In Defense of the Most Vulnerable Research Participants: Sick Patients and the Need for Additional Principles for Therapeutic Research in the Declaration of Helsinki

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First, I would like to thank Professor Chieko Kurihara for the invitation to share some ideas at this important seminar,

I would like to clarify that I have no conflicts of interest related to this presentation. My views and insights are based solely on my professional experience and research.

I'm grateful for the World Medical Association's transparency. I have had access to their archives and regular meetings and have responded to the open consultations.

I wish to offer a succinct reflection on the history of the Declaration of Helsinki to understand its present and anticipate its future. I'll address two primary themes: (1) the history of the process of its revisions and its consequences; and (2) the need for including additional principles for therapeutic research, where the research participant is the patient—the sick person—which must be differentiated from non-therapeutic research.

The Genesis of the Declaration of Helsinki

In 1953, L.A. Hulst (Netherlands) presented the document *Experiments on Human Beings*, which served as the draft for the *Resolution on Human Experimentation and the Principles for Those in Research and Experimentation* adopted by the WMA a year later in Rome (1954). The principles of this official WMA resolution were less protective of research participants than those of the Nuremberg Code.

In the 1950s there was a surge in double-blind randomized controlled trials and to comply with the Nuremberg Code researchers had to obtain the informed consent from the participants. The use of placebo in the control group was the first major controversy among WMA members.

In 1959, H. Clegg (United Kingdom), the president of the WMA Medical Ethics Committee, led a review of the Rome Resolution and proposed a new Research Ethics Code. The first draft of what would become the Declaration of Helsinki was presented at the XV General Assembly in Rio de Janeiro in 1961 and published in the British Medical Journal, where H. Clegg was editor-in-chief. Years of new drafts and controversies followed. Finally, at the 18th General Assembly in Finland in 1964, the Declaration of Helsinki was adopted and published. Eventually, the document thought to be the *Code of Ethics on Human Experimentation* was adopted as *Recommendations to Guide Research with Human Beings*. Simply put, it went from a strict "Code of Ethics" to more relaxed "Recommendations."

The 1964 DoH was divided into three parts: I. Basic Principles; II. **Clinical Research Combined with Professional Care; and III. Non-Therapeutic Clinical Research.** Unlike the Nuremberg Code, which considered consent to be 'absolutely essential,' the DoH allowed for consent 'whenever possible.' Controversial topics were evident from what was omitted. References to using "captive

groups" (such as prisoners, orphans, institutionalized mental patients, and students) and "control trials" were excluded from the final version adopted in Helsinki, Finland. The British criticized the Americans' influence on the Declaration, noting that an AMA member on the WMA Ethics Committee managed to align the final version with American research needs and legislation. From the start, the U.S. perspective on research ethics prevailed, generally weakening the principles protecting medical research participants.

The Scandinavian Declaration

For eleven years (1964-1975), the Declaration of Helsinki remained unchanged. In September 1974, at the insistence of the Scandinavian Medical Association, the inaugural review of the Declaration of Helsinki began. The Scandinavian draft was discussed with the national associations, WHO and CIBA-Geigy, now Novartis, and it was finalized in 1975 at the 29th General Assembly in Tokyo.

This review process was both the quickest and most expansive and progressive in the history of the Declaration, significantly increasing its length without removing any original content. It introduced the requirement for medical research protocols to be reviewed by an independent, multidisciplinary ethics committee, even **though some members of the WMA were hesitant to address central and organizational questions at that time** (Riis 2007). The process of obtaining informed consent was made more rigorous. Ethical guidelines were established for the publication of results, stipulating that studies not adhering to the Declaration's principles should not be published. The term "best current" was introduced as the standard for diagnosis and treatment in clinical studies.

Criticism of the Scandinavian Declaration followed its adoption (Belsey 1978, Shephard 1976), with the strongest coming from European Medical Research Councils and, of course, the Judicial Council of the American Medical Association. The latter criticized the overemphasis on individual interests, the impractical restrictions on scientific journals, and argued that the singular term "best proven" would hinder comparative studies.

The Scandinavian version of the Declaration of Helsinki (DoH) significantly influenced research ethics involving humans from 1975 to 2000, with only three small changes made during this period. However, the rise of ethical standards led to a decline in adoption by national medical associations. By 1979, only 24 international medical associations had adopted the new version, compared to 33 for the 1964 version. The American Medical Association also disregarded the 1975 DoH.

The Review of the Century

In 1996, during the AIDS epidemic, amidst controversies over the use of placebos in clinical trials, the DoH clarified its stance on placebo-controlled studies. This proposal, allowing placebo use in trials lacking proven diagnostic or therapeutic methods, was approved at the 48th General Assembly in South Africa. At the same time, the WMA's ethics committee received a proposal from the American Medical Association (AMA) for a comprehensive DoH review.

In 1997, the AMA's draft was sent to national medical associations for feedback. Among other changes, the draft proposed abolishing the distinction between therapeutic and non-therapeutic research, facilitating placebo-controlled studies. Debates on ethical double standards emerged, particularly concerning placebo-controlled studies of Zidovudine for HIV in low-income African countries, funded by French and US government organizations.

In 1998, Prof. R. J. Levine from Yale University, led a UNAIDS working group to develop international guidelines for HIV clinical research. At a UNAIDS meeting attended by the WMA President, Levine questioned the validity of the Declaration of Helsinki (DoH) regarding placebo use. Subsequently, the WMA President invited Levine to participate in the DoH revision.

In March 1999, Levine's draft of the DoH, similar to proposals from the American Medical Association, eliminated the distinction between therapeutic and non-therapeutic research. It aligned the control arm to medication with local availability (which could mean comparing the new drug with nothing in poor countries) and accepted placebos if scientifically justified and if they did not result in the participant's disability or death. This draft garnered considerable media scrutiny and disapproval for its double and flexible research ethics standards. Notable criticism came from the American group Public Citizen.

In 1999, the WMA established a new committee with the mandate to complete the review process within one year. The newly formed committee was referred to as "the three wise women" with members from the USA, Canada, and Finland.

These wise women completed the revision in one year, and the 2000 version of the DoH was adopted at the Assembly in Edinburgh, Scotland.

This version maintained the distinction between therapeutic and non-therapeutic research. The use of placebos in the control arm was deemed ethical only when no proven intervention existed. For the first time the guaranteed of access to the best interventions for all patients at the end of a study was included. This new principle became a new controversial issue.

As history shows, the increase in ethical requirements was accompanied by a decrease in adherence.

The Battle of Helsinki

The implementation of the 2000 version of the DoH sparked debates regarding the use of placebos, known as Standard of care debate, and post-trial access.

The FDA chose not to abide by the 2000 DoH. New ethical guidelines were published, such as the US National Bioethics Advisory Commission guidelines for medical research in 2001, and the UK's Nuffield Council on Bioethics guidelines, both supporting comparisons in control arm based on the host country's conditions. Additionally, the CIOMS guidelines were revised in 2002, with points diverging from the 2000 Declaration of Helsinki.

Because of the pressure from these rich and powerful countries, the WMA recognized the need for clarification on paragraphs 29 and 30. The first note of clarification, adopted in 2002, introduced more flexible provisions for using placebos to better conform to the stated guidelines. The second note, from 2004, emphasized the need of post-trial access.

Amidst ongoing disputes, a new committee was formed in 2007 which led an inclusive revision process involving national medical bodies and other stakeholders. Although there was some resistance, especially about the use of placebos, the draft passed and a revised version was adopted in Seoul, South Korea, in 2008.

A significant advancement of the 2008 revision was the mandatory registration of all clinical trials in a public database prior to patient recruitment; but the Big Pharma expressed concerns about the impact of clinical trial registries on patents. However, the issues of post-study access and placebo remained controversial.

While the US FDA abolished adherence to the DoH for research conducted outside the US, Brazil's National Research Ethics Commission began to refer to the 2000 version of the DoH, aiming for stronger guidelines regarding placebo use and post-trial access. This, led to the formation of the Workgroup on Placebo in Clinical Trials.

The Golden Jubilee Review

Finally, the seventh revision of the Declaration of Helsinki was approved on its 50th anniversary at the WMA General Assembly in Fortaleza, Brazil, in October 2013. Institutions from the global

North generally preferred flexible options for post-trial access, while those from the Global South requested a guarantee of drug availability after the trial.

Among some of the changes, a new principle reflecting the matter of compensation to participants who suffered harm for participating in biomedical investigations, was assured. The question of obtaining consent for Biobanks was introduced. The paragraph on post-trial access was completely modified.

The 2013 edition of the Declaration of Helsinki **removed the distinction between therapeutic and non-therapeutic research**. It marked a decrease in protection for these patients' participants, leading to the development of two separate medical ethics: one for medical research (DoH) and another for medical care (Declaration of Geneva - The Physician's Oath).

In therapeutic research, participants are patients requiring treatment for existing medical conditions, necessitating additional ethical considerations, including the obligation to provide ancillary care and continue PTA to demonstrably effective therapeutic agents. Research that produces scientific advances and provides direct therapeutic benefits to participants nonetheless demands careful risk-benefit assessment, access to effective interventions (where they exist), and adherence to strict ethical principles to protect vulnerable individuals (both those on the test and control arms of the study).

The Diamond Anniversary of the Declaration of Helsinki

The WMA will mark the 60th anniversary of the Declaration of Helsinki in 2024 by releasing its eighth amendment. Starting in April 2022, they have been revising the declaration to address current challenges in medical research, highlighted by recent public health crises like COVID-19. The revisions are coordinated by an international working group created by the WMA and led by the American Medical Association, with 13 national associations contributing. The WMA has planned at least seven regional meetings from 2022 to 2024 and two separate three-week periods for public feedback. The increase in regional participation, diversity of attendees, and opportunities for public input are significant improvements.

Considering the latest drafts of the DoH, social value was highlights as goal of medical research. The DoH clearly states that "While the primary purpose of medical research is to generate new knowledge, this goal can never overshadow the rights and interests of individual research participants".

If compliance with the principle of social value is maintained, a tendency toward researching "me too" drugs and conducting studies in resource-poor countries where the resulting treatments often remain inaccessible to the local population will be curtailed.

Also, minor changes to the 2024 DoH terminology include replacing "subjects" with "participants" to honor their rights.

Considering the ongoing revision process, I wish to revisit and emphasize the thoughts and appeals related to the DoH made by a remarkable Latin American personality from Argentina, His Holiness Pope Francis, during his discourse at the Vatican DoH conference. He called for solidarity and universal fraternity while decrying the overemphasis on economic interests above patient welfare. His message highlighted the stark challenges and injustices within clinical research in LMICs, and the global inequities that disadvantage poor nations. Pope Francis emphasized the need for solutions that balance research opportunities with patient welfare, ensuring equitable distribution of risks and benefits. He condemned the instrumentalization of individuals through economic interests and commercial alliances and noted the importance of preventing healthcare and clinical research inequalities. By advocating for placing the sick person at the center of ethics and calling for protection in vulnerable areas of clinical research, Pope Francis set a tone of ethical urgency. He urged concrete solutions to these international injustices, underscoring the need for global justice in

healthcare, especially critical in the aftermath of the pandemic. This call to action emphasized the importance of governance that transcends individual nations to achieve universal solidarity, promoting healthcare ethics and equity.

However, Otmar Kloiber, who's been the WMA Secretary-General since February 2005, criticized attempts to leverage medical research for justice or solidarity in healthcare, arguing that this could compromise research integrity through bias and errors. We disagree.

Final Considerations

The Declaration of Helsinki undoubtedly remains the main international document on ethical principles for medical research involving human participants. For this reason, it is essential to improve the DoH, particularly because it influences national and international legislation, especially in LMICs.

Even though the updates in 2013 and 2024 incorporated more collaborative and encompassing approaches, showing dedication to a range of viewpoints, The Declaration of Helsinki is continuously evolving, yet it remains influenced by intricate power relationships. The WMA faces the challenge of harmonizing diverse and often conflicting perspectives while contending with pressure from influential lobbying groups that don't always adhere to the highest ethical standards.

Some lessons can be learned from the history of the Declaration of Helsinki:

- **Historical lack of consensus** among global associations regarding the DoH is a long-standing issue.
- The goal of revision processes has been **to achieve a minimal ethical consensus**, a lowest common denominator, rather than the highest ethical standard.
- Historically, there has been **limited participation from Global South countries**, a trend that continues when discussions are conducted solely in English rather than in other predominant languages.
- The **American Medical Association has historically influenced the DoH**, often accommodating its interests in research ethics and generally lowering ethical standards.
- It is essential for the WMA to **include doctors without conflicts of interest with pharmaceutical companies** in the revision process and **more female participants**.
- **Challenges in Expanding Participation:** Ongoing challenges include expanding participation of the Global South, including listening to them in the languages of their countries, and involving research participants directly in the revision process.

It is important to advocate for maintaining in the DoH the "social value" criteria in medical research and to condemn the exploitation of the bodies of the poor, especially in Global South countries. Frequently, these communities contribute to pharmaceutical research but lack access to the resulting medical treatments. Finally, the differentiation between therapeutic and non-therapeutic research ethics is essential for ensuring that participants' rights, safety, and well-being are adequately and fairly protected.