VIEWPOINT

Revised CIOMS International Ethical Guidelines for Health-Related Research Involving Humans

Johannes J. M. van Delden, MD, PhD
Julius Center, Department of Medical Humanities, University Medical Center Utrecht, Utrecht, the Netherlands.

Rieke van der Graaf, PhD
Julius Center, Department of Medical Humanities, University Medical Center Utrecht, Utrecht, the Netherlands.

The Council for International Organizations of Medical Sciences (CIOMS) was established jointly by the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949 as an international, nongovernmental, nonprofit organization and now includes 45 international, national, and associate member organizations, representing many of the biomedical disciplines, national academies of sciences, and medical research councils. CIOMS recently released a new version of its International Ethical Guidelines for Health-Related Research Involving Humans.[1] These guidelines were developed in collaboration with WHO and based on authoritative ethical guidance documents, such as the World Medical Association's Declaration of Helsinki[2] and UNESCO's Universal Declaration on Bioethics and Human Rights.[3] The aim of the guidelines is to provide internationally vetted ethical principles and detailed commentary on how these principles should be applied, with particular attention to conducting research in low- and middle-income countries (LMICs).

Reasons for Revisions

Several challenges and reasons prompted CIOMS to revise its ethical guidelines. A first challenge was to provide clearer guidance for ensuring that research addresses important questions for improving health using sound research methods. The ethical acceptability of research fundamentally depends on its social and scientific value,[4] yet some of the research currently conducted is of questionable value.[5]

> The aim of the guidelines is to provide internationally vetted ethical principles and detailed commentary on how these principles should be applied....

A second challenge was to further clarify what can be regarded as fair benefits of research in low-resource settings. Although the CIOMS guidelines have always addressed the interests of research participants and those in LMICs in particular, the previous version of the CIOMS guidelines (issued in 2002) was criticized for not providing sufficient guidance focused on this issue. That version required that externally sponsored research should be responsive to the health needs and priorities of the host country and that any proven products, such as drugs, should be made reasonably available to that population or community. However, the requirement was difficult to apply in practice, in particular because of its narrow focus on benefits that may, but not always will, result from a trial.

A third challenge was to address the increased need to engage communities from the planning to the implementation phase of research.

A fourth reason was a change in global perspectives about inclusion of potentially vulnerable groups. In the 2002 version, certain groups, such as children and incompetent individuals, were explicitly labeled as vulnerable. However, a group approach to vulnerability may no longer be appropriate because it may have led to the routine exclusion of certain groups from research and hence has exacerbated knowledge gaps.[6,7] Moreover, a group approach could also lead to underprotection because it does not address different ways in which people can be vulnerable, for example, an illiterate woman in a low-resource setting participating in a study on domestic violence.[6,7]

A fifth challenge was that the increase in the collection, storage, and use of biological material and health-related data has changed the practice of research from an activity mainly carried out in individual projects to an activity that is organized around research infrastructures such as biobanks and databanks. CIOMS recognized the need to provide guidance to researchers, sponsors, members of research ethics committees, and other stakeholders in dealing with these challenges and started a revision process. The process of development and revision of these guidelines was approved by the WHO Guidelines Review Committee and received extensive input from the WHO Ethics Review Committee.

Significant Changes

As a general response to these developments in research involving humans, the scope of the guidelines has been broadened from biomedical research to health-related research because the term *biomedical research* would not cover research with health-related data. In addition, the 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects were merged with the CIOMS 2009 International Ethical Guidelines for Epidemiological Studies, which included topics such as biobanking and research with health-related data. The following major changes have been made to the previous guidelines as a response to the specific challenges that have emerged during the last decade.

First, the 2016 CIOMS guidelines include an increased emphasis on the scientific and social value of research: the prospect of generating the knowledge and the means necessary to protect and promote health (guideline 1). Many stakeholders in health-related research rely on the results of research for activities and decisions that affect individual and public health, welfare, and the use of limited resources. Therefore, researchers and sponsors must ensure that research

Corresponding Author: Johannes J. M. van Delden, MD, PhD, Julius Center, Department of Medical Humanities, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, the Netherlands (j.j.m.vandelden@umcutrecht.nl).

addresses important and unsolved questions to improve health and increase the reliability of scientific information, promote efficient translation, and reduce research waste, even when the research investigation poses few or only minor risks to study participants.

Second, the importance of social value is part of a larger effort to clarify considerations of fairness in research conducted in low-resource settings. The guidelines now recognize that low-resource settings are not limited to low-income countries but can exist within middle- and high-income countries (guideline 2). In addition, CIOMS now lists the obligation to make available the interventions proven effective in research as part of a broader obligation to care for participants' health needs (guideline 6). This broader obligation also requires, for example, that before a study begins, researchers and sponsors make plans for transitioning participants who continue to need treatment after their participation in research to appropriate health services.

Third, a new guideline on community engagement is included (guideline 7). Proactive and sustained engagement with the communities from which individuals will be invited to participate shows respect for them and for the traditions and norms that they share. Community engagement is also valuable for the translation of research into outcomes that are both clinically relevant and meaningful for patients and communities.

Fourth, the new guidelines no longer label entire classes of individuals as vulnerable. Moreover, CIOMS more clearly emphasizes that unless a good scientific reason justifies their exclusion, children and persons who are incapable of giving informed consent must be included in research investigations, provided that appropriate safeguards are in place. Moreover, the revised guidelines require researchers and research ethics committees to evaluate the specific context-dependent characteristics that may place study participants at increased risk of being harmed or wronged.

Just as the definition of vulnerability is context dependent, so is the delineation of special protections. Researchers and research ethics committees can devise special protections for groups considered to be vulnerable, including allowing for no more than minimal risks for research procedures that offer no potential individual benefits for participants, or requiring that the research be carried out only when it targets conditions that affect these groups. Researchers and research ethics committees should enable the participation of vulnerable individuals by protecting their rights and interests through special safeguards and protections.

Special protections are warranted in research involving pregnant and breastfeeding women to ensure that their rights and interests are protected. The 2002 guideline on research with pregnant women underwent major revisions to strengthen the specific protection mechanisms (guideline 19), such as the conditions under which risks in research with pregnant women are acceptable. In addition, the guidelines require that research that has the potential to harm the fetus should be conducted only in settings where women can be guaranteed access to a safe, timely, and legal abortion in the event that participation in the research makes the pregnancy unwanted.

Fifth, the traditional method of informed consent for specific research projects is proving inappropriate for the increasing number of studies that use biological material and health-related data. Concepts of broad informed consent and informed opt-out procedures have therefore been adopted in the new CIOMS guidelines for research in this area (guidelines 11 and 12). Broad informed consent in essence is consent for governance. Adequate governance systems substitute for the loss of an individual's control over her or his data and biological material. These governance systems should specify—among other items—to which legal entity the material is entrusted, how authorization from the donor is obtained, and what procedure determines whether unsolicited findings should be disclosed. Proper governance systems are also important because complete anonymization is becoming increasingly difficult owing to increases in cross-matching large data sets.

Progress toward a world in which everyone can enjoy optimal health and health care is crucially dependent on all kinds of research, including research involving humans. This research needs to be conducted according to guidelines such as the ethical principles set forth in the CIOMS guidelines. As research practice changes, new challenges emerge and guidelines need to be adapted. The changes in the new CIOMS guidelines reflect an international effort to provide well-reasoned answers to these challenges.

ARTICLE INFORMATION

Published Online: December 6, 2016. doi:10.1001/jama.2016.18977

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Additional Contributions: Members of the Working Group on the revision of the 2002 CIOMS guidelines include Anant Bhan, MBBS, MHSc, Eugenijus Gefenas, MD, PhD, Dirceu Greco, MD, PhD, David H.-U. Haerry, Bocar Kouyaté, Alex John London, PhD, Ruth Macklin, PhD, Annette Rid, MD, Rodolfo Saracci, MD, Abha Saxena, MD, and Aissatou Touré, PhD. Observers and advisors of the Working Group include Ingrid Callies, Joan Dzenowagis, Hans-Joerg Ehni, Dafna Feinholz, Sev Fluss, Melba Gomes, Carel Ijsselmuiden, Ronnie Johnson, Lembit Rägo, Gunilla Sjölin-Forsberg, Sheryl VanderPoel, and Urban Wiesing. More than 57 institutions and organizations provided comments and helped to shape the final version of the guidelines.

REFERENCES

1. Council for International Organizations of Medical Sciences. *International Ethical Guidelines for Health-Related Research Involving Humans*. Geneva, Switzerland: Council for International Organizations of Medical Sciences; 2016. http://www.cioms.ch. Accessed December 6, 2016.

2. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.

3. United Nations Educational, Scientific and Cultural Organization. *Universal Declaration on Bioethics and Human Rights*. Paris, France: UNESCO; 2006. http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/bioethics-and-human-rights/. Accessed November 21, 2016.

4. London AJ. A non-paternalistic model of research ethics and oversight: assessing the benefits of prospective review. *J Law Med Ethics*. 2012;40(4):930-944.

5. Ioannidis JPA. Why most published research findings are false. *PLoS Med*. 2005;2(8):e124.

6. Hurst SA. Vulnerability in research and health care; describing the elephant in the room? *Bioethics*. 2008;22(4):191-202.

7. Luna F, Vanderpoel S. Not the usual suspects: addressing layers of vulnerability. *Bioethics*. 2013;27(6):325-332.