The Declaration of Helsinki

Proposed Revisions 2024

WMA General Assembly
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WORLD MEDICAL ASSOCIATION

The Declaration of Helsinki

The **First** Set of International Principles Guiding Medical Research involving Human Participants

…and A Prominent Pillar in the WMA's Seminal Ethical Documents

- Declaration of Geneva (1948)
  - Pledge outlining basic ethical principles for physicians
- The International Code of Medical Ethics (ICoME) (1948)
  - Ethical principles defining professional duties of physicians
- Declaration of Helsinki (DOH) (1964, 60 years ago)
  - Ethical principles for medical research involving human subjects/participants
- Declaration of Tokyo (1975)
  - Guidelines for Physicians Concerning Torture and other Cruel, Inhuman or Degrading Treatment or Punishment in Relation to Detention and Imprisonment
- Declaration of Lisbon (1982)
  - Rights of the Patient
- Declaration of Taipei (2016)
  - Ethical considerations regarding health databases and biobanks

The DoH in Context

An Important Set of ***High-Level Principles*** Referenced by many International Bodies and by More Granular Guidelines

- World Health Organization (WHO) Guidance for Best Practices
- Council for International Organizations of Medical Research (CIOMS)
- International Conference for Harmonization (ICH) Good Clinical Practice (GCP) Guideline
- Regulation 536/2014 of the European Parliament on Clinical Trials
- UNESCO Universal Declaration on Bioethics and Human Rights
- US Belmont Report of 1979
- US Subpart A of 45 CFR Part 46 (Common Rule): no specific reference
- Codified in many national laws / regulations

The DoH as a *Living Document*

- **1954** • Resolution on Human Experimentation endorsed by WMA
- **1961** • Draft Code on Human Experimentation by WMA Cmte on Med Ethics published in BMJ
- **1964** • Declaration of Helsinki Adopted
- **1975** •Tokyo: **Ethics committees**, Research protocols, Environment, Animal use
- **1983** •Venice
- **1989** •Hong Kong
- **1996** •Somerset West: **Limited placebos** to when no proven therapy exists
- **2000** •Edinburgh: **Test against best current, Post-trial Access, Vulnerable Populations,** Monitoring
- **2002** •Washington: *Clarification* on Placebos (compelling methodological reasons, minor conditions)
- **2004** •Tokyo: *Clarification* on Post-Trial Access (considered, not required)
- **2008** •Seoul: **Trial registration, dissemination of results**
- **2013** •Fortaleza: New structure, stronger protection for vulnerable groups, compensation for harm
- **2024** •Helsinki: *(in progress)*

Why Revise?

- Some argue ethical principles should be timeless
- Sustaining relevance requires the Declaration evolve as
  - Evidence of new risks/harms comes to light
  - Research enterprise presents new challenges
  - Society Advances
- Stresses and tensions are inherent as ethical principles sometimes collide and resonate differently across cultures/geographies
  - Openly wrestling with them is essential

The 2024 Revisions

A 30-month, Thorough, Inclusive Process

- WMA Council established Working Group in April 2022
  - 19 Countries and Associate WMA members represented, plus many invited bioethics expert advisors
  - Smaller Drafting Group also engaged

- **Associate Members**: Syed Hussain, Natalia Solenkova, Anthea Mowat
- **Bangladesh**: Jamal Chowdhury
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- Regional and Topical Meetings Across the Globe to Gather Feedback

Regional and Topical Meetings

- Tel Aviv: Implications of Big Data, Machine Learning, AI
- São Paulo: Ethical Considerations on Use of Placebo
- Copenhagen: Emerging Trial Designs
- Tokyo: Research During Public Health Emergencies / Pandemics
- Vatican: Research in Resource-Poor Settings, Global Justice
- Johannesburg: Community Inclusiveness, Post-Trial Access, Vulnerability
- Munich: Specific and Particularly Vulnerable Groups
- Washington, DC: Final Consolidation

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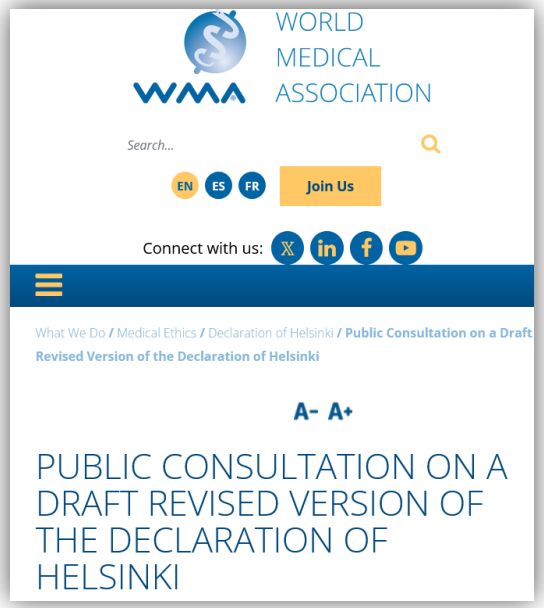
- Public Comment Periods
  - Phase 1 Occurred last winter
  - Phase 2 Occurred earlier this summer



Key Revisions Proposed for 2024

Declaration of Helsinki 2022-2024 Revision

WMA Working Group Recommendations following Regional/Topical Meetings and Public Consultations

Version Updated September 13, 2024

The Workgroup rationales and descriptions of proposed changes are included before each paragraph.

Underneath the rationale, the left-hand column shows the existing language from the 2013 revision, and the right-hand column shows the proposed text from the Workgroup. Additions are **bolded and underlined**, while deletions are indicated by ~~strikethrough~~.

Preamble

Paragraph 1

The Workgroup proposed replacing "subjects" with "participants" throughout the DoH out of respect for the rights, agency, and importance of those individuals. (See e.g., Workgroup Proposal paragraphs 1, 10, 12, 14, etc.).
Public comments in both periods one and two welcomed the change from subjects to participants.

2013 DoH Language:	**Workgroup Proposal:**
1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.	1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human ~~subjects~~ **participants**, including research **using** ~~on~~ identifiable human material ~~and~~ **or** data. The Declaration is intended to be read as a whole, and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

Paragraph 2

Declaration of Helsinki 2022-2024 Revision

WMA Working Group Recommendations following Regional/Topical Meetings and Public Consultations

Clean Version Without Tracked Changes or Rationales
Updated September 13, 2024

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human participants, including research using identifiable human material or data.

   The Declaration is intended to be read as a whole, and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. While the Declaration is adopted by physicians, the WMA holds that these principles should be upheld by all individuals, teams, and organizations involved in medical research, as these principles are fundamental to respect for and protection of all research participants, including both patients and healthy volunteers.

Participant and Community Engagement

- Replaced ***subjects*** with ***participants*** throughout the DoH out of respect for the rights, agency, and importance of those individuals

- Recognizes that participants may include **patients** and **healthy volunteers**

- New language in ¶6 demands *"**meaningful engagement** with potential and enrolled participants and their communities … before, during, and following medical research"* in recognition of study participants as **partners in co-creation**.
    - Specifically sharing priorities/values, participating in study design/implementation, engaging in understanding/disseminating results

WMA Urging DoH to be Broadly Upheld

- New language in ¶2 states that *"these principles should be **upheld by all individuals, teams, and organizations** involved in medical research, as [they] are fundamental to respect for and protection of all research participants…."*
- Language in many paragraphs now addresses ***"physicians and other researchers"***
  - While some question the WMA's authority to address nonphysicians, the Declaration is more than solely an exercise in self-regulation
  - The medical profession's morals and broader ethics include a duty to ensure respect for the health, dignity, integrity, autonomy, and privacy of research participants, no matter who is performing the research
- New ¶8: Essential to uphold DoH principles during **public health emergencies**

Distributive and Global Justice

- New language in ¶6 calls on researchers to *“carefully consider how the benefits, risks, and burdens of research are distributed.”*
    - Also recognizes that medical research enterprise does not have the capacity or bear sole responsibility to resolve all structural inequities

Purposes of Medical Research

- Contemplated adding ***"social value"*** to revised ¶7
  - but there was public concern with vagueness and different interpretations across cultures
- Instead added that new knowledge generation, in addition to furthering understanding of diseases and improving interventions, should ultimately *"advance **individual and public health**."*
- Retained existing language about those purposes never taking *"precedence over the rights and interests of individual research participants"*
  - Does not negate the fact that participants, with freely given informed consent, often make benevolent choices to take risks for the good of others with minimal expectation of personal benefit

Vulnerability

- Rewritten ¶19 Recognizes that:
  - individuals, groups, and communities may be in situations of **vulnerability** due to factors that may be **fixed** or **contextual** and **dynamic.**
  - their default exclusion from medical research has resulted in enormous gaps in medical knowledge and can potentially perpetuate or exacerbate disparities.
- Requires that “the harms of exclusion must be considered and weighed against the harms of inclusion”
- Calls for **fair and responsible inclusion** with specially considered **support** and **protections**
- Rewritten ¶20 retains additional protections for some **particularly vulnerable** groups.
  - Responsive to their health needs/priorities
  - Stand to benefit
  - Cannot be carried out in non-vulnerable **(unless exclusion perpetuates or exacerbates disparities)**

Scientific Requirements

- ¶21 newly calls out importance of **scientific rigor** to avoid **research waste**

- New language in ¶12: *"**Scientific integrity** is essential in the conduct of medical research involving human participants. Involved individuals, teams, and organizations must never engage in **research misconduct**."*

Research Ethics Committees

- ¶23 specifies need for **ethics committees** to have
  - Adequate *"**independence** and authority to resist undue influence"*
  - *"Sufficient **resources** to fulfill its duties"*
  - *"Adequate **education**, **training, qualifications, and diversity"*** among its members and staff
  - **At least one public member** and *"familiarity with local circumstances and context"*
  - Authority to *"withdraw approval and suspend ongoing research"*

- Inclusion of ethics review in **both sponsoring and host countries** when collaborative international research is performed

Growing Use and Risks of Personal Data Stored After Trials

- Complete rewrite of ¶32
- Calls for **free and informed consent** for the *"collection, processing, storage, and foreseeable secondary use of biological material and identifiable or re-identifiable data,"* and for ethics committee approval and monitoring of such databases and biobanks.
- **Cross-references the WMA DoT's** more detailed guidelines on rights of individuals and principles of governance for health databases and biobanks
    - Pertains to data collected "from research participants for multiple and indefinite uses" beyond the clinical care of individual patients"
- Acknowledges that consent for **unanticipated secondary research** on stored data is sometimes impossible or impracticable to obtain – but requires ethics committee consideration and approval of such unforeseen uses.

Use of Placebo

- Maintenance of balanced language in ¶33 **limiting use of placebo** or no intervention, or control groups using anything other than best proven intervention(s).
  - Amendment was considered broadening use of placebo to when no "proven safe and effective intervention exists"
  - Ultimately rejected after extensive consultations
    - São Paolo regional DoH meeting with participants from >10 countries in WMA's Latin American region, and leaders from CONFEMEL and the Pan-American Health Organization
    - Feedback from CONFEMEL
    - Focused session on DoH revisions at the World Conference in Bioethics in Brasília

Other Revised Principles

- Strengthening **post-trial provisions in** ¶34
  - **Must** be ***arranged*** for participants who still need intervention identified as beneficial and reasonably safe in a trial
  - Recognition that access can be ***provided by*** researchers, sponsors, healthcare systems, or governments
  - Exceptions allowed but require ethics committee approval
- ¶28/29: When seeking informed consent from legally authorized representative, must consider the preferences and values expressed by the potential participant
- ¶37: Use of **unproven interventions** (compassionate use) must never be undertaken to circumvent the protections for research participants
- Strengthened ¶11: "*Medical research should be designed and conducted in a manner that* ***avoids or minimizes possible harm to the environment*** *and strives for* ***environmental sustainability****."*

The 2024 Proposed Revisions

- Emerged from inclusive and lengthy worldwide stakeholder engagement
- Entail substantial changes to address a rapidly innovating research ecosystem and enhance future relevance
- Maintain brevity while some thirst for specificity
- Meaningfully renew this seminal ethical document that demands respect for and protection of all medical research participants

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