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Publication ethics of human studies in the light of the Declaration of Helsinki – a mini-review

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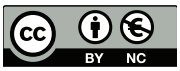

ABSTRACT

The Declaration of Helsinki is a set of ethical principles to be followed by scientists involved in medical research with humans or human cells and tissues. This Declaration defines how scientific research should be planned, conducted, documented, analysed, and published.

We summarise and discuss some ethical issues related to publishing original articles, including clinical trials, review papers, and case reports based on the seventh revision of the Declaration of Helsinki.

The principles of the Declaration of Helsinki refer primarily to the publication of medical research results, in particular clinical trials, as original articles. Such papers are required to meet several ethical requirements, particularly the study protocol transparency and the presentation of the results. In terms of case reports, the bioethical aspects related to their publication are twofold - they need to include informed and voluntary consent and the confidentiality of study participants. The review papers are of the least bioethical concern. However, whether patients' agreements with specific studies are valid if the data are used in meta-analyses is uncertain.

Adherence to ethical policies and standards helps to ensure the highest possible quality of scientific publications. Responsibility for compliance with the Declaration of Helsinki lies not only with the authors preparing their manuscripts, but also with the editorial board and reviewers, who must evaluate the ethical soundness of the submitted papers. The additional guidelines for the different types of studies facilitate the implementation of the Declaration principles.

Introduction

The Declaration of Helsinki is a fundamental document establishing principles for conducting scientific research involving humans [1]. Following the introduction of the Nuremberg Code in 1947, the World Medical Association (WMA) published the first version of the Declaration in 1964. The Nuremberg Code and the Declaration of Helsinki defined the legal principles for conducting medical experiments on humans for the first time.

Since its announcement, the Declaration of Helsinki has been improved and changed seven times. The latest version from 2013 is now in force [1]. In addition to the WMA official languages (English, Spanish, French), this document is also available in other languages, e.g. Polish, German, and Japanese.

The Declaration of Helsinki – seventh revision [2]

The preamble is addressed primarily to physicians. However, it is recommended that its contents be shared with other members of research teams involved in human medical studies. The same applies to research teams with no physicians, such as dieticians, psychologists, physiotherapists, coaches etc.

The 7th version of the Declaration of Helsinki introduces the new term. i.e. "medical research" to reflect all scientific medical studies on human material. Previous versions related the term "research" directly only to medical experiments on humans. It consists of 37 paragraphs describing various ethical issues and regulating conducting medical research.

Medical research involving humans and human biological material (e.g., cells, tissues) should be performed only by individuals with appropriate ethical and scientific education, training and qualifications (paragraph 12). Scientific aims to gain new insights and gather interesting data should not be superior to the rights of study participants by any member of medical research teams (paragraph 8).

Physicians who are researchers have various duties. In particular, they need to protect health and life, well-being and patients' rights, such as dignity, integrity, self-determination, privacy and confidentiality of personal data (paragraphs 4, 9 and 24). Each scientist must assess the study participants' risk, burden, and benefits to minimise the adverse effects of investigated interventions or employed methods. Participants' activities must be precisely and conscientiously monitored (paragraph 17). Each study participant or legal representative of such a person (e.g. unconscious or under-age or mentally disabled) must receive necessary information regarding the study protocol and forms. Informed and voluntary consent must be collected from all participants, or their legal representatives, preferably in writing (paragraphs 25-26). Similarly, in terms of research on human material stored in biobanks for re-use, informed consent from the donor is required (paragraph 32).

The Declaration of Helsinki considers the procedure in exceptional situations, including studies on vulnerable humans, the use of placebo and interventions with unproven efficacy (paragraphs 19, 33 and 37). Following the completion of clinical trials, it describes steps to be followed (paragraph 34).

Particular attention should be paid to the protocols concerning the design and conduct of medical research in light of the applicable bioethical principles. All study protocols must be submitted, reviewed and approved by an independent and competent local or regional bioethics committee (paragraph 23). Medical research involving humans must be designed and conducted strictly according to previous protocols. Developing each study protocol should be preceded by a thorough analysis of the scientific literature concerning specific topics (paragraphs 21-22). In this way, unnecessary repetitive studies concluded by "rediscovering" the already known facts can be avoided. Another crucial issue is the complete and reliable dissemination of research results. Ethical scientists should not select only some positive results which confirm their hypotheses. Publication of research results different from the assumed and anticipated, negative, or demonstrating harmful effects of interventions should be obligatory. The concealment of adverse or ambiguous study outcomes is always deliberate, and selective non-transparency is tantamount to scientific manipulation. Funding sources, institutional links and conflicts of interest must always be disclosed (paragraph 36).

Adherence to ethical policies and standards helps to ensure the highest possible quality of scientific publications. Responsibility for compliance with the Declaration of Helsinki lies not only with the authors preparing their manuscripts, but also with the editorial board and reviewers, who also need to evaluate the ethical soundness of the submitted papers. Scientific reports of original studies, review papers (including systematic reviews), and case reports which have not been prepared in accordance with the principles of the Declaration of Helsinki should not be accepted for publication.

Original articles

The Declaration of Helsinki is most relevant to original articles directly presenting the results of medical research involving humans and human material. Regulations of this Declaration also address clinical trials.

Following the Declaration of Helsinki rules is essential throughout the entire scientific process. Its regulations must be considered during the planning stage while conducting the designed investigation and disseminating the obtained results. Authors are required to report a detailed study protocol (to allow replication of the study by other researchers), with the prior approval of which the appropriate bioethical committee.

Both the details of the research methodology and protocols, as well asthe clarity of the results are important. Authors should present the results completely, not concealing ambiguous results that can undermine the assumed conclusions. The Declaration of Helsinki emphasises the transparency of clinical trials through their obligatory registration – it reduces publication and reporting bias and provides reliable evidence for decision-making [3]. Moreover, the 7th version of the Declaration extensively discusses and pays special attention to the use of placebo, or other interventions with unproven efficacy, assessment of the risks and benefits of the study, compensation for potential harm to study participants, and treatment continuation following the clinical trial completion. The authors should precisely describe all the above aspects [4,5]. It is also necessary to include statements about obtaining informed consent from study participants, conflicts of interest, and research funding sources [6].

The Consolidated Standards of Reporting Trials (CONSORT) statement has been developed to improve the quality of clinical trial reporting. The checklist has been prepared to increase the transparency and completeness of research protocols. In fact, the included items comprise recruitment criteria and flow, type of randomisation and blinding, or sample size justification. These guidelines emphasise the need to discuss the study limitations, considering potential bias sources and the generalisation of the obtained findings for their applicability in clinical practice [7]. Similarly, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and the Standards for Reporting of Diagnostic Accuracy Studies (STARD) statements have been developed for other types of research involving human subjects [8, 9].

Case reports

For the publication of clinical case reports, two bioethical issues are essential in view of the Declaration of Helsinki. Firstly, obtaining informed and voluntary consent, and secondly, securing the confidentiality of research participants.

The patient presented must be fully informed regarding the publication and its content, including the extent of the patient's medical data. Prior to the publication, the patient's consent must be obtained, based on the information provided to him/her previously. In case of underage, unconscious, or mentally disabled patients, this consent must be obtained from their guardian or legal representative. Prior to the manuscript submission, it is also advisable to provide the prepared material to the patient or the caregiver for authorisation. Some journals require written approval from the patient to publish such a paper [10].

Obtaining the authorisation entails the obligation to verify the published medical data (such as photos, imaging studies, etc.) to maintain the privacy of the presented persons. In order to protect the patient's confidentiality, all personal data and data identifying the patient should be removed from the case report. It is vital for people living in small communities where detailed information about their medical or family history may allow their identity to be established [11].

Importantly, both of the mentioned issues are included in the CAse REport (CARE) guidelines checklist (item 5a – "De-identified patient specific information", and item 13 – "Did the patient give informed consent? Please provide if requested") [12]. Case reports should contain all the necessary detailed data, including de-identified patient-specific information, concerns and symptoms, medical and family history, significant clinical examination findings, diagnostic evaluation and administered therapeutic intervention [13]. Transparently written case reports provide sufficient information for clinical research, allow the creation of clinical practice guidelines and improve medical education [14].

Review papers

In contrast to both original and case reports, review papers usually raise minor ethical concerns regarding the Declaration of Helsinki. The preparation of review papers does not require an opinion from the competent bioethics committee. The selection of the cited articles depends solely on the authors of the prepared review. They are responsible for ensuring the reliability and scientific soundness without raising ethical doubts.

In terms of the systematic reviews, their preparation and structure are strictly defined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [15]. Furthermore, authors have more freedom in the manuscript form for the narrative reviews. Systematic reviews may include a qualitative and quantitative analysis of the cited papers. The authors are responsible for formulating the objective, criteria for inclusion and exclusion of the articles, and assessing the risk of bias and evidence level.

The question arises to what extent the aim set by the authors of the meta-analysis should be comparable to the aims of the analysed original studies [16]. Participants are informed about the specific objectives and methods of specific studies, and it is uncertain whether their informed and voluntary consent can be extrapolated to other, not primarily planned, investigations, such as meta-analysis. Moreover, it is disputable if initial consent can and should be implied for future research by other authors.

The latest guidelines for reporting systematic reviews [15] also include the need to register the reviews which are prepared together with their protocols to avoid duplication of projects and increase their transparency. It is in line with the Declaration of Helsinki recommendation on the registration of medical research. Additionally, the authors of review papers are obliged to declare the financial and non-financial support sources for the review, as well ascompeting interests. It is also recommended to discuss the limitations of each review and its implications for clinical practice or further research.

As in the PRISMA guidelines, the criteria for assessing the quality of the included original papers practically do not consider the ethical evaluation of the conducted studies. Instead, they focus on methodological issues, such assample size, homogeneity of the study participants, and appropriate matching of the control group. It is difficult to assess, usually with hindsight, the ethical issues of the previously conducted research for multiple reasons. These include the demographic and ethnic diversity of the study participants and researchers, as well as the variability in time, place, and standards of conduct [16].

Conclusions

When publishing scientific papers on research involving human subjects and human material, the recommendations from the Declaration of Helsinki have to be respected. Responsibility for the compliance with this Declaration lies with the authors preparing the manuscripts, the members of the editorial boards developing the criteria for publication of papers in their journals, and the reviewers assessing the substantive and ethical value of the presented findings. Is is clear that the additional guidelines for the different types of studies facilitate the implementation of the Declaration principles and expand the range of issues covered in the field of research protocols.

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Conflict of interest statement
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