration and results reporting (25). Its new article 11.12 would impose a duty to register all clinical trials "with a recognizable and easily accessible public registry" (25). Such a registry, the document states, is important to allow access to ongoing trials and their results. The new draft also explicitly states that institutions and research ethics boards should ensure that results of clinical trials will be published or otherwise disseminated in a timely manner. According to the new article 11.11, "any prohibition or undue limitation on the publication or dissemination of scientific findings from clinical trials is ethically unacceptable" (25). However, the impact of the Tri-Council Policy Statement in Canada is somewhat limited. In principle, it only binds research that is funded by one of the major federal funding agencies, or research that is being undertaken in federally funded institutions that have signed a contractual agreement with the federal funding agencies to respect the Tri-Council Policy Statement. Clinical trials of pharmaceutical products that are sponsored by industry are subject to clinical trial regulations emanating from the Canadian Government and have to respect the International Conference on Harmonisation – Good Clinical Practice Guidelines (ICH-GCP) (26). There is currently no regulation requiring registration of all clinical trials and no requirement to publicize all results. As in many countries, there is clearly a need for a national regulation that requires clinical trial registration and results reporting on the clinical trials that are taking place outside publicly funded institutions.

The main task in front of us is to define international principles and standards of public disclosure of trial results, beyond publication in peer reviewed journals. This includes the elaboration of minimum and optimum requirements and the development of a long-term vision that would enable a gradual increase in details and levels of public posting of results to meet the needs of various user groups. Using this approach, we expect to achieve the level of transparency that would enable the critical appraisal of trials, protect trial participants from unexpected harm, and regain people's trust in research on humans and thus guarantee that research meets ethical requirements. Some pioneering work in defining international principles for results reporting has been done by the Ottawa Statement, especially its part 3 (13).

NATIONAL IMPLEMENTATION OF THE TRANSPARENCY REQUIREMENTS

The clinical trial results tables developed by the *ClinicalTrials.gov* registry as the implementation of the 2007 Amendment of the Food and Drug Administration Act (FDAAA), represent a big step in that direction (27,28). Our concerns regarding results posting, as defined by FDA Amendment Act and prior-publication, was addressed by the ICMJE's timely reaction in June 2008. Journal editors agreed that the registration of results in the same primary register in which the trial was registered will not be considered prior publication (29). However, without a global approach we cannot achieve the application of ethical principles worldwide and a consequent increase in transparency and safety of trial participants.

Initiatives are also needed to ensure the implementation of the Declaration principles. The WMA by itself has no power to ensure the implementation at a national level and no regulatory power to ensure compliance. It is expected that national medical associations and medical schools will adopt the Declaration and this will undoubtedly have an impact on research in which physicians are involved. Yet, professionals other than physicians are increasingly involved in health-related research involving humans. Some health research projects may not involve medical practitioners at all. While the Declaration has a high moral status in the world of medical research at large, the fact that it is enacted by a single professional organization may indicate its limits unless other professionals also endorse it. In paragraph 2 of the Declaration the WMA invites all those that design, conduct, and analyze clinical research to adopt these principles.

Furthermore, there is uncertainty as to the legal status of revisions to the Declaration in countries which explicitly refer in legislation to the need to respect the Declaration's principles. Indeed, national legislators or regulators would not normally be bound by a new version of a document emanating from another institution, to which they refer in their regulations or legislation (25,30). In October 2008, following several years of debate, the FDA in the United States removed the references to the Declaration, likely in reaction to the more stringent restrictions on the use of placebo controls in the 6th revision of the Declaration (31-33). This is regrettable for a variety of reasons, not in the least because it undermines the authority of the Declaration as a statement of ethical principles to which all nations can sign onto. In the context of registration and results reporting, it should, however, be mentioned that the US is in the forefront of moving toward a stringent regulatory system. Indeed, following the 2007 FDA Amendment Act, trial registration, and mandatory results reporting of at least phase II to phase IV trials are now stringent regulatory requirements that can be legally enforced in the United States.

We believe that it is important for national regulators not to invoke the limitations of the Declaration as an excuse to reject an important research ethics document that provides standards for ethical research to which all members of the research community should adhere. The Declaration has been widely endorsed as being among the most influential international medical research ethics documents. Its moral status can undoubtedly be used to put pressure on national governments and legislators to ensure that national regulatory systems live up to the principles embedded in the Declaration. They should use the current version of the Declaration's principles, and expand them if perceived necessary. Declaration's principles should be seen as a minimum standard, and national regulations or guidelines should not "reduce or eliminate any of the protections for research subjects set forth in this Declaration" (21).

We should seek ways to get the Declaration accepted as the code of ethics that binds all those that participate in clinical research anywhere and in whichever role. Organizations of health professionals, ethics committees, academia, registries, journal editors, funders, and sponsors, as well as those developing regulatory and scientific standards and guidelines, should explicitly embrace the Declaration's principles and build on them.

TOWARD INTERNATIONAL STANDARDS

Certain issues related to trial registration and results reporting need to be solved, including the scope, purpose, and form of results, to enable their public disclosure on the Internet, beyond publication in peer-reviewed journals. In spring 2008, building on international and its own initiatives, the Canadian Institutes of Health Research organized a meeting on the Public Reporting of Clinical Trial Outcome and Results (PROCTOR). The PROCTOR meeting started an international dialogue of different constituencies and identified issues regarding how, when, for whom, and in which ways results of clinical trials should be reported and how they might be used, and made recommendations for developing international standards for public disclosure of clinical trial results (unpublished). Outcomes

of the PROCTOR meeting are about to be published and we sincerely hope that they will contribute to the development of international standards. The new version of the Helsinki Declaration, with its explicit requirements for trial registration and results reporting, may provide the necessary impetus to move toward global registration and reporting systems.

Acknowledgment

We thank Genevieve Dubois-Flynn and Hugh Thompson, Canadian Institutes of Health Research, and John Williams, University of Ottawa for providing useful comments to an earlier draft of our editorial. We also thank Nevena Jeric, Apropo Media, for filming the video summary.

References

1 Williams JR. Revising the Declaration of Helsinki. World Med J. 2008;54:120-2.
2 Chan AW, Krleza-Jeric K, Schmid I, Altman DG. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. CMAJ. 2004;171:735-40. Medline:15451835
3 Lemmens T. Leopards in the temple: restoring scientific integrity to the commercialized research scene. J Law Med Ethics. 2004;32:641-57. Medline:15807352 doi:10.1111/j.1748-720X.2004.tb01969.x
4 Declaration of Geneva. (1948) physician's oath: adopted by the General Assembly of World Medical Association at Geneva Switzerland. Available from: http://www.cirp.org/library/ethics/geneva/. Accessed: April 10, 2009.
5 Lederer SE. Research without borders: the origins of the declaration of Helsinki. In: Schmidt U, Frewer A, editors. History and theory of human experimentation. Stuttgart (Germany): Franz Steiner Verlag; 2007. p. 145-64.
6 Annas GJ, Grodin MA, editors. The Nazi doctors and the Nuremberg Code: human rights in human experimentation. New York (NY): Oxford University Press; 1992.
7 Mitscherlich AMF. The Nuremberg Code (1947). In Doctors of infamy: the story of the Nazi medical crimes. New York: Schuman; 1949. p. 23-5.
8 Goodyear MD, Krleza-Jeric K, Lemmens T. The Declaration of Helsinki. BMJ. 2007;335:624-5. Medline:17901471 doi:10.1136/bmj.39339.610000.BE
9 Williams JR. The Declaration of Helsinki and public health. Bull World Health Organ. 2008;86:650-2. Medline:18797627 doi:10.2471/BLT.08.050955
10 Dickersin K. Report from the panel on the Case for Registers of Clinical Trials at the Eighth Annual Meeting of the Society for Clinical Trials. Control Clin Trials. 1988;9:76-81. Medline:3356154
11 Moher D. Clinical-trial registration: a call for its implementation in Canada. CMAJ. 1993;149:1657-8. Medline:8242504
12 Simes RJ. Publication bias: the case for an international registry of clinical trials. J Clin Oncol. 1986;4:1529-41. Medline:3760920
13 Ottawa statement on trial registration. Available from: http://ottawagroup.ohri.ca. Accessed: April 10, 2009.
14 DeAngelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. JAMA. 2004;292:1363-4. Medline:15355936 doi:10.1001/jama.292.11.1363
15 Laine C, Horton R, DeAngelis CD, Drazen JM, Frizelle FA, Godlee F, et al. Clinical trial registration: looking back and moving ahead. Croat Med J. 2007;48:289-91. Medline:17589970
16 Moher D, Bernstein A. Registering CIHR-funded randomized controlled trials: a global public good. CMAJ. 2004;171:750-1. Medline:15451838
17 Sim I, Chan AW, Gulmezoglu AM, Evans T, Pang T. Clinical trial registration: transparency is the watchword. Lancet. 2006;367:1631-3. Medline:16714166 doi:10.1016/S0140-6736(06)68708-4
18 World Health Assembly – ninth plenary meeting. WHA 58-34 Ministerial Summit on Health Research. May 25, 2005. Available from: http://www.who.int/rpc/meetings/58th_WHA_resolution.pdf. Accessed: April 10, 2009.
19 Krleza-Jeric K, Chan AW, Dickersin K, Sim I, Grimshaw J, Gluud C. Principles for international registration of protocol information and results from human trials of health related interventions: Ottawa statement (part 1). BMJ. 2005;330:956-8. Medline:15845980 doi:10.1136/bmj.330.7497.956
20 Ottawa group recommendations for the evaluation of the Declaration of Helsinki to WMA and WAME. Available from: http://ottawagroup.ohri.ca/news.html. Accessed: April 10, 2009.
21 The World Medical Association. Declaration of Helsinki. World Med J. 2008;54:122-5.
22 Krleza-Jeric K. International dialogue on the public reporting of clinical trial outcome and results – PROCTOR meeting. Croat Med J. 2008;49:267-8. Medline:18461682 doi:10.3325/cmj.2008.2.267
23 Ghersi D, Clarke M, Berlin J, Gulmezoglu A, Kush R, Lumbiganon P, et al. Reporting the findings of clinical trials: a discussion paper. Bull World Health Organ. 2008;86:492-3. Medline:18568282 doi:10.2471/BLT.08.053769
24 First Clinical Research. Canada – Canada Tri-Council Policy Statement. Ethical Conduct for Research Involving Humans. Available from: http://firstclinical.com/regdocs/doc/?db=INT_Canada_Tricouncil. Accessed: April 10, 2009.
25 The Interagency Advisory Panel on Research Ethics. Draft 2nd edition of the Tri-Council Policy Statement: ethical conduct for research involving humans. 2008. Available from: http://www.pre.ethics.gc.ca/english/newsandevents/newsreleases/draft_2nd_ed_of_TCPS.cfm. Accessed: April 10, 2009.
26 International Conference on Harmonisation/World Health Organization. ICH/WHO Good Clinical Practice standards. Available from: http://www.ich.org/cache/compo/276-254-1.html. Accessed: April 10, 2009.
27 Food and Drug Administration Amendments Act of 2007; Public law 110-85-Sept 27, 2007.
28 Tse T, Zarin DA. Clinical trial registration and results reporting: ClinicalTrials.gov and FDAAA. Update. 2009;(1):18-22.
29 Marusic A, Huic M. Registration of clinical trials still moving ahead – September 2008 update to Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

Croat Med J. 2008;49:582-5. Medline:18925691 doi:10.3325/cmj.2008.5.582

30 Sprumont D, Girardin S, Lemmens T. In: Schmidt U, Frewer A, editors. History and theory of human experimentation. Stuttgart (Germany): Franz Steiner Verlag; 2007. p. 223-52.

31 Regulations.gov. Human subject protection; foreign clinical studies not conducted under an investigational new drug application – notice of final rule. Available from: http://www.regulations.gov/fdmspublic/component/main?main=DocumentDetail&o=0900006480537f08. Accessed: April 10, 2009.

32 Kimmelman J, Weijer C, Meslin EM. Helsinki discords: FDA, ethics, and international drug trials. Lancet. 2009;373:13-4. Medline:19121708 doi:10.1016/S0140-6736(08)61936-4

33 Wolinsky H. The battle of Helsinki: two troublesome paragraphs in the Declaration of Helsinki are causing a furore over medical research ethics. EMBO Rep. 2006;7:670-2. Medline:16819460 doi:10.1038/sj.embor.7400743