THEME: CIOMS, 2016 - GAINS AND MISSED OPPORTUNITIES

Research ethics for a globalised world: the revised CIOMS international guidelines

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Abstract

On December 6, 2016, the Council of International Organisations of Medical Sciences published a new version of its guidelines with the title "International Ethical Guidelines for Health-related Research Involving Humans." In this article we briefly describe the revision process and the structure and content of these guidelines. We outline some of its main guidelines such as the ones on social value, post-trial access, and risk-benefit ratio. In our overall evaluation we come to the conclusion that the CIOMS guidelines manage to strike a balance between the protection of human participants in health-related research and the promotion of such research activities in an exemplary way. The guidelines combine key principles with a guide to their application based on the state of the art in research ethics. Thus they represent a timely and indispensable orientation for researchers, ethics committees, and other stakeholders in health-related research.

Introduction

The World Health Organisation (WHO) and the United Nations Educational, Scientific, and Cultural Organisation (UNESCO) cooperated in 1949 to establish the Council of International Organisations of Medical Sciences (CIOMS). The Council represents a substantial proportion of the international community of scientific organisations in biomedicine; according to its webpage, in 2013, 49 national and international organisations, such as national academies and medical research councils, were members. The goals of CIOMS are – among others - to serve the scientific interests of the international biomedical community and to foster international collaborations.

In accordance with this general focus on international cooperation and exchange, the Council also deals with the ethical and legal challenges that biomedical research continuously creates and must address. Health policy, values and bioethics are the focal areas of major on-going programmes. The recently revised and published *International Ethical Guidelines for Health-related Research Involving Humans,* which we discuss in this article, constitute one of the main achievements of these activities. CIOMS published an earlier version, the *Proposed International Guidelines for Biomedical Research Involving Human Subjects* in 1982 in close collaboration with WHO. These guidelines – which are still valid today – had two objectives: to apply the principles of the Declaration of Helsinki, and to specify these principles in the context of international biomedical research, especially in low resource settings. The first version of the *International Guidelines for Biomedical Research Involving Human Subjects* replaced these "proposed guidelines" in 1993. CIOMS updated and revised these guidelines from 1998 to 2002.

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The revision process

In 2010, the CIOMS executive committee discussed whether a new revision of the guidelines would be timely and necessary, and came to the conclusion that it was. The committee established an interdisciplinary working group in 2011, chaired by the Dutch physician and medical ethicist Hans van Delden, who was also CIOMS president at the time. Ten international experts participated in the working group, supported by advisors from different international organisations (WMA, UNESCO and the Council on Health Research for Development or COHRED). The working group met 10 times from 2012 to 2015 in an intense process of discussion of the suggested changes which were based on systematic reviews of the relevant literature (1). In September 2015 a draft of the guidelines was published on the CIOMS website for public comment. These comments were considered in the final version of the guidelines which the General Assembly of CIOMS accepted on November 29, 2016. CIOMS published this version on its website on December 6, 2016 (2). On the same day Hans van Delden and Rieke van der Graaf, the secretary of the working group, published a summary and overview of the revision process and the new guidelines in the *Journal of the American Medical Association* (3).

Since 2002 when CIOMS published the previous version, several trends have shaped the practice of biomedical research involving human participants and the ethical debates on the accompanying problems. Three major trends or debates should be highlighted in the discussion of the new CIOMS-guidelines.

These trends play an important role in the justification of the revision, and in the new version of the guidelines: the globalisation of clinical trials, the increase in biobanking and the digitalisation of research, and finally, the criticism by several authors that a substantial part of commercial clinical trials is biased and that the evidence they generate is unreliable. The WMA's Declaration of Helsinki also refers to these trends in its latest revision completed in October 2013. Revising the CIOMS guidelines was consequently a necessary and timely effort, since they still have the objective to specify the principles of the Declaration of Helsinki, in particular the problems generated by international research.

Firstly, the globalisation of biomedical research led to an increase in the volume of international clinical trials in low and middle income countries (4). There was, and still is, concern that the objective of such trials often is to develop a new intervention without ensuring their availability in the host country of the trial. Such interventions might only be available in the country of origin of the sponsor which is usually a wealthy country. Many experts considered such an outcome to be exploitative. This led to a debate on exploitation and justice in international research cooperation (5-7). In this context, the heated debate on placebo controls and the appropriate conditions for the choice of control group ended in completely opposed positions. How biomedical concepts such as placebos are understood in different cultures is another important topic raised by the globalisation of clinical trials. As a consequence, ethicists have called for the involvement of local communities in addressing this and other issues. At the same time, there is too little biomedical research targeting conditions which prevail in low and middle income countries, such as parasitic and other infections. This leads to a fundamental ethical dilemma in the regulation of what is increasingly globalised biomedical research: How can guidelines address such problems as justice in international biomedical research and cultural difference? And how can they do this without preventing necessary research?

Secondly, new technological possibilities in analysing huge amounts of data open up avenues to new ways of gaining medical knowledge. Examples are genome-wide association studies or research with health records. These possibilities lead to an increase in biobanking and in databases and registers. Such institutions create new challenges for the informed consent process and data protection. For instance, it has been discussed to what degree general or broad consent is ethically acceptable. And in the field of data protection, experts doubt whether the principle of anonymity can be upheld. The reason is that big data makes it increasingly easy to re-identify a person even if personal identifiers have been stripped from data sets or tissue samples. As a general consequence of this trend, the CIOMS guidelines now use "health related research" as the overarching term for the research they are referring to. "Biomedical research" may be too narrow as a concept which should also encompass new digital methods to gain knowledge on health issues.

Thirdly, authors such as John PA Ioannidis (8) and Peter Gøtzsche (9) criticise biomedical research in general and commercial research in particular for being biased and shaped by conflicts of interests, and resulting in unreliable evidence. This can happen because data which does not fit the desired outcome of a study may be falsified or suppressed. As a result, trial participants are exposed to risks of harm without the prospect of benefit, and evidence-based medicine is compromised. This may in turn harm patients, deprive them of benefits, and undermine trust in health-related research and in medical practice. Research which is not scientifically sound lacks any social value. Consequently, such research lacks the fundamental ethical justification for biomedical research formulated by many ethical guidelines including the new version of the CIOMS-guidelines and the Declaration of Helsinki.

Structure and content of the new guidelines

General structure of the guidelines

The 25 CIOMS guidelines put forward a fundamental justification for research (Guideline 1: social value). They formulate well-known principles for health-related research (for instance Guideline 4: adequate risk-benefit ratios; Guideline 9: informed consent) and consider the specific ethical conditions for research in low resource settings and international research cooperation (Guideline 2: research in low-resource settings). Finally, they also address some particular types of research and research situations (Guideline 20: research in disaster situations, Guideline 21: cluster randomised trials). As in previous versions each guideline is divided into two sections. The bold text lays out its general principles and the most important ethical requirements based on these principles. The commentary includes more detailed definitions, explanations, specifications, and examples which help to understand and apply the principles.

In a brief overview, one may group the guidelines as follows: Guideline 1 lays the normative foundation of health-related research with social value and scientific validity. Guidelines 2 and 3 extend this foundation to low-resource settings by arguing for specific aspects of justice in the distribution of social value and the fair selection of participants. Guideline 4 is another fundamental guideline: a precise description how an appropriate risk-benefit ratio can be determined. Guidelines 5 and 6 contain further specifications relating to risk-benefit evaluations: the choice of the control group, whether an effective established intervention exists, and the requirements on care for participants' health needs. Guidelines7 and 8 spell out principles for community engagement, collaborative partnership and capacity building. Guideline 9 is the fundamental guideline on informed consent. Guidelines 10, 11, and 12 address specific contexts of informed consent, namely, the conditions for waivers, biobanking, and research with health data (obviously, the requirements for biobanking and data registers go beyond questions of informed consent). Guideline 13 treats general questions of reimbursement and compensation, while 14 is dedicated to

treatment and compensation for research-related harms. The subject of Guideline 15 is vulnerability, and Guidelines 16, 17, 18 and 19 address individuals and groups who may potentially be vulnerable in specific ways (those incapable of giving consent, children and adolescents, women, and pregnant and breastfeeding women). Guidelines 20, 21, and 22 deal with specific types of research, which recently became more important (research in disasters and disease outbreaks, cluster randomised trials, and the use of online environment and digital tools). Guideline 23 describes requirements for ethics review. Rules for transparency, which should contribute to meeting some of the challenges for social and scientific value, are described in Guidelines 24 and 25 (public accountability, and conflicts of interest).

It is beyond the scope of this article to discuss the substance of all these guidelines even very briefly. In the following sections we want to outline some of the key guidelines. We have chosen these particular guidelines because they address fundamental principles and because they address issues which have been in the focus of recent debates. Together they provide important examples which may give the reader an idea about the specific approach of the guidelines. These guidelines are on: scientific and social value and respect for rights; research conducted in low-resource settings, and potential individual benefits and risks of research. We also want to briefly compare major aspects of these guidelines to the Declaration of Helsinki.

Guideline 1: Scientific and social value and respect for rights

The CIOMS guidelines start with a detailed explanation of social value and its ethical importance. The concept of social value in research is defined as "the prospect of generating the knowledge and means necessary to protect and promote people's health". Further, Guideline 1 also specifies who is responsible for social value by ensuring that biomedical research is scientifically sound: researchers, sponsors, research ethics committees, and health authorities. The commentary explains that scientific value is a necessary but not a sufficient condition for social value. In order to be socially valuable, a study must also ask a relevant question, for instance a question which has not been answered already in previous research.

Other guidelines sometimes do not explicitly contain the concept of social value, but make comparative references to the possible benefit of biomedical or health-related research for society and individuals (10). For instance the current version of the Declaration of Helsinki of 2013 highlights the need for biomedical research involving human subjects for the development of better preventive, diagnostic and therapeutic interventions and overall medical progress (Paragraphs 5 and 6). Furthermore, Paragraph 16 of the Declaration of Helsinki requires that the risks and burden to research participants be outweighed by the importance of the objective. Paragraphs 21 and 22 of the Declaration spell out in more detail the scientific requirements for biomedical research, and specify the need for a research protocol and what such a protocol should contain. Such details can be found in Appendix 1 of the CIOMS guidelines.

The second paragraph of the bold text of Guideline 1 emphasises that research must be carried out in accordance with human rights and must respect research participants and the host communities of research. This corresponds to Paragraph 8 of the Declaration of Helsinki which states that "the goal to generate knowledge can never take precedence over the interests and rights of individual research participants". The social value of health-related research does not justify violating the rights of research participants or their interests, either understood as interests expressed by themselves in the informed consent process, or as their best interests in accordance with their rights.

The Declaration of Helsinki starts with a reference to the Declaration of Geneva and its famous quote: "the health of my patient will be my first consideration". In contrast, the CIOMS guidelines first highlight the principle of social value. As a consequence, they may appear to represent a basically utilitarian approach to research ethics. But we have already described, above, how both the Declaration of Helsinki and the CIOMS Guideline take the same position regarding the basic justification of research by its importance for medical progress and medical practice. At the same time, both sets of guidelines limit this justification by social value or benefits to others by reference to the rights of individuals. This is a good example of how the two guidelines basically take the same position, while they highlight different concepts. An important prescription which both the WMA and CIOMS give is that both guidelines have to be read and interpreted as a whole.

Guideline 2: Research in low-resource settings

Contributors to the international debate on research in resource-poor settings have put forward two conditions to avoid exploitation: responsiveness to local health needs or priorities; and reasonable post-trial availability of new interventions developed during the research. These conditions aim to prevent research being carried out in disadvantaged communities or populations when the results are intended to benefit other communities or populations who are generally better off. CIOMS Guideline 2 specifically supports these conditions. This position is fundamentally in line with the Declaration of Helsinki (Paragraph 20, which relates these conditions to vulnerable populations, and Paragraph 34 which formulates a broader requirement of post-trial access). Consequently, the CIOMS guidelines require that the social value generated by research be distributed fairly. In particular, the value must reach those who participate in research and the communities to which they belong. The CIOMS guidelines add that such communities should be involved right from the planning process of the research. Their additional focus on communities and not just individuals is one of their particular features. Community engagement and involvement is also aimed at determining the distribution of benefits. Such benefits may go beyond those associated with study participation. Thus, they may include improvements of infrastructure, capacity building, and education of the public on specific health issues.

Guideline 4: Potential individual benefits and risks of research

The Declaration of Helsinki merely states that risks should be assessed and minimised, and that the general importance of a study should outweigh the risks and burden to the participants. In contrast, the CIOMS Guideline 4 describes in detail how to proceed in the assessment of risks, and in balancing them against potential benefits. This assessment must be taken in two steps.

In the first step, each separate intervention or procedure of a study must be evaluated. For this purpose, interventions and procedures are divided into two separate categories. The first category encompasses those interventions with a potential benefit for research participants, and the second category covers those without such potential benefit. The basic requirement in the first category is that any procedure or intervention will be at least as advantageous as any established effective intervention. In the second category, acceptable risks depend on the social and scientific value of the research. A third specification spells out the acceptable risk-benefit-ratio of single interventions and procedures -- if it is not possible or feasible to obtain the informed consent of trial participants. In this context, interventions or procedures without the potential of benefit should not exceed a minimal risk. However, exceptions of a minor increase over minimal risk are possible, provided some additional conditions are met (permission of a research ethics committee, no alternative to the research, and compelling social and scientific value).

In the second step of the CIOMS risk-benefit assessment, the aggregated risks of the entire study must be balanced against its potential individual benefit and social value. Guideline 4 adds that risks to groups and populations must be taken into account, and that the risk-benefit ratio of a study must be discussed with the community involved. The guideline does not use the concept of "burden" which is common in other guidelines including the Declaration of Helsinki. The commentary on this guideline explains that the concept of risk encompasses the concepts of discomfort, inconvenience or burdens as "harms of a very small magnitude that are almost certain to occur".

Timely and indispensable guidelines

In sum, the CIOMS guidelines address key issues in the contemporary development of health-related research. They lay down a solid foundation for health-related research in its social and scientific value. They highlight the importance of including community perspectives and vulnerable individuals and groups. They formulate adequate requirements for research with tissue and health data in biobanks and registers. Some conflicts in research ethics, as in ethics in general, are unresolved and will probably remain so. The disagreement regarding the conditions for placebo controls thus is not settled, as with the problem of adequate requirements of justice for research in resource-poor settings.

The general problem is to strike a balance between the protection of individual research participants and the medical needs of future patients. Agreements on where to draw the line are difficult and sometimes even impossible. However, for example, exclusion of vulnerable individuals and groups from research is not an adequate solution either; it simply means that the health needs of these groups remain unmet. The achievement of the CIOMS guidelines lies in an exemplary and reasonable balance between protection of participants and promotion of research. This balance is subject to constant change, and needs to be continuously evaluated in the light of changes in practice and new empirical evidence. New developments may show that some aspects of a particular regulation are hard to put into practice, or that new trends may escape regulation. Therefore, guidelines must be continuously and critically reflected upon and discussed in a transparent way. Discussion must be based on a thorough knowledge of current trends in health-related research, and the ethical literature identifying possible problems of these trends. We believe that this has been done in the current revision of the CIOMS guidelines; it has been done in a way which represents the best practice in the field. This practice should also be followed in the future.

Note

[1] *The authors of this article represented the WMA in the meetings of the CIOMS working group, and were involved as a member (Urban Wiesing) and an advisor (Hans-Joerg Ehni) of the working group established by the WMA for the last revision of the Declaration of Helsinki, Fortaleza, 2013.*

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