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This statement was discussed (by e-mails and two times web meetings on Oct 15 and 19-20 connecting from Helsinki with global participants) and agreed among the authors/signatories and published online in October 18; and was updated in Oct 21 with clarifications reflecting the 2024 Declaration of Helsinki adopted by the World Medical Association in October 19, 2024. Additional signatories are welcome until November 30, which will be updated in publication. Please express your agreement in the form:

https://forms.gle/wHVSKA8Wo7qW7bQZ8

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Helsinki Statement from an Independent Stakeholders' Group to Expand the Impact of the 2024 Revision of the WMA Declaration of Helsinki

We would like to congratulate the World Medical Association (WMA) on the 60th anniversary of the Declaration of Helsinki (DoH) since its first adoption in 1964.

Significant revisions to the 2024 DoH include but are not limited to the items listed below. We urge all those engaged in research involving humans to carefully consider the newly agreed ethical principles, particularly pointed below, in every research and research review settings for the implementation of and adherence to it:

1. Throughout the Declaration, the words "research subjects" are replaced with "research participants".
2. Although the recommendations are directed to physicians, their scope should be also applied to non-physicians, research teams and organizations. (§2*[1])
3. In recognition of "various structural inequalities" in research, considerations on benefits, risks, and burdens must be reinforced. (§6)
4. Meaningful engagement with participants and their communities is fundamental and should be required at all stages of the research. (§6)
5. The principles of the Declaration must also be upheld during public health crises. (§8)
6. The contextual and dynamic nature of vulnerability must be recognized and it is important to emphasise that the exclusion of vulnerable can exacerbate their disparities. Therefore, their inclusion in research aiming at their benefit must be

[1] The numbers with § mean the numbers of paragraphs in the 2024 DoH: https://www.wma.net/policies-post/wma-declaration-of-helsinki/

promoted, with adequate protection. (§19, 20)

7. The functions of research ethics committees have been strengthened. And the committee must be familiar with the local context and involve at least one member of the general public. (§23)
8. The preferences and values of incapable research participants shall be considered during the process of deciding to participate in research. (§28, 29)
9. Data or specimens from research shall be handled in accordance with the "Declaration of Taipei" on Health Databases and Biobanks. (§32)
10. Clinical use of unproven intervention must never be undertaken to circumvent the protection set forth in the DoH, and must be the object of research to evaluate safety and efficacy. (§37)

However, we express our concern that the items below were rejected following discussions during the revision process. We very much hope that these ethical principles will be agreed by relevant stakeholders, their institutions or organizations and jurisdictions, and implemented in research and research review settings, and consequently reflected in future revisions of the DoH:

1. All texts must be written in plain language that is understandable to research participants.
2. The "social value" of research has already been incorporated into policy in several jurisdictions and guidelines. Although it was included in the first public consultation version, it was deleted in the approved 2024 DoH. It goes together with the notion that the purpose of research "*never takes precedence over the rights and interests of individual participants"*. Thus, social value must be reinforced in order to implement relevant research and also to ensure that benefits are shared through co-creation with community.
3. The use of placebo in clinical trials can only be acceptable when there is no proven effective and safe comparator. This was stated in the 2000 DoH[2], in accordance with DoH's fundamental principle that the purpose of research "*never takes precedence over the rights and interests of individual participants*". Some of the signers are in favour of the CIOMS 2016 language: that is, placebo "*in exceptional circumstances could be used even when there is an active comparator if delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of effective mitigation procedures*". However, since the 2008 DoH the accepted level of risk to the participant is even much higher than CIOMS' and this

[2] 2000 DoH (Rescind, archived version): https://www.wma.net/wp-content/uploads/2018/07/DoH-Oct2000.pdf

was kept in 2024[3] .

4. At the end of the trial, research participants who still need interventions that have been shown to be safe and effective must have access to them ensured by the sponsor(s). The 2024 DoH is a lot weaker than the 2000 in relation to participant right. This is because instead of ensuring access it just says “it must be arranged” (§ 34). In addition, to tackle health disparities, scientific sound, and ethical strategies are needed to ensure access in public health system in the host community, and most importantly, for all in need globally.
5. The timely dissemination of research results and technology transfer of the products of research involving humans must be recognised as public goods, so that transparency is ensured and everyone can have fair and equitable access to the research results and benefits.

In closing:

The 2000 DoH presented the highest protection to research participants in terms of placebo use and post-trial access. As the DoH has long been a driving force and respected document for ethics in human research, WMA should aim for the ideal of the highest ethical standards being applied.
We will collaborate to strengthen research ethics principles with the equal participation of all relevant stakeholders, including civil society, and in relation to the 2024 DoH, we present the current proposal aimed at maximizing the ethical impact of the DoH on research practice, research review process and in the protection of participants globally.

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[3] 2024 DoH in §33, placebo can be used, even if there is proven intervention, when the participant “*will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention*”.

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List of References

1) Kurihara C, Greco D, Dhai A, Matsuyama K, Baroutsou V. Vulnerability, social value and the equitable sharing of benefits from research: beyond the placebo and access debates. *Front. Med.* 2024; 11:1432267. doi: 10.3389/fmed.2024.1432267 https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2024.1432267/full
2) Kurihara C, Kerpel-Fronius S, Becker S, Chan A, Nagaty Y, Naseem S, Schenk J, Matsuyama K, Baroutsou V. Declaration of Helsinki: ethical norm in pursuit of common global goals. *Front Med* (Lausanne). 2024 Apr 2;11:1360653. doi: 10.3389/fmed.2024.1360653. https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2024.1360653/full
3) Kurihara C, Greco D, Dhai A., editors. *Ethical innovation for global health: pandemic, democracy and ethics in research*: Springer; 2023. https://link.springer.com/book/10.1007/978-981-99-6163-4
4) Kurihara C, Baroutsou V, Becker S, Brun J, Franke-Bray B, Carlesi R, Chan A, Collia LF, Kleist P, Laranjeira LF, Matsuyama K, Naseem S, Schenk J, Silva H and Kerpel-Fronius S. Linking the Declarations of Helsinki and of Taipei: Critical Challenges of Future- Oriented Research Ethics. *Front. Pharmacol*. 2020. 11: 579714. doi: 10.3389/fphar.2020.579714
5) Clinical Evaluation. Vol. 52 Preprint Online Publication on Oct 10, 2024. Special Issue: The 60th-year Anniversary of the WMA Declaration of Helsinki http://cont.o.oo7.jp/52pop/52pop_contents_e.html
   - The 2024 Declaration of Helsinki: Taking Forward Bioethics and Human Rights. http://cont.o.oo7.jp/sympo/eigh.html
   - Interview with Dr. Peter Lurie on the ethical controversies of placebo-controlled trials. http://cont.o.oo7.jp/52pop/Preprint_Interview_Lurie.pdf
6) Kurihara C, Saito Y, Kai H, et al. Patient Public Declaration of Research Ethics (1st edition): Research ethics of the people, by the people, for the people – Expanding the impact of the 2024 revision of the Declaration of Helsinki. *Clinical Evaluation.* 2024; 52. Preprint Online Publication on Oct 10, 2024. http://cont.o.oo7.jp/52pop/Preprint_Patient%20Public%20Declaration.pdf
7) Saio T. Noblesse oblige of the WMA in peril: Saving its honor at the Diamond Anniversary. *Clinical Evaluation*. 2024; 52. Preprint Online Publication on Oct 10, 2024. http://cont.o.oo7.jp/52pop/Preprint_Noblis%20Oblige.pdf

8) Clinical Evaluation. Patient and public perspectives on the WMA Declaration of Helsinki http://cont.o.oo7.jp/grareco.html
9) COVID-19 and bioethics Part 3: Pandemic and research ethics – Democracy, placebo and post-trial access. *Clinical Evaluation*. Vol.49, Suppl XXXVIII 2021 http://cont.o.oo7.jp/49sup38/49sup38contents_e.html
10) Council for International Organizations of Medical Sciences. International ethical guidelines for health-related research involving humans. 2016. https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans/

(Added after the announcement of this Statement)

11) Sindicato Médico del Uruguay. SMU propone cambios en la Declaración de Helsinki. miércoles 16 de octubre de 2024. https://www.smu.org.uy/el-smu-en-la-asamblea-de-la-asociacion-medica-mundial-propone-cambios-en-la-declaracion-de-helsinki/
12) CONFEMEL. Intervención de la Dra. Zaida Arteta en la Asamblea General de la AMM. 16 octubre, 2024. https://www.confemel.com/intervencion-de-la-dra-zaida-arteta-en-la-asamblea-general-de-la-amm/
13) Sindicato Médico del Uruguay. World Medical Association Submission of a Motion to Amend (on Paragraph 33, submitted to) 227th Council Session and General Assembly, Helsinki 2024, October 2024. 8/10/2024.
14) Sindicato Médico del Uruguay. World Medical Association Submission of a Motion to Amend (on Paragraph 34, submitted to) 227th Council Session and General Assembly, Helsinki 2024, October 2024. 10/10/2024.
15) World Medical Association. Proposed revision of WMA Declaration of Helsinki. MEC 227/DoH/Oct2024.
16) World Medical Association. Revised Declaration of Helsinki adopted by the global medical community, strengthening ethical standards in clinical research involving humans. 21st October 2024. https://www.wma.net/news-post/revised-declaration-of-helsinki-adopted-by-the-global-medical-community-strengthening-ethical-standards-in-clinical-research-involving-humans/
(Adopted 2024 DoH, related papers published from JAMA, and other information are available.)