Clinical Evaluation 2024 Vol.52
Preprint Online Publication on Oct 10, 2024

Opinion

Noblesse oblige of the WMA in peril: Saving its honor at the Diamond Anniversary[1]

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Abstract

At the 60th anniversary of the Declaration of Helsinki (DoH), its core principle to prioritize patient interests to scientific goal has been exposed to peril.

Though a critic points out that this principle contradicts the placebo clause, the author asserts that it is the placebo clause that rather must be changed. This is because it also contradicts the CIOMS guidelines which has implemented the DoH to resource-limited settings.

This discrepancy of opinion is attributable from the difference between utilitarianism and deontology. We must note that the majority of the World Medical Association (WMA)'s statements are based on deontology until now.

The critic mentioned above also argues that research regulation issued by regulatory authorities is enough for protecting research participants. However, the WMA is an association regulated by professional autonomy. Thus, their basic principle is not constrained by regulatory authorities.

The WMA should save its honor through procedural justice with ensuring accountability toward this contradiction between placebo clause and core principle.

Key words

Declaration of Helsinki, utilitarianism, deontology, placebo-controlled trial, procedural justice

[1] This article was expanded from the manuscript which was submitted to JAMA as letter to editor, responding the article by Menikoff but rejected. Preprint version was published just before the adoption of the 2024 revision of the Declaration of Helsinki, with the final publication after the adoption.

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1. The Core Principle in peril

1.1 Annoying suggestion to terminate the core principle

A thought-provoking article was published in the Journal of the American Medical Association (JAMA)[1] just before the last one of the series of regional meetings for the revision of the Declaration of Helsinki (DoH) [2] held by the World Medical Association (WMA) and the American Medical Association (AMA), at Washington DC in August 2024. It was written by Jerry Menikoff, the former Director of the United States (US) Office for Human Research Protection (OHRP).

He suggested to terminate the core principle of the DoH to prioritize patients' interests to the goal of research. This crucial principle has been kept long time in its paragraph 8, or in paragraph 7 in the draft revision for the second public consultation. He recommends to replace this core principle of the DoH with the statement of the exact opposite one in celebrating its 60th-year anniversary to adopt the revised version in October 2024.

1.2 Physician's obligation versus scientific goal

His recommendation discredits all the other deontological statements issued by the WMA, including, but not limited to, the Declaration of Geneva[3], which was derived from Hippocratic Oath, the International Code of Medical Ethics[4] (both of them are quoted in the DoH) as well as the Declaration of Lisbon on the Rights of the Patient[5].

We, physicians, with conscientious sense of duty of care, will surely refuse to conduct research if we are mandated by government officials to discard this core principle in return for prioritizing scientific goal.

Such conflict may happen in such a case as the consultation process of clinical trial design among regulatory authorities or sponsor companies and physician-investigators.

1.3 Clear distinction between research and practice

Menikoff argues based on logical distinction between research and clinical practice as described in the Belmont Report[6]. He makes out that the principle leads "therapeutic misconception" which means patients misunderstand as they will receive the best care in research.

His standpoint is the same as some US bioethicists in placebo debates arguing that setting condition of comparative study to be "clinical equipoise" is actually deceptive[7] because the study's true aim is to prove the significant difference of efficacy between comparative arms.

1.4 Utilitarianism versus deontology

The Belmont Report also suggests to ensure maximizing benefit of individual and the society to outweigh the minimized risk of research. The problem would be difference of the level of acceptable

risk between utilitarian justification and deontological obligation[8].

The utilitarian stresses the distinction between research and practice, although both may "*occur together (as in research designed to evaluate a therapy)*" [6]. Thus, they argue that participation in research must be based on willingness to accept the risks specific to research.

The deontologist requires additionally that the risks specific to research should be limited to the extent that they do not undermine the physician's responsibility to provide the best care to the patients, paying special attention to the Belmont Principle to state that "*the risks and benefits affecting the immediate research subject will normally carry special weight*" [6] .

2. Placebo debate

2.1 Acceptable risk in placebo-controlled trials

Menikoff points out the critical discordance in the DoH to be the one between this core principle and placebo clause (paragraph 33). This analysis is apparently correct, but I refute him with pointing out that what must be amended is not the core principle but rather the inappropriate placebo clause.

The DoH allows placebo study when there is proven intervention if there is "no *risk of harm of serious or irreversible harm*". We asserted that this inconsistency must be corrected by means of revision of this threshold to "*minor increase above minimal risk*" in accord with the Guidelines by the Council for International Organizations of Medical Sciences (CIOMS) [8, 9]. CIOMS guidelines were developed for implementing the DoH in resource-limited settings.

However, there is no change in the WMA's proposed revision of the DoH. This generous stance of the DoH to allow high-risk placebo study (to cause e.g., burden, pain of long lasting but not "serious" and not "irreversible") led vehement objection of the DoH from Latin American communities[8].

2.2 Fairness and accountability in procedural justice

During the process for 2024 revision of the DoH, a regional meeting to discuss this topic involving Latin American community was organized by the WMA, in February of 2023. Although dissenting opinions were expressed, they were insincerely dismissed without disclosing any reasons as well as rational arguments why such opinions were dismissed.

For such a topic that has been raising international controversy over the decades, fairness and accountability in due process is extremely important in terms of procedural justice.

2.3 Methodology to preserve duty of care

In order to observe the core principles, physician-investigators are required to set criteria for early termination of study participation of each patient to give rescue treatments by means of "early escape" on the grounds of careful observation about each patient as well as setting criteria for study

termination with reviewing the interim analysis of the Independent Data Monitoring Committees[10].

The core principles of the DoH has encouraged research community to explore methodological development to prove the effectiveness of treatments for serious diseases through the Bayesian statistical analysis and/or the use of real-world data[11][12][13].

3. Professional autonomy in peril

3.1 Do regulations take precedence over professional autonomy?

Menikoff also claims that the principle that physicians must prioritize patients' interest to the goal of research could be removed on the ground that research risks would be controlled by research regulations. Yet, the US laws on human research including research regulations are applicable only to research of medicinal products and others with governmental funding.

His contestation is similar with the administrative decision of the US Food and Drug Administration (FDA) which was criticized when they replaced the DoH with ICH-GCP in its regulation on research outside the US with the results submitted to the US for new drug approval[14].

3.2 Laws for physicians losing autonomy

In fact, clinicians who already lost neither professional autonomy[15]nor effective professionally-led regulations[16] might be acquisitive of maximizing their economic self-interest in exchange for patients' health. Such iniquities of physicians might be discouraged by the righteous legislations including criminal punishments mainly made by non-physicians.

This would be similar to the code of conduct, derived from Nuremberg Code[17], which was first proposed just before the adoption of the first version of the DoH. It was proposed as the result of collaboration with lawyers but rejected by professional society of physicians[18].

4. Diamond anniversary with contradiction

In the countries and/or research areas with effective research regulations, abolishment of its core principles would lead to silent neglect of the DoH. It may be easier to get into the line with written regulations than following one's own clear conscience comparing with the internal and autonomous code of conduct in oneself. Furthermore, the DoH without core principles will obviously loses the power in the jurisdictions which lack sufficient regulations, and eventually its authority will disappear from the scope of physicians.

At the 60 years of the diamond anniversary, noblesse oblige of the WMA is now its in jeopardy. The core principle criticized by Menikoff seems to be defended. However, controversial placebo clause does not seem to be changed, keeping contradiction with the core principle.

Conflict of interest

There is no conflict of interest to be disclosed related to this article. Author is an associate member of the World Medical Association but not directly involved in the revision of the Declaration of Helsinki, except responding to the public consultations.

Acknowledgment

The author appreciates Chieko Kurihara for her advice with the expertise of research ethics.

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