

CIOMS 2016

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In November 2016, the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization published the fourth revision of its ethical guidelines. The *International Ethical Guidelines for Health-related Research Involving Humans* (1) are the culmination of a four-year process.

In October 2013, a year after the CIOMS revisions commenced, the Declaration of Helsinki (DoH), another influential international ethics guidance, published its seventh revision (2). Since then, three important regulatory regimes have been under revision: the Common Rule of 1991 (applicable in the United States of America), was revised after 25 years and this revision published in January 2017 (CR 2017) (3); the European Union Directive 2001/20/EC (4), or Clinical Trials Directive (EU-CTD) was repealed by the European Parliament and replaced with the Clinical Trial Regulation (536/2014) (EU-CTR) (5) in April 2014, and will be implemented from 2019; and the Good Clinical Practice (GCP) (6) guidelines of the International Conference of Harmonization (ICH) are under revision.

It is important to understand the place of international ethics guidelines in the revised regulatory frameworks. For example, though EU-CTR (Article 80) refers to DoH (the 2008 version, not the most recent version of 2013), it explicitly states that in situations of conflicts between DoH and GCP the latter would take precedence (Article 43). Similarly, CR 2017 has removed references to the DoH in relation to US-funded research in foreign countries on the grounds that "...providing a specific example of an internationally recognized ethical document is concerning because such a document is subject to change independent of Common Rule department or agency policies, and therefore might be modified in ways that create standards that are inconsistent with US laws and regulations." (3: p 7159). And though CR 2017 repeatedly refers to the Belmont Report as an ethical standard for CR departments or agencies, this may be of symbolic rather than practical value, as the Belmont Report is inadequate to respond to emerging ethics issues in a research context characterised by complexities and commodification of research (7).

It is well known that GCP lacks the moral authority enjoyed by the DoH and the CIOMS guidelines stemming from their exclusive focus on substantive ethical reasoning as opposed to GCP's focus on regulatory harmonisation. However, over time GCP has found a firmer place in regulatory frameworks across the world. The growing discord between regulatory frameworks and international ethics guidance regardless of the jurisdiction of these frameworks is cause for concern. This discord is especially troubling when clinical trials are being globalised and shifting to lower and middle income countries (LMIC). Revisions to both ethics guidelines and regulatory frameworks are motivated by the changing landscape of research involving human research participants. But revisions to the former embody concerns for social justice and protection of human rights of research participants. And revisions to the latter are more for procedural and efficiency related matters towards facilitating faster growth of drug trials with less attention to improving the ethics standards and participant protection.

It is against this backdrop that this issue carries a theme section on the fourth revision of CIOMS ethical guidelines (henceforth CIOMS 2016). Three commentaries (Ehni and Wiesing, (8); Schuklenk (9); and Ho (10) on the revisions are followed by a response by Macklin (11), a member of the Working Group constituted for CIOMS revisions, to Schuklenk (9). These commentaries collectively offer insights into select aspects of CIOMS 2016. Ehni and Wiesing (8), advisors to the CIOMS revision Working Group, offer a brief overview of the revision process, the structure of CIOMS 2016, and the key changes from its earlier version. They conclude: "... 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." (11: p 1). Ho (10) discusses the approach CIOMS 2016 has adopted to the concept of vulnerability. He criticises the revisions for confining the provisions on vulnerability to consent and harm reduction, saying that they "...do not go far enough to enable a more holistic visualisation of vulnerability, particularly the implicit social injustices." (13: p 4).

Schuklenk acknowledges that CIOMS 2016 is "...a significant improvement over the guidelines it replaces." (9: p 1) but criticises the procedures adopted for the revision, highlighting that the majority of the CIOMS authoring group hails from the global North while the guidelines are intended to influence policies in the global South. "Procedural fairness" is an important aspect which is increasingly being discussed in the context of developing new international guidance or revising international ethics and

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regulatory guidance. For example, Ravinetto (12) questions the processes adopted for revisions to the International Conference on Harmonization's Good Clinical Practices. Macklin's response (11) to Schuklenk (9) is instructive. However, Schuklenk's (9) critique will resonate with a segment of the global peer community.

Some observations must be made about the processes adopted by CIOMS. As reflected in its preamble, CIOMS 2016 has tried to optimise the opportunity to engage with the peer community, presenting the draft guidelines at conferences or network meets, and seeking inputs; it received 57 responses from organisations and individuals worldwide (1: Appendix 4) and this has given transparency to the revision process. Substantive changes seen throughout the final CIOMS 2016 indicate the Working Group's engagement with these comments.

Does the fact that CIOMS received just 57 responses compared to the 2,100 for CR 2017 concern us as a peer community engaged with bioethics? Does this suggest that international ethics guidelines such as the CIOMS guidelines or the DoH, due to their non-statutory nature, are losing their relevance in a globalised and commercialised research context? Second, the omission of bioethics journals from LMICs for reviewing the literature in bioethics is indeed intriguing. What inference should the peer community, especially from LMICs, draw from this omission? And how ought it to be viewed alongside Schuklenk's critique (9)? In the absence of any specific rationale, this omission seems contrary to the aims of CIOMS 2016, that is, to address research ethics concerning LMICs.

Overall, CIOMS 2016 is an impressive effort to respond to research ethics issues emerging since the last revision in 2002. Two distinctive features are: the merging of CIOMS 2002 (13) guidance for biomedical research and CIOMS 2009 (14) ethics guidance for epidemiological studies; and broadening of its scope from biomedical research to all health-related research. The guidelines (GL) have been increased from 21 to 25 and the materials in the 2002 version have been substantively revised. Below I mention some salient additions and briefly compare some with DoH 2013.

1. CIOMS 2016 explicitly states that research must have both social value and scientific validity to be considered ethical (GL 1). It also states that "social value" cannot legitimise human rights violations, a statement that aligns with DoH 2013 (paragraph 8).
2. The guideline on "community engagement" (GL 7) is a major step forward, and a potential game changer if the peer community takes it seriously. DoH 2013 missed the opportunity on this front. The concepts of "collaboration" and "community engagement" are two central themes running through the CIOMS 2016 document.
3. The ethics in research on disaster and disease outbreaks is acknowledged in a new guideline (GL 20).
4. Guidance is included on research ethics concerning the use of online data and digital tools in health-related research (GL 22);
5. A guideline on publication ethics and data sharing obligations (GL 24) addresses the research ethics obligation for public accountability. One of its recommendations is that all negative and inconclusive findings should be published or made publicly available. DoH 2013 (paragraphs 14, 15) also mentions this obligation for the first time albeit more strongly than CIOMS 2016. The explicit mention, in CIOMS 2016, of disseminating study findings to study communities and the lay public is noteworthy. This is missing in DoH 2013. Data sharing is another obligation elaborated in GL 24, holding funders and sponsors responsible for requiring their grantees to commit to this obligation, and for providing support for this purpose.
6. A dedicated guideline on conflict of interest (GL 25) responds to the increasing commercialisation of research with adverse implications for people's access to safe, effective and rational health interventions.

These additions are timely responses to the changes to the landscape of the research enterprise. Some other important revisions made throughout the guidance document are mentioned below.

1. There are separate guidelines on the collection, storage and use of biological materials and data (GL 11, 12). These were discussed in CIOMS 2002 under individual informed consent (GL 4). The revisions require institutions to have a governance system in place to seek authorisation for future use of biological materials, health and employment records (GL 11) and health related data (GL 12) in research. They enlist items which must be regulated via this governance structure. The provision for 'opt-out consent' if certain conditions are met enables the use of stored samples for research unless explicitly objected to by research participants. Furthermore, the governance structure must have representation from the study communities where the data are collected, and data collection and storage for such purposes must be done in collaboration with local health authorities. It is mandatory for biological material to be transferred under the Material Transfer Agreement (GL 11). GL 11 and 12 together are a major advance from both CIOMS 2002 and DoH 2013, responding to issues resulting from advances in science and opportunities presented. However, how this plays out remains to be seen.
2. The notion of "vulnerability" is now conceived as context-dependent as opposed to labeling any particular group, such as women or children, vulnerable.
3. The revisions explicitly mention obligations for ancillary care (GL 6) and post-trial access (GL 2).
4. The section on "Order of involvement in research" (GL 17) brings a nuanced understanding of inclusion of children and adolescents in research, especially those involving new investigational interventions. For example, it says, "The current

Guidelines do not require that research first be conducted in adults if the research includes interventions that have a prospect for potential individual benefit for children and adolescents.” (p 66). Various qualifiers ensure sufficient protection; for example, studies on the toxicity of new drugs must be conducted in adults before they are conducted amongst children.

CIOMS 2016 widened its scope to include health related research, certainly a welcome move. However, it has not followed through to articulate certain key concepts. This is a missed opportunity given that the next revision is not anytime soon. It states that “... there is no clear distinction between the ethics of social science research, behavioural studies, public health surveillance and the ethics of other research activities.” (1: p ix). The critical point is not whether the ethics of research across these domains is distinct but how ethics issues manifest across these domains and how they can be addressed. The CIOMS 2016 in the present form is predominantly biomedical and epidemiological in spirit and has covered research ethics issues specific to such other research only marginally and in an ad hoc manner. There are a number of essential questions such as when is it obligatory to respond to incidental findings and how; what constitutes ancillary care; and what constitutes risk, and how to capture them in social science and behavioral research in health. Such questions remain unaddressed in CIOMS 2016, or left open to interpretation.

Social science research in health is increasingly integrated into a larger biomedical research initiative. Without clear guidelines, neither researchers nor ethics review committees are capable of understanding the complexities that arise from specific aspects of social science and behavioural research. My own experience is that such research protocols are often of poor quality and get implemented without robust ethics review.

On a related note, generally speaking CIOMS 2016 has expanded the responsibilities of ethics review committees, especially on newer themes such as compensation, ancillary care, and data sharing. However, given the lack of clarity on the ethics of social science research in health, it may be risky to entrust ethics review committees with expanded responsibilities, at least in this domain.

Structurally, CIOMS 2016 maintains its format with each guideline supported by a substantive comment to develop and anchor ethics reasoning in various situations. Making available the bibliography used and the literature reviews undertaken towards the current revisions would be useful as a “ready reference” for the global peer community.

In closing, it is noteworthy that a number of countries draw on international ethics guidance such as CIOMS and DoH despite their known limitations. One reason seems to be the lack of resources to develop guidance documents sensitive to the local context. However, a few ethics codes developed locally by ethnic groups, such as the code developed by the San people of South Africa (15), question the dominance of international guidance.

Conflict of interest: Some members of the Working Group, CIOMS revisions are known to SVSB in various work-related associations.

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