EBERHARD KARLS UNIVERSITÄT TÜBINGEN

INSTITUT FÜR ETHIK UND GESCHICHTE DER MEDIZIN

# The Declaration of Helsinki in the bio-ethical literature

Urban Wiesing
Tel Aviv, Dec. 9, 2022

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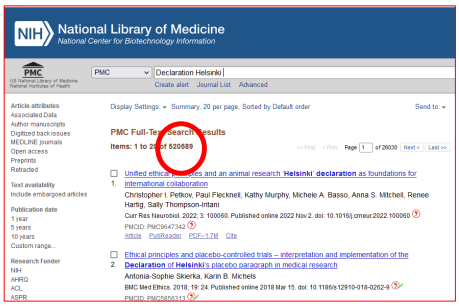
## The DoH in the literature

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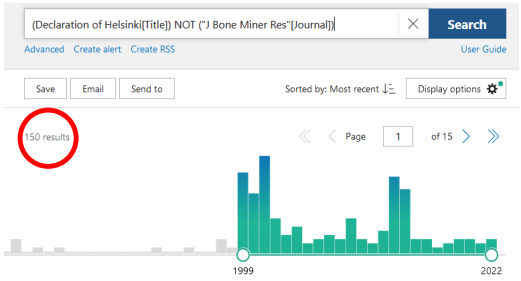


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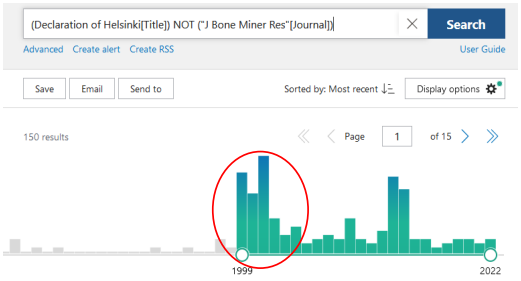


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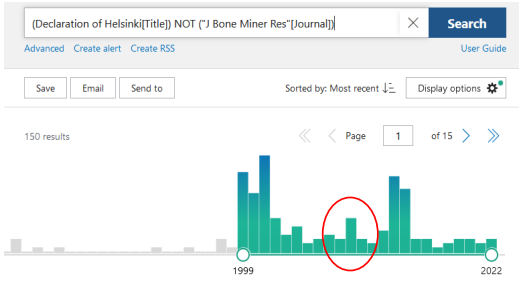


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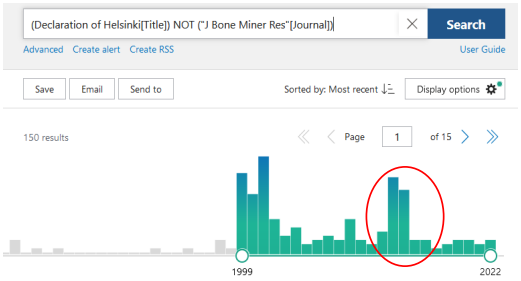


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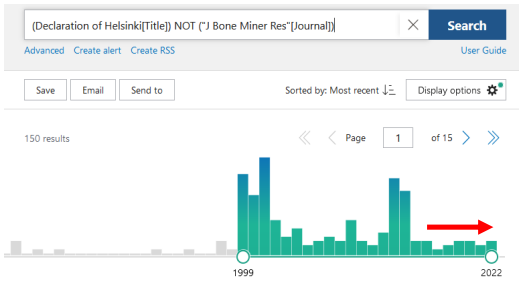


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## The DoH in the literature

- Enormous number of references to the DoH
- The DoH itself: currently not a "hot spot" in the bioethical literature!
- Other ethical issues are more discussed, e.g.,
  - ~ 700 publications on conscientious objection
  - > 1000 on genome editing and ethics

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## General critique (before and after 2013)

- **Frequency of revisions:**
  - "living document" (Ndebele 2013)
    or
  - concentrated on a few "eternal" principles – "tentative immortality"? (Emanuel 2013)

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## General critique (before and after 2013)

- "Genuine ethical obligations do not change every few years."

(Emanuel 2013, p 1247)

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## "Does your organization adhere to a specific version of the DoH?"

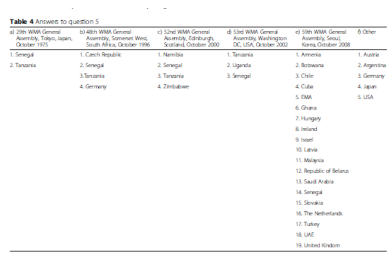

**Table 4** Answers to question 5

| a) 29th WMA General Assembly, Tokyo, Japan, October 1975 | b) 48th WMA General Assembly, Somerset West, South Africa, October 1996 | c) 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 | d) 53rd WMA General Assembly, Washington DC, USA, October 2002 | e) 59th WMA General Assembly, Seoul, Korea, October 2008 | f) Other |
|---|---|---|---|---|---|
| 1. Senegal | 1. Czech Republic | 1. Namibia | 1. Tanzania | 1. Armenia | 1. Austria |
| 2. Tanzania | 2. Senegal | 2. Senegal | 2. Uganda | 2. Botswana | 2. Argentina |
| | 3.Tanzania | 3. Tanzania | 3. Senegal | 3. Chile | 3. Germany |
| | 4. Germany | 4. Zimbabwe | | 4. Cuba | 4. Japan |
| | | | | 5. EMA | 5. USA |
| | | | | 6. Ghana | |
| | | | | 7. Hungary | |
| | | | | 8. Ireland | |
| | | | | 9. Israel | |
| | | | | 10. Latvia | |
| | | | | 11. Malaysia | |
| | | | | 12. Republic of Belarus | |
| | | | | 13. Saudi Arabia | |
| | | | | 14. Senegal | |
| | | | | 15. Slovakia | |
| | | | | 16. The Netherlands | |
| | | | | 17. Turkey | |
| | | | | 18. UAE | |
| | | | | 19. United Kingdom | |

Skierka/Michels 2018, p 6

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## General critique (before and after 2013)

- **Outreach and mandate**
- 2013, § 2: "Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles."

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## General critique (before and after 2013)

- **Outreach and mandate**

Internal contradiction: The DoH addresses

- § 9: "physician or other health care professionals"
- § 23: "research ethics committees" (not all members are physicians)
- § 34: "sponsors, researchers and host country governments"
- § 36: "Researchers, authors, sponsors, editors and publishers"

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## General critique (before and after 2013)

- **Outreach and mandate**
- "[…] a statement of ethical principles does not require a mandate from the people who ought to follow those principles."

(Millum et al. 2018, p 2143, also Emanuel 2013)

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## General critique (before and after 2013)

- **Terminology:**
- "[…] the terms "human subjects", "patients", "research subjects" and "research participants" are used interchangeably."

(Muthuswamy 2014, p 4)

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## Fundamental critique (before and after 2013)

- **Legitimation?**
- "merely […] ex cathedra declarations"

(Schüklenk 2015, p ii)

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## Fundamental critique (before and after 2013)

- **The revision process:**
- "[…] it should be that the normative prescriptions are developed within a collaborative dialogue between professionals and patients, their families and advocates."

(Woods/McCormack 2012, p 250)

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## Fundamental critique (before and after 2013)

- **The revision process:**

"[…] the present make-up of the committees engaging in the process of reforming ethics guidelines cannot be taken reliably to track the interests of all those groups affected by the guidelines"

(Smith/Weinstock 2017, p 318)

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## Fundamental critique (before and after 2013)

- Dissemination and worldwide adoption?
- DoH – a "minority report"? (Reider 2015, p 792)
- Prominent example: FDA/NIH

  since 2008: ICH-guidelines, which refer to the principles of the DoH.

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## Positive commentaries to the DoH 2013

- Many commentators: positive
- "the most accepted and adopted ethical guideline" (Skierka/Michels 2018, p 11)
- 2018 version "better organized, clearer and more precise, received 12 subheadings" (Hellmann et al. 2014)
- "a significant improvement over previous versions" (Millum et al. 2013, p 2143)

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## Important changes in the 2013 version

- Structure
- Vulnerable Groups
- Post-Study-Arrangements
- Research Ethics Committee
- Compensation
- Biobanks
- Placebo
- Registration
- publication **and dissemination** of results

21



## Important changes in the 2013 version

- Structure
- Vulnerable Groups ⇐
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- Placebo ⇐
- Registration
- publication **and dissemination** of results

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## § 19, Vulnerable Groups

- **Definition?**

2013, § 19: "Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection."

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## § 19, Vulnerable Groups

- General description or list of vulnerable groups? (Millum et al. 2013)
- "separation between: disadvantaged populations; vulnerability due to diminished decisional capacity or undue influence by the recruiting researchers; and vulnerability to risks of increased harms by nature of the population under study." (Moris 2013, p 1890)

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## § 19, Vulnerable Groups

- The "[…] shift to an approach to vulnerable groups based on wrongs or harms rather than labeling is to be welcomed. One advantage of this approach is that it allows tailored protections for different forms of vulnerability, rather than blanket protections"

(Hurst 2014, p 1252)

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## Vulnerable Groups, draft submitted to GA

- § 20: Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research. Consideration should be given to ensuring that the community receives a fair level of additional benefits.

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27



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**Reasonable availability approach!**

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**Fair benefit approach**

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## Vulnerable Groups, version accepted by GA

- § 20: Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research. ~~Consideration should be given to ensuring that the community receives a fair level of additional benefits.~~

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## § 19, Vulnerable Groups

- The fair benefit approach was skipped by the GA because of the fear of exploitation, expressed by resource poor countries.

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## § 19, Vulnerable Groups

- Critique: Without fair benefit approach no benefit is possible for vulnerable people in phase 1 or 2 trials.
- "participants from poor countries with limited access to medical services are unlikely to benefit" (Millum et al. 2013, p 2144)
- The reasonable availability approach alone is insufficient for vulnerable people!
- Contra: Fair benefit is not explicitly forbidden (Hurst 2014)

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## § 32: "biobanks or similar repositories"

- § 32: For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. [...]

33



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## § 32: "biobanks or similar repositories"

- "More clarity is needed on issues related to biobanking." (Muthuswamy 2014, p 4)
- "more precise description of which samples and data count as identifiable" (Colledge/Elger 2013, p 150)

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## § 32: "biobanks or similar repositories"

- No explicit broad consent in the DoH!
- Detailed broad consent in the Declaration of Taipei 2016!
- Relationship to the Declaration of Taipei?
- How detailed in the DoH when detailed in the DoT?
- Reference to the DoT in the DoH?

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## § 33, placebo control

- The "never-ending" controversy!
- Historical background: HIV-transmission studies in the 1990s in Africa, testing against placebo
- Proven intervention was available but too complex to be used in resource poor settings.

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## § 33, placebo control

- Controversial ethical debate about different standards
- "placebo orthodox" vs. "active control orthodox"
- In particular MLIC, South America: "active control orthodox"

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## § 33, placebo control

- DoH: Controversial since 2000
- DoH 2000, § 29: "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists".

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- (Similar since DoH 1975)

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## § 33, placebo control

- 2002 Note of Clarification added:
- "However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
- 1. Where for compelling and scientifically sound methodological reasons it is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- 2. Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm."

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## § 33, placebo control

- 2008, §33:

"[…] - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention
- and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm.
- Extreme care must be taken to avoid abuse of this option."

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## § 33, placebo control

- 2 WMA-conferences on placebo control in Sao Paulo in 2010, 2011, GA in Fortaleza 2013
- 2013 version:
- No change in ethics, but more systematic

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## Placebo DoH 2013

- § 33: "[...] where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
- and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention 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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## § 33, first condition for placebo control

- "compelling and scientifically sound methodological reasons […] to determine the efficacy and safety of an intervention"

= vague, not precise

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## § 33, first condition for placebo control

**Table 6** Answers to question 7: "What are "compelling and scientifically sound methodological reasons" as outlined in paragraph 32 of the Declaration of Helsinki for your institution which would justify the use of placebo?"

| Compelling and scientifically sound methodological reasons | Country |
|---|---|
| Questionable effectiveness of standard treatment | Armenia, Canada, Cuba, Israel, Namibia |
| Assay sensitivity/ when placebo is the most rigorous test of efficacy | Germany, Ghana, USA, The EU |
| No current proven intervention exists | Namibia, Uganda, Zimbabwe |
| High placebo response rate | Canada, Chile, Cuba |
| None if effective treatment exists | Japan, United Arab Emirates, Zimbabwe |
| Standard treatment is too toxic | Ghana, Tanzania |
| Available treatment is too expensive | Botswana, Uganda |
| Non-responders | Israel, Tanzania |
| Add on | Ghana, Saudi Arabia |
| Size of placebo groups may be smaller than in active control studies | Saudi Arabia |

Skierka/Michels 2018, p 8

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## § 33, second condition for placebo control

- "no risk of serious and irreversible harm"

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## § 33, second condition for placebo control

- "no risk of serious and irreversible harm"

**Table 7** Answers to question 8, "How does your institution define "serious harm" as outlined in paragraph 32 of the Declaration of Helsinki for a patient which would restrict the use of placebo?"

| Definition of serious harm | Country |
|---|---|
| Persistent or significant disability/incapacity | Armenia, Botswana, Germany, Ghana, Japan, Latvia, Malaysia, Namibia, Republic of Belarus, Saudi Arabia, Slovakia, The EU, The Netherlands, USA |
| Life-threatening events | Botswana, Cuba, Czech Republic, Germany, Ghana, Hungary, Israel, Namibia, Republic of Belarus, Saudi Arabia, Tanzania, The EU |
| Death | Botswana, Ghana, Namibia, Republic of Belarus, Saudi Arabia, Tanzania, The EU, USA |
| Inpatient hospitalization or causes prolongation of existing hospitalization | Germany, Ghana, Namibia, Saudi Arabia, The EU, United Arab Emirates |
| Congenital anomaly/birth defect | Germany, Ghana, Namibia, Saudi Arabia, |
| Requires intervention to prevent permanent impairment or damage | Saudi Arabia, The EU |
| Maintenance therapy for schizophrenic patients | Hungary |

Skierka/Michels 2018, p 9

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## § 33, second condition for placebo control

- "no risk of serious and irreversible harm"

  = absolute limit

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## § 33, second condition for placebo control

- § 28: "research subject who is incapable of giving informed consent […] only minimal risk and minimal burden"

  = another absolute limit
  (and criticised by Westra/de Beaufort 2013)

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## § 33, second condition for placebo control

- § 16: "if the importance of the objective outweighs the risks and burdens to the research subjects"
- = no absolute limit, but balancing!
- **Internal contradictions regarding risk/benefit**

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## § 33, double standard?

- "The term "best proven intervention" remains ambiguous. Where is it applicable – locally or globally?" (Muthuswamy 2014, p 1)
- But: Any wording in favour of the double standard like "available best proven intervention", "locally available best proven intervention" was not implemented!

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## § 33, double standard?

- "[…] the phrase 'less effective than the best proven' [allows] double standard in medical research in low-resource countries."
  (Hellmann et al. 2014, also Hellmann et al. 2016)
- But: 'less effective than the best proven' does not allow double standard!

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## § 33, double standard?

- Exceptions from best proven comparator only allowed for scientific reasons,
- everywhere, not only in low-resource countries
- **The DoH and WMA never supported a double standard!**

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## § 33, placebo control

- **"placebo orthodox" for double standard:**
- "The danger is that it may preclude vital research that promises to improve the condition of the worst-off. […] A future and better Declaration should allow such trials under strict conditions, especially when no one is deprived of treatment they would otherwise receive and the research has the potential to save many lives and improve the care of poor populations."
  (Millum et al. 2013, p 2144, also Millum/Grady 2013)

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## § 33, Paradox:

- The DoH never supported a double standard!
- The DoH is accused of supporting double standard! ("active control orthodox")
- The DoH is accused of not supporting double standard! ("placebo orthodox")

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## § 33, placebo control

- A symbolically charged political dispute
- The factual arguments have only limited persuasive power!
- The current version: the best middle ground?

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## § 34, post trial provisions

- "In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial."
- Who is responsible?
  (also for § 15, compensation; Hellmann et al. 2016)
- "how far it is practicable"?
  (Shah 2014, p 63)

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## § 34, post trial provisions

- "should": weakens the 2008 version: "are entitled to" (Shah 2014, p 63)
- "This definition has diluted the provision in the 2008 version, according to which post-trial provisions signified "access to interventions identified as beneficial in the study **or to other appropriate care or benefits.**"" (Muthuswamy 2014, p 4)

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## § 34, post trial provisions

- "I criticize the disappearance of 'access to other appropriate care' […] and the narrow scope given to obligations of access to information after research." (Mastroleo 2016, p 80)
- "is drafted rather strangely" (Malik/Foster 2016, p. 188, also Hellmann et al. 2016)

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## § 37, Unproven Interventions in Clinical Practice

- "perhaps the most philosophically intriguing [paragraph], because it evokes the sometimes hazy distinction between medical care and research"

(Reider 2015, p 792)

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## § 37, Unproven Interventions in Clinical Practice

- 2013, § 37: "In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available."

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## § 37, Unproven Interventions in Clinical Practice

- "The need to revise the Helsinki Declaration" (Asplund/Hermeren 2017, p 1190)
- Not strict enough! Cases of abuse!
- "opens a Pandora's box" (Shah 2014, p 64)
- "[…] only safeguards listed in the DH – expert advice and informed consent – do not seem to provide sufficient protection for patients" (Borysowski et al. 2018, p 505).

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## § 37, Unproven Interventions in Clinical Practice

- Better: **Guidelines for stem-cell research and clinical translation** by the **International Society for Stem Cell Research (ISSCR)**

**written plan**: procedure, scientific rationale and justification, reasonable chance of success, preclinical evidence efficacy and safety
- approved through a **peer-review process**
- **voluntary informed consent**
- **action plan for adverse events**
- **reporting of outcomes** (including negative outcomes and adverse effects), enabling critical review of the intervention by the scientific community
- (Asplund/Hermeren 2017, p 1190)

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## DoH: Ethical problems not addressed

- "Furthermore, ethical issues in **human enhancement** research are still being uncovered."

(Hellmann et al. 2014)

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## •How should the DoH react to new technologies?

- Digitalization, data, AI, Genome-editing, biobanks, personalized medicine

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## Literature review

- Shall the DoH be revised because of

| | |
|---|---|
| • digitalization? | no results! |
| • AI? | no results! |
| • genome editing? | no results! |
| • CRISPR/cas? | no results! |
| • personalised medicine? | no results! |

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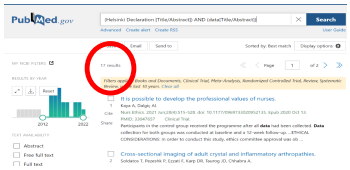
## Literature review

"Declaration Helsinki" and "data"




The 17 articles are confirming that the research with data has to be performed according to the DoH.

No revision of the DoH regarding research with data is required!

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## General consideration: New principles or further explanation?

- "The current effort, as has been the case with previous revisions, is aimed not at changing core ethical principles but at determining whether additional guidance is needed."

(Cecil B. Wilson 2013, former President of the WMA)

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## Summary: DoH in the literature

- Many comments to the 2013 version: **positive!**
- **General criticism:**
  - frequency of revision
  - mandate/outreach
  - internal contradictions
  - terminology
  - revision process
  - legitimation
  - dissemination/adoption

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## Summary: DoH in the literature

- Main criticism to the 2013 version:
  - vulnerable groups
  - post-trial provision
  - biobanks
  - placebo
  - unproven intervention
- Shall the DoH react to new technologies? So far not addressed in the literature!

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## Summary

**The best answer to criticism?**

**Quality!**

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# The Declaration of Helsinki in the bio-ethical literature

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Tel Aviv, Dec. 9, 2022

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