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EDITORIAL

The approval of clinical research by an independent ethics committee – a compulsory requirement and not a matter of the investigator's choosing

For four decades, a requirement for investigators aiming to conduct clinical research that involve human subjects has been to submit their research protocol to an independent ethics committee (EC) for ethical considerations prior to commencing the study participant recruitment. Many believe incorrectly that this requirement is based on a declaration made by the general assembly of the World Medical Association (WMA) assembled in Helsinki in 1964.[1] WMA is the federation of national medical associations and was established in 1947. This organization is analogous to the World Dental Federation- FDI, which is the federation of national dental associations. Declarations made by a majority vote in the general assemblies (GA) of WMA and FDI are not legally binding under any international legislation and regulations. Perhaps this is a reason why some clinical investigators seemingly continue to ignore the requirement for an ethics committee approval prior to conducting clinical research. This issue of Clinical and Experimental Research contains a critical appraisal of all systematic reviews published by the Cochrane collaboration on oral and dental interventions over the last 5 years. Out of the 960 primary studies included in the 95 systematic reviews, as many as three out of ten papers contain no information about any IRB/EC approval.[2]

Legally binding requirement for an independent ethics committee approval appeared in the early seventies in several countries, which includes from 1974 the National Research Act in USA.[3] One of the first publications in the scientific literature on the need for an ethics committee appear in the inaugural issue of the *Journal of Medical Ethics* in April 1975.[4] By then, several health care institutions in USA had for more than 10 years required investigators to seek approval from an Institutional Review Boards (IRB), albeit for various motives.[5] In the first revision of the text, labeled as the *Declaration of Helsinki*, a need for an independent oversight by a research ethics committee was added as article 2 and the revised version was approved by the WMA GA in October 1975.[6] The initiative prompted more countries to embark on legislating the requirement on a national basis. The Council for International Organizations of Medical Sciences (CIOMS) is a non-governmental organization (NGO) that had been established in 1949 by WHO and UNESCO. This body published in 1993 the first version of the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*,[7] which has served as a framework for lawmakers on national and international levels. References to several tasks of an EC/IRB committee are recurrent in the original and subsequent revisions of the document. The European Union established legally binding standards across national borders in 2001 by the introduction of directive *2001/20/EC*[8] that subsequently has been replaced by regulative *EU/No536/2014* introduced in 2014.[9] In parallel, WMA has amended the requirement for, and tasks and qualities of an external IRB/EC in the *Declaration of Helsinki*. Article 23 in the current 7th revision approved by the WMA GA in 2013 are quite explicit regarding details and responsibilities of IRB/EC committees,[10] which is intriguing given the lack of a legal foundation of the organization. Obviously, national regulations takes precedence regarding such details.

Notwithstanding the legal requirement in most countries to require an approval from an IRC/EC, there are also considerations of minimum quality standards for clinical research. Several NGOs identify the need for an external IRB/EC committee approval for clinical research on humans or animals, e.g., the International Organization for Standardization (ISO),[11] the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH),[12] the European Medicines Agency (EMA),[13] and in USA the U.S. Food and Drug Administration (FDA).[14] Stated in other words, clinical research undertaken without prior approval by an IRB/EC can be considered today as substandard clinical research.

It has been argued that it must be the editors of scientific journals that should be responsible for assuring that adherence to ethical standards is being followed. In fact, WMA has declared bluntly in article 36 of the current version that "*Reports of research not in accordance with the principles of this Declaration should not be accepted for publication*"[7]. One may interpret in this context that ethical publishing must be considered as an important element of ethical clinical research. While the latter was the focus the *Declaration of Helsinki* versions two to five, the term "guidelines for ethical reporting" appeared in the 6th version in 2008.[15]

The recommendation by WMA to deny publication is actually stricter than the wording formulated by voluntary medical ethics organizations such as the International Committee of Medical Journal Editors (ICOMS) and the World Association of Medical Editors (WAME). Their respective guidance documents opens for publication even in lack of an IRB/EC, i.e. "*…if no formal ethics committee is available, a statement indicating that the research was conducted*

according to the principles of the Declaration of Helsinki should be included",[16] alternatively stated "*For those investigators who do not have access to formal ethics review committees, the principles outlined in the Declaration of Helsinki should be followed*".[17] There is no guidance as to how an editor should proceed to authenticate any claim of inaccessibility to a formal IRB/EC. The Committee on Publication Ethics (COPE) is somewhat more explicit on the need for an independent ethical approval, citing cases on their website where the lack of approval in a submitted manuscript should raise concerns of proper ethical conduct of clinical studies.[18] It is likely that the discrepancies of opinion amongst the voluntary medical editor organizations for the need for a formal statement in the materials and methods section about ethics committee approval is reflected in instructions to authors, e.g., within the fields of oral-cranio-maxillofacial-facial plastic surgery.[19]

On the other hand, an argument can be made that once an editor has received a manuscript, the unethical clinical research has already been conducted and completed. True, a problem getting their research paper published may be a deterrent for the investigator-author, but it is hardly a comfort for the study participant recruited into an unethical clinical study. Moreover, publishing is today facilitated by a burgeoning predatory publishing industry that welcome anything from anyone without much peer-review scrutiny,[20] and it seems like nobody are able to stop the activity. Perhaps in the future, the main criteria for differentiating between a predatory and a scholarly publication is whether there is a statement in the M&M about an IRB/EC.

For this journal, we hope that the section in the instructions to authors titled "Protection of human subjects and animals in research" is unambiguous.[21] We believe that it is appropriate and in the best interest of all stakeholders that a statement must be included in the Methods section of all submitted manuscript indicating that the protocol and procedures employed were reviewed and approved by the appropriate IRB/EC.

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ENDNOTES

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