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Critical analysis of the Council for International Organizations of Medical Sciences 2016 International Guidelines for health-related research involving humans

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Abstract

This paper presents a preliminary discussion of the Council for International Organizations of Medical Sciences (CIOMS), recently issued "International Ethical Guidelines for Health-related Research Involving Humans" (2016) that acknowledges the document's declared concern of the protection of human subjects and awareness of their needs and interests in "low-resource settings". Nevertheless, guideline recommendations present exceptional situations –vulnerability, mental incompetence- wherein voluntary and consented participation may be reduced or omitted under three concurrent conditions: compelling scientific value, the need to include persons that will not benefit directly from participation, exposure to minimal or slight risks.

Introduction

The Council for International Organizations of Medical Sciences (CIOMS) was created in 1949 under leadership of the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO), as a non-governmental, non-profit organism. In 2002, CIOMS issued its "International Ethical Guidelines for Biomedical Research Involving Human Subjects" [1].

After many years of study and deliberations, as well as widespread public consultation, a revised digital version of the guidelines was presented on December 6, 2016 [2]. The present paper intends a preliminary and succinct analysis of that document, with the aim of detecting whether this considerable effort helps the adequate resolution of some controversial aspects of research bioethics with human beings. Such an analysis is relevant and timely, in view that various Latin American countries are actively revising their laws concerning such matters, including Chile where unsolved discrepancies appear in Law 20584 on "Rights and Duties of patients", and Law 20850 on "Financial Protection for high-cost diagnoses and treatments" also known as the Ricarte Soto Law (2015), both laws addressing and regulating diverse aspects related to biomedical research involving human beings.

Formal aspects

The majority of participants in the elaboration of Guidelines CIOMS 2016, are members of nations with high level of development, placed as high-income economies according to the World Bank's classification also used in the CIOMS document, a point to be considered in view of the frequent mention of research in low-resource settings. The meticulous and comprehensive text merits attention to four controversial aspects: the distinction between therapeutic and non-therapeutic studies, debate over post-research benefits, the inclusion of vulnerable persons and

populations, and the also debated but unresolved issue of conflicts of interests in biomedical investigations.

The therapeutic/non-therapeutic distinction
Only the early versions of the Declaration of Helsinki made the explicit distinction between therapeutic clinical investigations that study issues directly related to the diseases of patients recruited as research subjects, and non-therapeutic studies that include patients in biomedical research that are unrelated to the medical needs of the individuals investigated [3]. Pioneers in bioethics have emphatically stated that research on harmed individuals is ethically impermissible, unless their medical problems are directly focused [4],[5] The perspective of risk insists on the need to respect the different ethical standards between therapeutic and non-therapeutic studies [6]. Other authors, like Robert Levine [7], consider that the distinction is irrelevant and should be dismissed [8]. It has been postulated that the distinction should also be eroded in research involving children and individuals unable to give informed consent, thus paving the way for research on persons who are incompetent and put at risk without the expectations of medical benefits [9].

CIOMS 2016 avoids directly addressing the distinction, but it does allude in some of its guidelines to research interventions or procedures that do not offer participants any potential benefits to subjects, thus admitting that their inclusion in clinical studies may be justified under special conditions that preclude or limit the feasibility of obtaining informed consent (Guideline 4), thus authorizing a modification or even the avoidance of informed consent (Guideline 10), supporting non therapeutic studies in incompetent adults (Guideline 16) as well as in children and adolescents (Guideline 17). In all these situations, presented as special, individuals may be included without consent or with a modified form of it, provided the convergence of the same three conditions that have been argued to justify the use of placebos and sham surgeries in control groups:

- The study has compelling scientific [and/or social] value.
- No other research method can replace the inclusion of participants that will accrue no personal benefit.
- The research has no more than minimal or minor increase of minimal risks.

These three arguments, previously employed in the Declaration of Helsinki, are fallible by being discretional. Scientific value is endogamous and self-referring, without being subject to external evaluation [10]. The more compelling an investigation, the more unlikely that it will have only minor or slightly increased minimal risks; furthermore, the definition of minimal risks is also discretional. A true sliding slope obtains if these criteria justify non- therapeutic research involving incompetent human beings. The previously mentioned tension between research ethics and protection of research subjects is thus increased.

Post-trial benefits
The polemics about post research benefits has not been clarified beyond formulations that are conditional and non-committal, presented as "reasonable" but with no guarantees for the protection of probands. Similarly undetermined as the amendments of the Declaration of Helsinki, CIOMS' Guideline 2 suggests deploying "every effort, in cooperation with government and other relevant stakeholders, to make available as soon as possible any intervention or product developed, and knowledge generated, for the population or community in which the research is carried out, and to assist in building local research capacity".

Guideline 6 "Caring for participants' health needs" remarks that "supporters and investigators should at least", among other considerations, "provide continuous access to studied interventions that have proven significantly beneficial"; this "access could be arranged by an extension study or by compassionate use".

Resorting to compassionate use is erroneous, for its definition is "to be employed in individual patients not included in a clinical study of drugs under investigation" [11]. The procedure of continuing therapeutic measures in experimental therapies, also known as oncologic studies Phase 1 is an ethical must that cannot be circumstantial or discretional and thus deny protection to critically diseased persons [12].

Research with vulnerable persons and groups
CIOMS insists on presenting as "vulnerable" all those who are damaged and already suffer damage or detriment, causing them to be fragile and susceptible to further harm and risks. The document also reaffirms that the vulnerable suffer from diminished decisional capability, thus justifying their inclusion in research without informed consent due to incompetence (Guidelines 15 & 16).

Conflicts of interests
According to Guideline 25, conflicts of interests may occur "between the primary goal of health-related research and secondary interests". The definition is similar to the one presented by the Institute of Medicine [13], without specifying the nature of a primary objective of biomedical or health related research, that may well be spurious and often explores a drug intended to occupy a market niche – me too drugs-, or aimed at extending patent rights, rather than being studied to fill a therapeutic void. The primary cognitive interest is thus distorted, allowing secondary interests to taint and harm the central objective of gaining medical knowledge: probands become means, not ends.

Agreeing that conflicts of interests are undesirable and potentially harmful, the CIOMS Guideline suggests two approaches: mitigate the conflict, and resort to open declaration. Both propositions are weak, for they do not eliminate or dissuade conflicts of interests from affecting the requirements of scientific investigation purified from ethical distortions due to personal, corporative or market interests.

Comments on Guideline 19: Pregnant and breast-feeding women as research participants

Towards the end of a lengthy comment, the penultimate paragraph, sub-titled "Severe damages and access to abortion", states:

[cases] in which there is a realistic basis for concern that significant fetal abnormality may occur as a consequence of participation in research… projects can be conducted only if a local research ethics committee determines that the research has compelling social value for pregnant women and the women are informed about existing restrictions on abortion and possible options for obtaining an abortion in another country.

It is hard to imagine that nations with restrictive abortion laws would accept the suggestion of an eventual illegal abortion in a foreign country. Considering the risk of experimentally provoking a malformed fetus in a woman that is legally prohibited from aborting, the comment of Guideline 19 cannot legitimately suggest an abortion in another country. When the risk of a "significant" fetal malformation exists the study should not include the participation of pregnant women.

Discussion

Comment of the "preface"

The Guideline stresses the widening of its perspective when preferring the concept of "health-related research" in order to include other disciplines beyond the biomedical ones: "The Working Group also acknowledged that there is no clear distinction between the ethics of social science research, behavioral studies, public health surveillance and the ethics of other research activities". It is to be commended that the document explicitly includes in its list of studies with human beings such "classical activities as observational research, clinical studies, biobanks and epidemiological research". Nonetheless, it would be convenient to critically analyze such issues that, if related to healthcare, might lead to medicalization of behaviors or trivial biological variations, such as attentional deficit and hyperactivity in adults, baldness, andropause, or the unsettled discussion of homosexuality as a life option [14].

President and secretary of the Working Group that elaborated the document published the reasons and challenges that justified the revision of CIOMS 2002 [15], including:

1. Acceptability of an investigation should consider its social and scientific value. Social value enhances "the public good by generating high quality knowledge, socially relevant, without compromising the rights, welfare and moral status of those making this progress possible" [16]. This definition contains tautological elements and should be used with caution so as to avoid a placeholder that unfoundedly proclaims an investigation's contribution to the common weal.
2. Proclaiming social value is unconvincing when it fails to specify social value for those hosting investigations [17]. When explicitly denying direct benefits to individuals being recruited for a study, these studies disavow having any local social relevance. Local needs are neglected in the increased tendency to off-shoring and transferring research protocols planned and sponsored in highly influential centres, to be carried out in host countries where they lack relevance [18]. Neglected diseases and the persistent of 90:10 strategies that dedicate resources to research problems of the affluent showing no concern for local issues of receptive communities, are examples of indifference to the need of the local venues that host these studies for the benefit of foreign corporative interests.

   Consider the equity of research benefits for scenarios and situations of scarce resources and unequal access to healthcare and medical services. In this scenario, there is evidence that investigations carried out in Latin American nations and leading to the registration of new pharmaceutical products, have had difficulties in providing accessibility and availability to nations where they had been successfully researched [19].
3. Involvement of communities in all stages of the research program, from its inception to its implementation. The spirit of this proposal is impeccable, but its ethical value depends on being practical and, therefore, practiced. Initial obstacles emerge when defining and circumscribing a community, and identifying its legitimate representatives. The mantle of a "fair benefits approach" masks the pursuance of a number of interests that entail exploitation and the concentration of benefits by high-income countries to the detriment of communities with limited resources [20].
4. Protect the inclusion of potentially vulnerable groups, stressing the importance of considering vulnerable individuals rather than groups, in order to avoid the exclusion of certain cohorts and the risk of neglecting variations of individual members of a group. The grammatically incorrect and conceptually erroneous use of "vulnerable" to label individuals mentally unable to consent their participation in studies that have no beneficial purpose for their underprivileged condition, necessarily confirms the confusion to be avoided between the vulnerable –potentially harmed- and the actually injured [21],[22]. Emphasizing particular characteristics of individuals may affect a rigorous inclusion/exclusion selection –internal validity- [23],[24], and uphold discrepancies between what Feinstein called the "fastidious" and the "pragmatics", an issue that CIOMS does not help to clarify.

Conclusion

Revision of the 2002 CIOMS Guidelines has been necessary and timely considering the weakening of the Declaration of Helsinki through its multiple revisions, corrections and addenda that finally led to its dismissal as a non-binding document by the FDA. Sensitive to current unrest, CIOMS acknowledges the importance of social value to be considered in research and takes into consideration its impact on low-income countries. The issue of benefits that ought to accrue to host communities and be continued beyond the termination of the trial is repeatedly mentioned.

The document respectfully acknowledges that "research ethics inherently involves tension between two ethical objectives: 1) promoting socially valuable knowledge aimed at improving medical care and public health and 2) protecting research subjects from exploitation and harm" [25].

Even though the document was offered to public scrutiny during the year that preceded its promulgation, and diversified the fundamental issues of research with human being, CIOMS 2016 nevertheless includes commentaries that dilute and relativize what the Guidelines correctly require, thus tolerating and facilitating a status quo of disparities and inequities infecting biomedical research ethics involving human beings. The document is an improvement on its previous version, but it already has been questioned: "I remain sceptical that small organisations such as CIOMS should try this hard to influence the research ethics policies that countries of the global South give themselves, because it is this that is attempted here" [26]. In this context, it may be feared that CIOMS 2016 will suffer a similar fate as the Declaration of Helsinki: instability, weakness and insufficient protection of communities and individuals recruited for investigations predominantly subject to corporative and market interests. Research ethics committees are more necessary than ever, being urgently called upon to carefully scrutinize and defend the interests of the needy, the harmed, and patients included in healthcare research.

Notes

From the editor

The author originally submitted this article in Spanish and subsequently translated it into English. The *Journal* has not copyedited this version

Conflicts of Interest

The author has completed the ICMJE declaration of conflicts of interest form, and declares not having received funding for writing this report; not having financial relationships with organizations that might have interests in the published article in the past three years; and not having other relationships or activities that could influence the published article. Forms can be requested by contacting the responsible author or the editorial board of the Journal.

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