REVIEW ARTICLE

Council for International Organizations of Medical Sciences (CIOMS) Ethical Guidelines: advancements and unsolved topics in 2016 upgrade

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Abstract

In 2016, the new edition of the Council for International Organizations of Medical Sciences (CIOMS) Ethical Guidelines was released. These guidelines are universally acknowledged as the ethical standard in biomedical research. In this article we critically appraised the potentialities and weaknesses of this revised version. The issues we considered were most successfully addressed were: the relevance assigned to the social value of research and its effects on decision-making, and creation of public policies; research development in low resource settings; community involvement in research; determination of participants' vulnerability, and proceedings related to informed consent. Although the new version is properly adapted to scientific, technological and social changes, and represents a useful tool for researchers and ethics committee members as well, some topics remain unsolved; these include management of more than minimal risk, conflicts of interest, and research in low-income settings. Nevertheless, the update represents progress, especially regarding the context and needs of populations under investigation, and community involvement in different phases of research, which would allow direct access to potential benefits. The impact of the CIOMS Ethical Guidelines 2016 should be assessed over time, particularly in scenarios of social-sanitary inequities and in the context of commercial interests of industry in biomedical research.

Introduction

The International Ethical Guidelines for Health-Related Research Involving Humans of the Council for International Organizations of Medical Sciences (CIOMS)[1], an ethical reference standard universally used in biomedical research, has been recently revised and released. This new version merges the "Green Book" (The CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, 2002)[2] with the "Blue Book" (The CIOMS International Ethical Guidelines for Epidemiological Studies, 2009)[3]. The 2009 Guidelines were developed as an independent document, and were not complementary to those of 2002, thus several topics were repeated across both documents. As subsequent revisions of one of these documents would necessarily impact the other, it was decided to merge them into one common document[1].

The new guidelines were motivated by the following:

1. The growing importance of translational research
2. The urgent need to clarify what is considered "fair research" in low-resource settings
3. The need to involve communities in the development of health studies
4. The exclusion of potentially vulnerable groups has generated knowledge gaps and a lack of evidence that paradoxically affects them
5. The emergence of large volumes of electronic health records and the increase in big data

This article aims to critically reflect on the 2016 CIOMS guidelines, with respect to the available evidence and informed by the authors' personal experience as investigators and members of research ethics committees. Emphasis is placed on the contributions of this version, and issues that are perceived as unresolved by our team.

Advances in the CIOMS 2016 Guideline

The remarkable advances in the updated guidelines arise from a new scenario in health research. Five main purposes are presented[1,4,5].

1 The social value of research

Investigators and sponsors conducting research involving human subjects must ensure the social value of their protocols. The explicit inclusion of the social value of research in the guideline is an important but yet to be developed initiative[6].

Wertheimer argues that the evaluation of social value can only be objective and executable in publically financed investigations[7].

However, Wendler and Rid argue that social value should be transversally implied in clinical research[8]. Nayak and Shah propose investigators and sponsors to be responsible, in part, for a positive impact on global poverty[9]. From this perspective, it is worth asking what type of health research should be carried out, considering that social value is an aspect that must be considered by researchers and members of research ethics committees when evaluating proposals. The CIOMS guidelines give the same relevance to social value as it does to other ethical requirements (e.g. scientific validity, informed consent, fair selection of subjects), providing guidance about considering social value when evaluating risk-benefit of research that does not directly benefit participants.

Although a "minimum threshold of social value" has not been established, investigators and sponsors should consider four aspects:

1. The knowledge / information that is sought
2. The capacity of the study to respond to significant health challenges of the population under investigation
3. The contribution of the study in the creation / evaluation of interventions, public policies or practices that promote individual and / or public health
4. The disclosure of results

Regarding the capacity of the study to respond to significant health problems of the population in which it will be carried out, and its contribution in the creation / evaluation of interventions, public policies or clinical recommendations, it may not always be possible to count on a government document or guideline, nor an agenda, identifying problems that deserve attention. Therefore, it is important to emphasize that although the definition and establishment of priorities should inform health research strategy in each country[10], not all health priorities will necessarily be translated into health research priorities. It is possible that from the definition of health priorities debate may arise concerning the link between health and research[10]. It must also be considered that some health conditions might be excluded from the priority agenda, e.g. orphan diseases[11].

With respect to research aims, differences become apparent between the interests of researchers and those who determine the health research agenda. The first difference lies in topics that should be addressed: researchers select topics within the scope of their experience and skills, not necessarily those recognized as priorities by society. This creates a gap between topics that are "interesting" and those that are "relevant". Another discrepancy lies in the selection of projects of shorter duration by those in charge of the research agenda. Some reasons may include feasibility for implementation at a financial and political level, and the desire for the rapid application of results to benefit the population.

It is important to consider that researchers generally seek to publish their studies in recognized scientific journals, which in most cases are aimed at communities of scientists and not policy makers[12]. Two types of health research can be differentiated: health services research and applied health benefits research. The former tends to respond to academic interests and not research policy, while the latter usually addresses research agendas, but may lead to guidelines elaborated by private organizations, companies or institutions whose interests might not be explicit[12].

2. Limited resource scenarios

The new guidelines highlight four fundamental concepts, the first two from the 2002 guidelines and the latter two introduced in the current version:

1. Research conducted in a population should respond to its specific needs
2. Every effort should be made to guarantee the availability of the intervention or product that was studied in that community
3. Limited resource scenarios are not confined to low-income countries, but can occur in all nations
4. Local research capacity should be established and investments made in the local health infrastructure in order to equitably distribute the costs and benefits of research[1].

Macro- and microanalysis should be conducted, both of the vulnerability and risk of exploitation of the population, and of the vulnerability and exploitation that might be caused by the conduction of the study.

3. Community participation in research

The community participation during the early stages of research development has had positive reports. The guidelines recommend achieving the commitment to the community through "negotiation," developing a collaborative partnership to generate research capacity. Is negotiation the best model for generating collaborative partnerships? It is worth considering whether negotiation as a process can give moral validity to what is "agreed," especially with regard to the fairness of norms that are established and expected compliance by both researchers and the community, each being co-responsible[13]. This is especially relevant when it is not possible to ensure that stakeholders are recognized, nor elect delegates or gatekeepers with adequate training and experience in representing and protecting the interests of the population. What occurs in communities where there is insufficient institutionalism to ensure that negotiation is conducted properly?[14]. One option is to apply criteria proposed in discourse ethics with adaptation to the socio-cultural and political context, contemplating dialogue as a means to reach an agreement with community members as valid partners[15].

4. Determining the vulnerability of individuals or populations

The 2016 guidelines introduce a useful new approach compared to the 2002 version of CIOMS, that use to classify the vulnerable groups and possible risks to populations depending on study type. The new concept is that determination of vulnerability is dynamic, considering a given context rather than an a priori static categorization of the subject or groups according to intrinsic characteristics. This idea of vulnerability goes hand in hand with that proposed by Luna and Vanderpoel[16], presented as a flexible concept that includes multiple social, economic, and educational variables, together with the research context, in addition to the intrinsic characteristics of the participant (e.g. cognitive state). This new approach places individual differences at the center and dynamism in the conception of vulnerability, in which any individual could be vulnerable, or not, depending on the context; this eliminates fixed labeling of specific groups of people. The evaluation of vulnerability becomes more demanding and challenges members of research ethics committees and researchers to recognize and mitigate this condition at the individual level in "real participants."

5. Update and regulation of the consent process, including broad consent, exemptions and opt-out procedures

Individuals capable of giving consent should grant or deny it when invited to any investigation involving human beings, while researchers should provide all information prior to this process (Guide 9)[1], unless a research ethics committee has approved a modification or an exemption to consent (Guide 10)[1]. These modifications or consent waivers require justification and committees should seek to preserve the consent process as much as possible. The CIOMS guidelines do not apply rigid recommendations in this regard, but rather believe that researchers and committees should carefully analyze whether any modification of the process will preserve participants' understanding of the purposes of the study, and informed decision to participate.

Research ethics committees may approve modifications or exemptions of informed consent in three cases:

1. When an investigation cannot be performed without the exemption (e.g. samples or data from deceased patients
2. When it has an important social value
3. When the investigation does not pose more than a minimum risk for participants

The guidelines set forth in Guideline 12 regarding the collection, storage and use of information in health research consider the use of a broad informed consent for the donation of biological waste samples with the objective of being used in research (biobanks), providing optional exclusion (opt-out). This is a measure that makes it easier to obtain and use biological samples for research, where risks are associated with the characteristics of the donor population, the type of sample, the procedures / techniques that will be carried out on the sample, the information that is sought and its management. The informed consent model will depend on the assessment of these aspects and their potential risks. It should be noted that none of the models exempt informing the donor. The opt-out model is probably the most complex to be evaluated by the members of a committee, as there is not necessarily proof that it was applied. An "opt-out plus" model[17], where the patient receives information actively, can be used as an intermediate model.

Governance of a biobank will directly affect the informed consent process and the evaluation of the risk / benefit balance, which makes it the responsibility of the committees to request sufficient background information from researchers with respect to obtaining and managing samples.

Unresolved aspects in the new CIOMS 2016 guidelines

1. Conflicts of interest

Compared to the previous CIOMS guidelines, the inclusion of Guideline 24 on public responsibility of research represents an improvement, demanding that all results should be published, whether positive, negative or inconclusive. Guideline 25 is devoted to conflicts of interest and establishes that researchers, institutions and research ethics committees must identify and mitigate conflicts of interest. Both recommendations are weak attempts to achieve transparency and integrity, considering the large body of evidence surrounding the distortion that conflicts of interest produce in clinical decisions, with consequences to patients[18-21]. In the absence of explicit recommendations, the problem requires concrete and satisfactory initiatives. Although good practices in health should be based on the best available evidence, pharmaceutical companies generate most of the evidence used for clinical decisions, investigating molecules they design that are later destined to be used by health professionals in the same human beings who participated voluntarily in clinical trials. Results are published in scientific journals that receive payment from companies for pre-prints used to promote the use of the same products[18,19]. Results from research produced by the industry are four times more likely to favor the intervention drug[19] and are almost always reported as superior or equal in efficacy and toxicity in relation to the comparator drug[20]. On the other hand, 50% of the trials financed by industry are unpublished[21], primarily due to a lack of reporting of data with negative implications for the manufacturer[22,23]. Furthermore, favorable results tend to be published more than once[24]. Considering that the ethics of the dissemination of knowledge becomes as important as its generation[25], the new CIOMS guidelines regrettably does not account satisfactorily for this problem. It would therefore be necessary to establish firm recommendations regarding the ethical obligation of researchers funded by the industry to publish unfavorable results[22,26,27].

Guideline 25, dedicated to conflicts of interest, lacks mention of the ethical obligation to declare benefits received by investigators (gifts, events, registration to courses and conferences, paid conferences, etc.). In the period since the previous CIOMS guidelines great advances have been made in patient protection, such as the Sunshine act in the United States[28,27]. The new CIOMS guidelines do not mention the importance of this type of disclosures in the context of health research. These types of payment, an issue insufficiently addressed in many countries, in addition to significantly raising cost for patients[29], generate potential biases that are difficult to avoid on the part of research ethics committees or study participants[25].

Limited resource settings

In Guideline 2, concerning research conducted in limited resource settings, a striking example is presented of a community in which a phase I study for an Ebola vaccine is undertaken. This community had not experienced an outbreak, and the example is presented as an example of solidarity with the community. Is solidarity an ethical value that justifies research practice? If we take into account that what gives solidarity a moral value is the characteristic of universality (i.e. engaging all to contribute in the development for the less fortunate)[30], the scenario can be read as a double standard as the burden of research continues to be assigned to less fortunate groups. From a technical point of view, it is not a requirement that participants in phase I studies come from a socioeconomic and developmental context similar to the population in which the results will be applied[31].

2. More than minimum risk

Another situation that was not been fully resolved and that has been exposed in the literature[32,33], is the lack of clarity regarding the meaning and scope of "more than minimum risk," especially in the use of placebo as control (Guideline 5), participation of individuals unable to provide consent (Guideline 16) and research involving children, adolescents, pregnant and lactating women (Guidelines 17, 18, and 19 respectively). Ethical-scientific committees are indicated as responsible for estimating this risk, and no resources are provided for performing this task.

Final considerations

The update of international reference standards such as the CIOMS guidelines for biomedical research is not only necessary to adapt to rapid scientific, technological and social advances in this area, but also to adapt the efforts of researchers and members of research ethics committees in their responsibility of safeguarding the health, rights and welfare of the participants under investigation.

There will likely be diverse articles dedicated to the analysis of the new CIOMS guidelines, however, it must be understood that it is difficult for a set of guidelines to respond to all challenges that arise in the planning, evaluation, execution and dissemination of research. Researchers and experts in research ethics should be constantly attentive to address and deliberate on these issues. The guidelines make a positive contribution with respect to the context and needs of the population in which research is to be carried out, opening the possibility of community participation in different phases of the investigation and access to the potential benefits. This represents a challenge that should be observed and assessed over time, especially in scenarios of social and health inequalities and commercial interests.

Notes

From the editor

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The authors have completed the ICMJE Conflict of Interest disclosure form, and state that they have not received funding for the report; have no financial relationships with organizations that may have an interest in the published article in the last three years; and have no other relationships or activities that could influence the published article. Forms can be requested by contacting the responsible author or the editorial management of the *Journal.*

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