Proceedings

The 2024 Declaration of Helsinki: Taking Forward Bioethics and Human Rights*

Co-organized by:
The Brazilian Society of Bioethics (SBB);
International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP);
Clinical Evaluation Inc.;
The 129th Pharmaceutical Study Group

Supported by:
The Japan Association for Bioethics (JAB)

Cooperation:
Japanese Association of Pharmaceutical Medicine (JAPhMed);
Japanese Institute for Public Engagement (Ji4pe);
Clinical Research Risk Management Study Group

共催：ブラジル生命倫理学会，国際製薬医学会（IFAPP），臨床評価刊行会，
第129回くすり勉強会
後援：日本生命倫理学会
協力：日本製薬医学会（JAPhMed），医療開発基盤研究所（Ji4pe），
臨床研究リスク管理研究会

(Monday, 5 and Monday, 26, August, 2024, Zoom webinar)

* This is proceedings of the webinar, updated from the Preprint published on October 10, 2024, of which related information and video-recorded version are available at:
http://cont.o.oo7.jp/52pop/52pop_contents_e.html
All of presentations are panelists' personal views, not of affiliations, nor explanations from the WMA's, unless specific reference is made.
（本稿はウェビナーの講演録であり，2024年10月10日のプレプリント公開から更新してあり，関連情報と録画は上記URLより閲覧できる．全ての発表は発表者の個人的見解であり，特に出典が明記されない限りは所属機関のものではなく，世界医師会としての説明ではない．）

Abstract

The World Medical Association (WMA)'s Declaration of Helsinki (DoH), ethical principles for research involving humans, was first adopted in 1964. This webinar was hosted by external stakeholders to discuss important topics shortly before the final adoption in October 2024 of the revision of the 2013 version. Critical topics which have been discussed thus far in the WMA's regional meetings in various places in the world and twice at public consultations are: involvement and protection of patients and communities in research; promoting inclusion and protection of vulnerable people; research in low-resource settings including disaster situations; access to interventions proven to be effective; and the most controversial issue of the of placebo-controlled trials when proven intervention exists (including consistency with CIOMS guidelines). Linking with the WMA Declaration of Taipei on Health Databases and Biobanks is also an important topic to promote data-driven research.

This webinar provided an overview of the WMA review process from an external perspective (including insight into some collaborative relationships with the WMA), and considered the direction forward from the perspective of the cornerstone for the protection of the dignity and rights of research participants in the context of bioethics.

Key words

Declaration of Helsinki, bioethics, human rights, placebo-controlled trial, post-trial access, patient and public involvement

Rinsho Hyoka（*Clinical Evaluation*）. 2025；52(3)：375-452.

抄録

世界医師会（WMA）による人を対象とする研究の倫理原則である『ヘルシンキ宣言は』，1964年に初版が採択された．2024年10月の改訂版採択の直前に，WMAの外部ステークホルダーにより重要トピックを議論するためこのウェビナーを開催した．WMAの地域会議と2回のパブリックコンサルテーションでは，コミュニティや患者の研究への参画とその保護，弱者の研究組み入れ推進とその保護，低資源環境・災害状況下での研究，試験終了後に有効性が証明された介入へのアクセス，そして最も論争を喚起してきたプラセボ対照試験の許容条件（CIOMS指針との整合性を含む）などが重要な争点となっている．ヘルスデータベースとバイオバンクについての台北宣言との関係性もデータ駆動型研究を推進する上で重要課題である．

本ウェビナーでは，第三者的な立場（協力関係を持つ場合を含む）から，WMAにおける改訂状況を概観し，今後の研究倫理の潮流の方向性を検討するとともに，研究参加者の尊厳と人権の保護のために必要な基軸を，生命倫理学の観点から明らかにする．

キーワード

ヘルシンキ宣言，生命倫理，人権，プラセボ対照試験，試験終了後アクセス，患者市民参画

Program

Day 1 (August 5, 2024)

Program

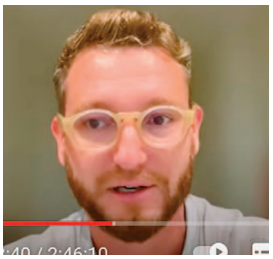
Day 2 (August 26, 2024)

Dirceu Greco

Elda Coelho Azevedo Bussinguer

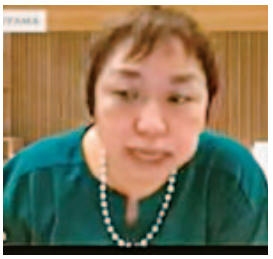
Diego Zanella

Laís Alves de Souza Bonilha



Fernando Hellmann

Varvara Baroutsou



Kotone Matsuyama

Chieko Kurihara

Kyoko Imamura

Yoshiko Saito

Ames Dhai

Takeo Saio

Peter Lurie

Sarai Keestra

Day 1 (August 5, 2024)

Welcome Remarks

Dirceu Greco
Professor Emeritus of Infectious Diseases and Bioethics, School of Medicine, Federal University of Minas Gerais, Brazil
Member of the UNESCO International Bioethics Committee
Associate Member of the World Medical Association
Past President of the Brazilian Society of Bioethics

Today I am honored to share this conversation with all of you. I represent the Brazilian Society of Bioethics, as our President, Elda Bussinguer, will join us only in the session of the second day, which will be held on August 26, and I am the Past President. I have no conflict of interest to declare. This seminar is organized by many important entities, including the Brazilian Society of Bioethics, the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP), the 129th Pharmaceutical Study Group, and supported by the Japan Association for Bioethics, with the cooperation of the Japanese Association of Pharmaceutical Medicine (JAPhMed), the Japanese Institute for Public Engagement (Ji4pe), and the Clinical Research Risk Management Group.

We will discuss opinions and experiences related to the Declaration of Helsinki, which belongs to the World Medical Association. Its 60th anniversary will be commemorated in October in Helsinki with the approval of the new declaration.

The Declaration of Helsinki was taken as an example by many, even if they did not fully agree with it. This seminar aims to discuss what could be improved in the new version.

The Brazilian Society of Bioethics is represented by three other board members: Fernando Hellmann who will present today and Elda Bussinguer and Diego Zanella, who will present on August 26th. I hope you all enjoy the discussion aimed at improving the new Declaration.

Day 1 (August 5, 2024)

Commitment of the Ethics Working Group of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)

Kotone Matsuyama
Professor, Department of Health Policy and Management, Nippon Medical School, Japan
Chair of Ethics Working Group of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)
Member of the Japan Association for Bioethics

1. Remarks from the IFAPP President

Thank you for inviting me to this important seminar. I'm Kotone Matsuyama, the current chair of the Ethics Working Group of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP). I'd like to begin by sharing a message from our IFAPP President, Dr. Varvara Baroutsou:

> "*I sincerely apologize that circumstances have prevented me from being here to extend a personal welcome. However, I extend my warmest greetings and deepest gratitude for your presence, which will enrich our perspective and discourse. I would like to express my gratitude to the organizing committee, especially to my colleagues in the IFAPP Ethics Working Group, Chieko Kurihara, Kotone Matsuyama, our distinct speakers, and each participant.*
>
> *This webinar is not just an academic exercise. It is a call to action. As we delve into the ongoing revisions of the Declaration of Helsinki, your views and questions may have transformative potential for human life and bioethics. Our discussions can influence changes in medical research for the benefit of participants. I wish you a stimulating dialog and mutual inspiration.*"

2. Introduction of IFAPP

IFAPP's primary objective is to unite physicians and scientists from the pharmaceutical industry, contract research organizations, academia, medicines regulatory agencies, and patient organizations to advance global knowledge in pharmaceutical medicine.

Currently, 25 National Member Associations represent thousands of professionals in pharmaceutical medicine.

I would now like to introduce the Ethics Working Group, which aims to share and deepen the understanding of various ethical issues in pharmaceutical medicine, discuss current topics, and explore potential solu-

Table 1　IFAPP Ethics Working Group

- The aim of this Ethics Working Group (EWG) is to share and deepen the understanding of the wide range of ethical issues in Pharmaceutical Medicine, and to share current topics and their potential solutions. Currently, the EWG is working on the following topics on an ongoing basis:
  - Recommendations for the revision of the World Medical Association's 'Declaration of Helsinki'.
  - Ethical issues in clinical trials in disaster settings.
  - Ensuring access to new investigational drugs and vaccines and benefit sharing.
  - Ethical principles and frameworks in Pharmaceutical Medicine.
- The EWG will monitor new trends in research ethics and raise awareness publicly.

Joint Activities;

- CIOMS WG on Principles of Good Governance for Research Institutions (PGGRI)
- Considerations for the Declaration of Helsinki; preparation for publication – The World Medical Association

tions (Table 1). There are joint activities with Council for International Organizations of Medical Sciences (CIOMS)[1] as well as the World Medical Association (WMA).

3. Collaboration with the WMA

Our working group is focusing on collaborating with the WMA to recommend revision of the Declaration of Helsinki, addressing ethical issues in clinical trials, especially in disaster settings, ensuring access to new investigational drugs and vaccines, and benefit sharing, and developing ethics principles and frameworks in pharmaceutical medicine.

Since the memorandum of understanding between IFAPP and WMA was signed in 2017, we have cooperated on mutual projects. Recent activities include: Participation in WMA regional meetings, with Varvara Baroutsou invited as IFAPP Delegate President in Copenhagen, Denmark and Chieko Kurihara invited as part of the IFAPP Ethics Working Group in Washington DC, United States. Varvara, Chieko, and I will join the WMA General Assembly.

We invited the WMA representatives to IFAPP's meetings, the International Conference on Pharmaceutical Medicine (ICPM) in Athens, Greece, in 2022 where we discussed with Dr. Jack Resnick, American Medical Association and the workgroup chair for the revision of the DoH, and Dr. Otmar Kloiber, Secretary General of the WMA. We participated in the Public Consultation by the WMA for the revision of the DoH.

4. Proposals for the revision of the DoH in peer-reviewed papers

Our first publication to discuss the amendment of the Declaration of Helsinki is on linking it with the

1) Council for International Organizations of Medical Sciences. International guidelines on good governance practice for research institutions. 2023.
https://cioms.ch/publications/product/international-guidelines-on-good-governance-practice-for-research-institutions/

Declaration of Taipei, published in 2020 [2]. Essential requirements include valid consent for data and materials collected in health databases or biobanks, robust governance, privacy protection, and material transfer agreements.

An infographic shows the connection between the Declaration of Helsinki and Taipei, focusing on data and material use and future possibilities [3]. Our proposal includes combining both declarations to address secondary use, ethical approval, and the issue of consent for secondary data use.

Next, we propose a comprehensive review of the Declaration of Helsinki, focusing on ethics in data-driven research, placebo use, and post-trial access. The second scientific paper was published in April of 2024 [4].

Another paper on vulnerability, social value would be published soon [5].

5. Future works

Future work will address emerging technologies, data privacy laws, genomic ELSI, and patient public involvement, ongoing through the IFAPP Ethics Working Group. Here is an example of the topics we are discussing (Table 2). We always welcome you to participate in our discussion.

Table 2 Next Issue; ELSI with new emerging technology

- Genomic ELSI
  1. Genomic data ethical issues related to the subject itself
  2. Genomic ethical issues related to relevance, systemic issues, etc. (stakeholder, training, etc.)
  3. Ethical issues related to special design or use of
  4. Local regulations (comparison with other countries)
  5. Ethical issues due to culture, custom, and medical environment
  6. issues due to language differences
  7. Genomic editing technology: newly emerging the ELSI (artificial nucleotide insertion)
  8. RWD with genomic information (use, privacy, etc.)
  9. Medical insurance (private company)
  10. Relatively high cost of the genomic treatment
  11. The privilege for the intellectual property of the genetic testing

2) 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

3) Kurihara C, Baroutsou V, Becker S, Brun J, Franke-Bray B, Carlesi R, Chan A, Collia L, Kerpel-Fronius S, Kleist P, Laranjeira LF, Matsuyama K, Naseem S, Schenk J, Silva H. A proposal for the Revision of the Declaration of Helsinki to promote data-driven science and strengthening human subject protection. *IFAPP TODAY.* 2021; Nov/Dec (19): 13-5.

4) 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. PMID: 38628806; PMCID: PMC11019506.

5) 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

Day 1 (August 5, 2024)

Overview of the revision process of the 2024 Declaration of Helsinki: Part 1- focusing on placebo study

Takeo Saio
Department of Internal Medicine and Psychiatry, Fuji Toranomon Orthopedic Hospital, Shizuoka, Japan
Member of the Japan Association for Bioethics; Associate Member of the World Medical Association

1. Introduction

I am a Japanese physician practicing internal medicine, psychiatry, and occupational health. I am one of the early advocates of evidence-based medicine in Japan. I present you my opinion from the stand point of a clinician who has some knowledge on bioethics as a whole.

2. WMA Regional Meetings

There have been seven regional meetings of the World Medical Association (WMA) on the revision of the Declaration of Helsinki (DoH) until now. The main themes of each meeting are shown her (Table 1). The WMA put public consultations two times.

Table 1　WMA Regional Meetings and General Assembly

(video-recordings available at URLs)
- December 9 – 11, 2022 Tel Aviv, Israel: **General** discussion
- February 24 – 25, 2023 Sao Paulo, Brazil: **Placebo**
- September 21 – 22, 2023 in Copenhagen, Denmark: **New clinical trial design**
- 30 November – 1 December 2023 in Tokyo, Japan: **Disaster** settings
- Jan 18, 19, 2024 Vatican City: Research in **resource-poor** settings
  https://www.wma.net/events-post/wma-conference-on-the-revision-of-the-declaration-of-helsinki-research-in-resource-poor-settings/
- Feb 18, 19, 2024 Johannesburg: **Vulnerability**
  https://www.wma.net/events-post/wma-regional-meeting-in-africa-on-the-revision-of-the-declaration-of-helsinki/
- May 14, 15, 2024 Munich, Germany: Research with **vulnerable** people
  https://www.wma.net/events-post/research-with-vulnerable-people-a-targeted-interdisciplinary-discussion-within-the-scope-of-the-wma-declaration-of-helsinki-revision/
- August 15-16, 2024 Washington DC, US: **Advocacy and Communication**
  https://www.wma.net/events-post/wma-declaration-of-helsinki-revision-advocacy-and-communication/
- October 16-19, 2024 Helsinki, Finland, WMA General Assembly: **Adoption**

Kindly, some of the regional meetings accepted online observation by the public, which I almost all participated, but the numbers of online participants were strictly limited because their opening announcements are always just a few days before the event, which made a sort of barrier for physicians, patients and general public to view the meetings. However generous enough, the video-recordings of some of them are available from these websites.

3. Public consultations

As of the public consultations, In the Phase 1 public consultation, I submitted a comment co-authoring with Prof. Dirceu Greco; and for Phase 2 co-authoring with Prof. Greco and Prof. Elda Bussinguer, the past and the current Presidents of the Brazilian Society of Bioethics, representing the society. This is a great honor of me.

4. Paragraph 33: conditions of placebo study

Most important topic I wish to focus is the condition of placebo-controlled study when there is a proven intervention. The 2000 version the DoH permits placebo study only when there is no proven intervention.

However, in 2002, a small working group changed this condition to current idea “no additional risk of serious or irreversible harm”, in accordance with ICH-GCP E10 guidelines. It was discussed by small group to reverse the 2000 General Assembly decision. We argued during this time that this process is unfair.

Then current proposed revision keeps this condition that placebo study when there is a proven intervention is permitted if there is no additional risk of serious or irreversible harm.

However, this condition is inconsistent with CIOMS 2016 guidelines [1] that states that placebo study when there is a proven intervention can be permitted when there is only minor increase above minimal risk. Our opinion is that the DoH should follow the CIOMS.

5. WMA’s explanation in public consultation document

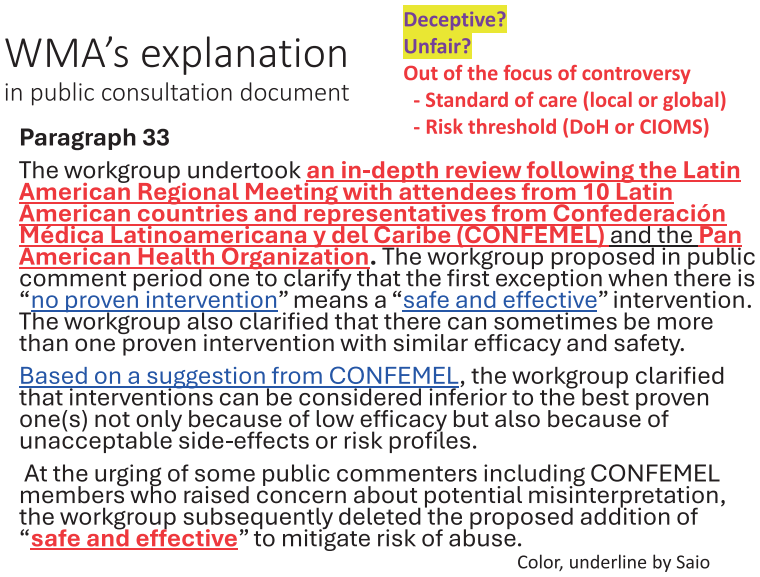
What I would like to point out now is that WMA’s explanation in public consultation document about the paragraph 33 seems to be Deceptive or Unfair for me (Fig. 1).

They omitted in the revision drafts for two times of public consultation the most important two points of debates. One is the “Standard of care” which means local standard or global standard, and another is the Risk Threshold. It seems that there is a consensus among the WMA that they take a position of global standard. With the risk threshold, it is obvious that the DoH’s high risk standard is inconsistent with the CIOMS standard which allows only minor increase above minimal risk.

However, the WMA’s explanation in the public consultation document is confusable treating Latin

1) Council for International Organizations of Medical Sciences. International ethical guidelines for health-related research involving humans. 2016. Available at: https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans/

Fig. 1　WMA's explanation of Paragraph 33 on placebo use in public consultation documents



American countries and the CONFEMEL agreed with proposed version to keep 2013 version at the regional meeting in Sao Paulo. The draft only changed "proven intervention" to "an intervention proven to be safe and effective". And there is some minor change. Adding "safe" is important but not the focus of international debate.

6. Questions

So I would like to ask Latin American colleagues whether Declarations of Cordoba in 2008, Buenos Aires in 2008, and Pachuca in 2013 are still now effective or not (Table 2).

I learned that Latin American organizations rejected the DoH because of weakened protection in placebo and access paragraphs.

Table 2　Questions on Latin American Declarations

• 2008 "Declaration of Cordoba"
• 2008 "Buenos Aires Declaration"
• 2013 "Declaration of Pachuca"
Latin American organizations rejected DoH because of weakened protection in placebo and access paragraphs. Still effective...?

7. JMA's view at the time of 2000 (not necessarily same views are kept)

I would like to introduce what late Dr. Eitaka Tsuboi stated [2], when he was the President of Japanese Medical Association and also the President of the WMA at the time of 2000 revision.

He stated that the JMA did not accept the 2002 note of clarification to permit placebo study when there is a proven intervention if there is no additional risk of serious or irreversible harm. For this reason, JMA did not publish a Japanese translation of this note on the JMA website.

Dr. Tsuboi explained that Japan expressed objection to proposal from American Medical Association because developing countries were not in a position to express objection because they benefited from the US. For this reason, we expressed non-Western spirit that ethical reason takes precedence over scientific needs and pragmatism.

Dr. Tsuboi stated that the placebo clause in the 2000 version is a perfect, prima facie norm.

More in depth analysis on placebo study was discussed in our paper [3] and will be discussed by other speakers of this symposium.

2) Tsuboi E, Kurihara C, Interview. The 2000 revision of the Declaration of Helsinki and its implications in medical ethics: interview with the WMA Immediate Past President, Eitaka Tsuboi. *Clin Eval.* 2002;30(1):99-107. Japanese. http://cont.o.oo7.jp/30_1/p99-107.pdf.

3) Kurihara C, Greco D, Dhai A, Saio T, Tsubaki H. Ethics of placebo-controlled trials: historical analysis including experiences during the COVID-19 pandemic. In: *Ethical innovation for global health: pandemic, democracy and ethics in research.* Springer; 2023.

Day 1 (August 5, 2024)

Overview of the revision process of the 2024 Declaration of Helsinki: Part 2 - General descriptions and some highlights

Chieko Kurihara
Specially-appointed Professor, Kanagawa Dental University
Member of Ethics Working Group of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)
Member of the Japan Association for Bioethics

1. Introduction

I will present overview of the revision process of the 2024 Declaration of Helsinki (DoH), General descriptions and some highlights. All the content is my personal view, not from World Medical Association (WMA) side, not representing any organization.

I have been engaged in the discussions of the Declaration of Helsinki (DoH) since 2000 revision from external position from the WMA, and most recently in November 2023 published a book as a leading editor collaborating with co-editors Prof. Dirceu Greco and Prof. Ames Dhai. Ames Dhai will attend the second day of this webinar August 26. The book title is *Ethical innovation for global health: pandemic, democracy and ethics in research*, published from Springer [1]. This book acquired 2,700 downloads in 109 countries worldwide during 8 months form publication. Then we planned NEXT publication within next year, to discuss about the new version of the DoH.

DoH new version will be adopted in October, and for this revision, there were 2 times of public consultations. I led two times of comment submissions from the members of the Ethics Working Group of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP), which was not officially representing IFAPP. And today's presentation is my personal view, not representing IFAPP.

There were WMA's Regional meetings discussing several topics. IFAPP President Varvara Baroutsou was invited to discuss new clinical trial design. She will attend the next day of this webinar. I was invited to coming Washington DC meeting held on August 15 and 16, focusing on advocacy and communications, this invitation is as I am a member of IFAPP Ethics Working Group.

1) Kurihara C, Greco D, Dhai A, editors. *Ethical innovation for global health: pandemic, democracy and ethics in research.* Springer; 2023.

2. Overview of the draft revision of the DoH

Next about some key changes of the revision and my personal opinions.

● **Paragraph 1, 2: Scope**

Through the document the word “human subject” is changed to “human participant”. Because this is the same as ICH GCP Renovation, the impact of the DoH is not so much, but there would be some impact on academic research.

Another point is that recommendation to non-physician researchers became strengthened. This is in line with the IFAPP’s position.

● **Paragraph 7: Community engagement (New)**

One of the highlights is the new paragraph on Community engagement. It is important to stress that research takes place in the context of various structural inequities. Meaningful community engagement is recommended to avoid inequities in the conduct and result implementation of the research.

● **Paragraph 6～8: Purpose of research**

Next about the purpose of research that can never take precedence over the rights and interest of individual research participants. This core principle of the DoH is not changed. A new paragraph states that even in the public health emergency the principles in the DoH does not change. The word “social value” was added in the first draft as the ultimate goal of research but it was deleted in the second draft. It was disappointing because social value is established concept in the CIOMS 2016 guidelines for health research [2].

● **Paragraph 19: Vulnerability**

There is also extensive discussions on vulnerability. The world trend is changing from stereotypical categorization of vulnerable groups such as children, pregnant women, to context-based vulnerability, which means vulnerability is changing up to the situations. Another point is to promote inclusion of vulnerable people in research rather than protection by means of excluding them. This is because better health of vulnerable people needs more inclusion in research with strengthened protection. This is already clearly discussed in CIOMS.

● **Paragraph 21: Scientific requirements**

Another interesting point is to include new word “research waste”. This is because during the COVID-19 pandemic many meaningless research results were published. Something missing is that there is no mention of prevention of scientific misconduct. [Note: “research misconduct” is mentioned in adopted version.]

● **Paragraph 23: REC, strengthened**

Research ethics committee’s function is strengthened. Most importantly, in case of international research both in sponsoring and host country reviews are required.

● **Paragraph 25～32: Informed consent**

In terms of informed consent electronic documentation comes to be mentioned.

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2) Council for International Organizations of Medical Sciences. International ethical guidelines for health-related research involving humans. 2016. Available at: https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans/

● **Paragraph 32: Informed consent for the collection, storage, secondary use of biological material and data**

This is the most important highlight of this revision. During the process you obtain informed consent of research participant, if there is a possibility of future secondary use of the data/materials from the research, you have to adhere to the Declaration of Taipei (DoT). The content of the DoT is not easy, not limited to privacy protection or security, you have to consider handling of incidental findings, intellectual property rights and material transfer agreement. We have to learn more about the Declaration of Taipei.

● **Paragraph 33: Conditions of placebo study**

Condition of placebo study when there is a proven intervention is the most controversial points of debates. Unfortunately, there seems to be no change at this moment. Since 1975 to 2000 the DoH describes physician's duty to provide best-proven intervention even in comparative study. However, according to the ICH E10 guidelines in 2000, the DoH changed its position to Utilitarian pragmatism to allow placebo study when there is a proven intervention if there is no increase of risk of serious or irreversible harm. On the other hand, CIOMS guideline 2016 takes a different risk threshold "minor increase above minimal risk". IFAPP members paper for which I am a leading author supported this CIOMS position of risk minimization.

● **Paragraph 34: Post-trial access**

"Post-trial access" is ethical standard, first included in the 2000 version of the DoH, of ensuring that participants in a trial are provided with an intervention proven to be effective in that trial, at the completion.

In the case of a placebo trial, the intervention shown to be effective would be made available to participants in the placebo arm.

In any study design, a participant who still needs the study intervention at the end of the study should be provided with this intervention after the end of the study.

Without post-trial access, the trial participants are being **exploited**.

However, sometimes it is difficult for the sponsor to provide access because of the time gap before regulatory approval.

Because of these difficulties, since 2004 "post-trial access" has become an item to be described in the protocol and informed consent, whether or not there is post-trial access.

● **A proposal for "post-trial access"**

In the 2024 revision (draft), the requirements for "post-trial access" are strengthened, but there is an excuse: "Exceptions to these provisions must be approved by a research ethics committee".

Argument of IFAPP members: (not official statement of IFAPP) is that post-trial access should be available to:

- Participants who still need the trial intervention;
- People in the trial host community;
- Those most in need worldwide.

＜Discussion＞

David R. Curry, MS, President, GE2P2 Global Foundation * The element in your post-trial access proposal around post-trial access for patients in need worldwide intersects with another access phenomenon – sometimes called compassionate use or expanded access. When sufficient efficacy and safety are established during clinical trials, developers can elect to make medicines and therapies available under various programmatic constraints.

Your bullet suggests that such patient access should be included as part of any trial, which would shift the current practice under which it is a decision taken solely by developer/manufacturer's decision. I am curious if your thinking has considered the current range of compassionate use and expanded access programs and how these two areas intersect in your considerations.

Kurihara This is a crucial perspective, and I have discussed it many times. Some participants, including company staff as well as academic researchers collaborating with companies, regulatory people, at every opportunity of discussions, have addressed this same issue. Post-trial access should follow regulatory guidelines, including expanded access, safety studies or extension studies, depending on regulatory jurisdictions, or the status of each product (how efficacy and safety data have been obtained during the clinical trials).

The DoH is not a guidance for industry. Regulatory bodies or pharmaceutical companies should have policies aligned with their strategies and the regulatory track suitable for each study and intervention.

The DoH provides ethical principles, suggesting ethical obligation of those who are involved in the study to achieve post-trial access for patients in need, host community and then eventually those most in need worldwide. This is challenging and not explicitly outlined in the DoH, though some scholars during the WMA's regional meeting argued these points.

A paper by leading author Koto and a Springer book discuss benefit sharing [3] and post-trial access, focusing on regulatory drugs, technology transfer, and manufacturing capacity development in resource-poor countries. Implementing these strategies could make the third point feasible. This is a challenge for the global community, as the DoH is an ethical principle we strive for, not a regulatory guide.

Curry Thank you for that useful distinction. We also recognize that the DoH is an ethics document, not a regulatory one. However, many pharmaceutical development organizations reference Helsinki appropriately in their public positions, policies, etc., and apply it in their clinical development operations.

So, while a normative statement in Helsinki around post-trial access as including "those most in need worldwide" would not have regulatory authority, it could significantly impact how commercial development organizations perceive their responsibilities.

In one sense, such access would be a powerful advancement in the access to medicines space. In another

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* the GE2P2 Global Foundation advances scientific rigour, ethical resilience and integrity in research and evidence generation. It functions as the secretariat for the Global Forum on Research Ethics and Integrity.
https://gfrei-ge2p2global.org/
The Forum has responded to the DoH revision Phase 1 and Phase 2 public consultations and engaged most of the regional DoH revision meetings.

3) Matsuyama K, Kurihara C, Crawley FP, Kerpel-Fronius S. Utilization of genetic information for medicines development and equitable benefit sharing. *Front Genet.* 2023 Jun 14;14:1085864. doi: 10.3389/fgene.2023.1085864.

sense, providing such access worldwide would involve significant costs and program infrastructure for the development organization involved. As such, these costs would likely be a significant deterrent to pursuing clinical development programs for many, if not most organizations – regardless of their scale, financial resources, or organizational form [commercial; government-public sector; academic, etc.]. Such trade-offs should be carefully considered by all stakeholders.

Kurihara　Thank you very much. Several participants of some discussions also mentioned about the issue of cost of post-trial access to impact on drug cost. There is also some experience that the cost for post-trial access is not so much high comparing with expenditure of company for post-marketing promotion [4]. Another participant of discussion mentioned that some global companies "impound" post-trial markets with "ethical justification" of post-trial access. At the time of successful COVID vaccine development companies changed protocol and then participants in placebo group came to be able to switch to active group. The companies negotiated with the FDA that it was from ethical obligation of post-trial access. This was a good example of win-win relationship between company, regulators and participants, however, this "good" example is only during short term because vaccine did not reach to those most in need in the world. There is a need for collaboration among stakeholders, including pharmaceutical companies and regulatory bodies, not only in the revision of the Declaration of Helsinki, but also for developing some practical guidelines outside of the DoH. It needs to clarify the issues of regulatory tracks such as expanded access, safety/extension studies, health technology assessment, technology transfer for manufacturing capacity development, as well as the issues related to intellectual property rights. We already discussed these issues in various opportunities including scientific paper publications [5, 6], but it is necessary to consolidate into one authoritative document. This can be possible to be proposed to CIOMS or ICH. This is not the task of revision of the DoH. (Added after the completion of webinar.)

4) Greco D, Invited lecturer. Kimura R, Special guest. Victoria Perottino M, Guest Discussant. Saio T, Kurihara C, Organizers & Discussants. Ethics of international collaborative research: Perspectives from Brazil: Part 1 Selected notes on Paulo Freire: Part 2 Access, Compulsory license, Case Study. *Clin Eval*. 2020; 48(1): 273-301.

5) Kurihara C, Greco D, Dhai A, editors. *Ethical innovation for global health: pandemic, democracy and ethics in research.* Springer; 2023

6) 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

Day 1 (August 5, 2024)

Introduction of the Japanese Institute for Public Engagement (Ji4pe)

Kyoko Imamura
President, the Japanese Institute for Public Engagement (Ji4pe), Japan
Former president, International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)

I am Kyoko Imamura. Currently, I am the President of Japanese Institute for Public Engagement, Ji4pe in short. I established this organization when I was serving as a President of International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine, IFAPP in the year 2020.

In our organization, we are providing education and training to patients and the public as well as the pharma industries and academic institution professionals (Table 1).

The next presenter is Yoshiko Saito. She has been an active member of our organization, and she is currently leading the Bioethics Working Group of Ji4pe, together with many colleagues who have participated in the publication of the Springer book, which was presented by Chieko Kurihara just a minute ago. I expect that Yoshiko can make a beautiful presentation today in challenging your ethical interest.

Table 1 History and mission of Ji4pe

Our History
As drug development becomes more complex and competitive and targeting more rare diseases and intractable diseases, education and training (E&T) are of paramount importance not only for drug developers in industry and academia, but also for patients and public to accelerate their engagement.

With dedicated professionals in E&T in and out of Japan, JI4PE was established in June 2020 to provide opportunities to learn together to achieve public engagement where safe and effective drugs can be available in the value-based health services network.

Mission
We aim to build stronger trust and ties between patients and society by actively participating in the resolution of public issues such as development and use of drugs, analysis of medical data, and the introduction of technological innovation.

Source: https://ji4pe.tokyo/index_en.html

Day 1 (August 5, 2024)

Patient and public opinions to the revision of the Declaration of Helsinki: Our proposals to the WMA

Yoshiko Saito
Breast cancer survivor, Japan
Fellow Member of the Japanese Association for Bioethics
Slides prepared in collaboration with Chieko Kurihara, based on discussions among patients and the public

1. Introduction: Our WMA Declaration of Helsinki

Today I will cover the opinions of patient and public on the revision of the Declaration of Helsinki (DoH). The DoH is a set of ethical principles for medical research involving humans that are directed at physicians. It was developed by the World Medical Association (WMA). It is assumed that research participants often first see its title in an informed consent document when asked to participate in medical research. But it is not widely known in society. This is why our working group has been holding monthly online meetings since November 2020 to discuss its contents.

During the process, some members initiated to re-write and explain the Declaration of Helsinki in our own words using plain language addressed to patient and public. This process led to the project to develop a three -part document titled “Our WMA Declaration of Helsinki” (Fig. 1).

First part of each paragraph is a Reproduction of the Declaration of Helsinki under the permissions of WMA and Japanese Medical Association (JMA).

Second part is re-written and explained in our plain language.

And third part is about our opinion on the Declaration of Helsinki from our perspectives.

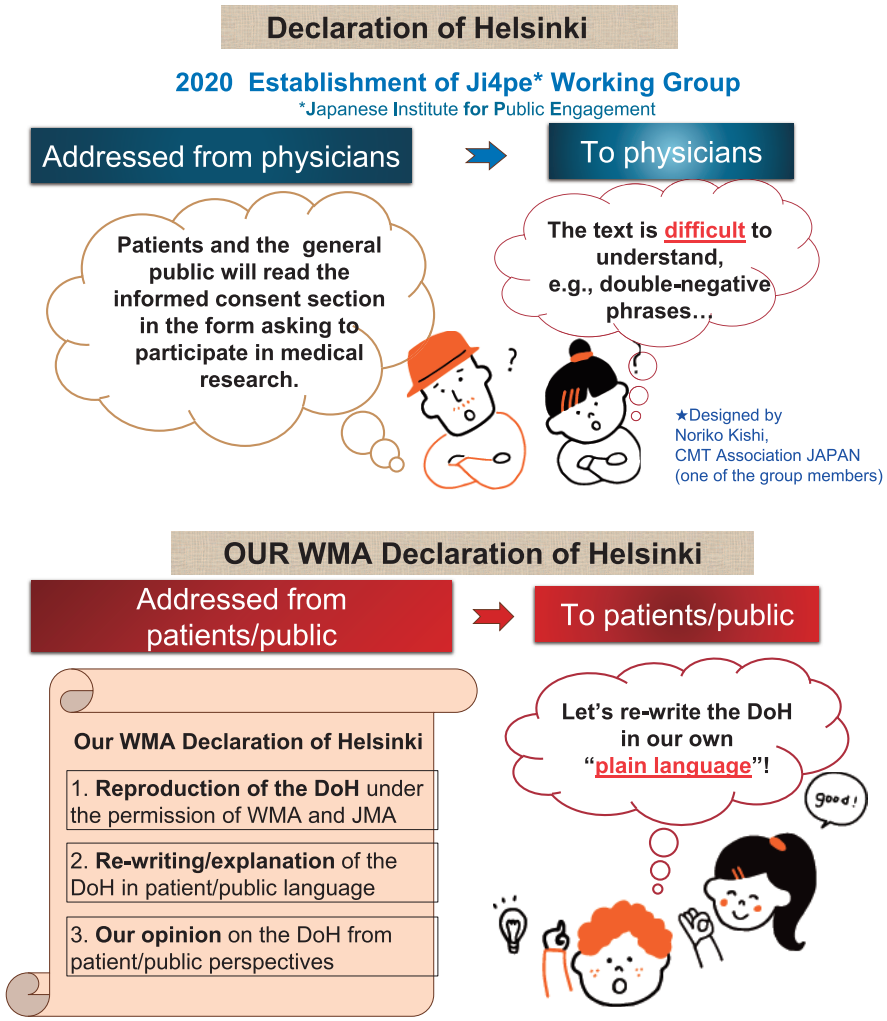
Because the Declaration of Helsinki is a set of basic principles that are internationally recognized, we thought the issues and proposals that we had noticed would be worth sharing internationally, and we were given the opportunity to have them published as a part of a book.

Its title is “Ethical Innovations for Global Health”, and it was published by Springer in November 2023.

In addition, “Our WMA Declaration of Helsinki” was published in its entirety in the July 2024 issue of the Japanese journal “Clinical Evaluation.”

Responding to the WMA Public Consultation, we submitted opinions based on our past discussions and publications in February and June this year.

Fig. 1 Our WMA Declaration of Helsinki



2. International norms and important principles of the WMA

In order to understand the Declaration of Helsinki, it is necessary to have a common understanding of various international treaties, domestic norms, and various WMA declarations.

Furthermore, from the South African Constitution, we learned that the Japanese Clinical Research Act does not establish fair protection for research participants.

In addition, we strongly believe that research ethics principles must ensure the protection of privacy rights.

We also learned that the WMA has issued many declarations and statements not only on research ethics but also on medical practice and patient care.

Recently, large amounts of patient data have been used to develop various medicines, including artificial intelligence.

Therefore, the “Taipei Declaration” on health databases and biobanks is particularly important.

3. Our Opinion on the WMA’s draft for revising the DoH

In the second part, we present our opinions on the WMA’s draft document for revising the Declaration of Helsinki. We have two key points:

● **Simplifying the language**

First, simplifying the language. The Declaration of Helsinki is written in very difficult language, and hard to understand for patients. Patients also encounter it in informed consent documents when they are asked to participate in clinical research.

● **From “subjects” to “participants”**

Secondly, we support the change from “subjects” to “participants”, as the word ‘participant’ accurately describes a person who voluntarily takes part in research. However, the DoH as a whole is paternalistic. We are concerned that people in weaker and more vulnerable positions will be left without a sense of participation despite being described as “participants.” We believe the term “participants” will only have its true meaning when the importance of advocates is also emphasized.

4. Opinions submitted to the WMA responding the two public consultation

Next, I would like to talk about the two public consultations in detail. All nine members of the Working Group prepared the Public Consultation comments last February and June.

● **Social value**

The term “social value” was once added in the first draft, but it was omitted in the second draft. Omitting social value might cause us to lose sight of the trajectory towards achieving the Sustainable Development Goals (SDGs).

● **Advocates who best protect participants’ rights and interests**

For research participants who cannot consent themselves, we must find advocates who best protect their rights and interests.

● **Shared decision-making based on informed consent**

We proposed the concept of shared decision-making based on informed consent.

● **Fairness of research ethics committees**

We hope the fairness of research ethics committees and the participation of general committee members will be clearly stated in the DoH.

● **Placebo-controlled trials**

It’s nearly impossible for patients to understand the conditions for using a placebo when an intervention has been already proven.

● **Post-trial access**

We believe that post-trial access should be guaranteed, and also it should be included in the informed consent document. Without documentation at the time of participation in clinical research, the patient cannot request the continuation of the study drug even though it is necessary at the time of completion.

● **Use of unproven interventions**

Regarding the use of unproven interventions, the proposed revision lacks provisions for accumulating data and monitoring safety and effectiveness, which are already included in the WHO document.

5. Future perspectives

Finally, we look towards the future. As we continue to learn, we have restarted a Bioethics Working Group made up of patient and public as one of Ji4Pe's working groups last month. Our group came up with three goals.

● **Patient and Public Declaration of Research Ethics**

We plan to develop a "Patient and Public Declaration of Research Ethics". This comes from Professor Ames Dhai's advice in a webinar last December at the time of the Springer book publication.

● **Second edition of Our WMA Declaration of Helsinki**

And, with permission from the WMA and JMA, we will publish the second edition of Our WMA Declaration of Helsinki after the 2024 version of the Declaration of Helsinki is released. We hope it will be a guide from the perspective of patient and public.

● **Survey on patient and public participation**

Third goal is to conduct a survey on patient and public participation in medical care based on the report from CIOMS.

Acknowledgement

By the way, our presentation slides, video-recordings of webinars and open access papers are available on the website in both Japanese and English.

You can also see the Graphic Recordings by Ms. Kanna Yoshikawa. She joined our several discussions and provided illustrations to describe our questions and opinions.

Lastly, let me introduce the members of the Bioethics Working Group of Ji4Pe. Also, I would like to express my heart-felt gratitude to the President of Ji4pe, Dr. Kyoko Imamura.

Day 1 (August 5, 2024)

In Defense of the most vulnerable research participants: Sick patients and the need for additional principles for therapeutic research in the Declaration of Helsinki*

Fernando Hellmann
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Bioethics and Public Health Research Group (NUPEBISC)
Saludy Fármacos
Pandemic Ethics Research Consortium (led by the University of Oslo)
UNESCO Bioethics Network for Latin America and the Caribbean
Brazilian Bioethics Society

1. Introduction

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.

2. 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

* This presentation is based on the author's doctoral thesis:
Hellmann F. A Declaração de Helsinque como estratégia biopolítica: uma genealogia do duplo standard para ensaios clínicos em países periféricos [tese de doutorado]. Florianópolis: Universidade Federal de Santa Catarina, Centro de Ciências da Saúde, Programa de Pós-Graduação em Saúde Coletiva; 2014. Available in Portuguese at:
https://repositorio.ufsc.br/xmlui/bitstream/handle/123456789/132405/333075.pdf?sequence=1&isAllowed=y

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.

3. 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.

4. 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.

5. 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.

6. 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, neces-

sitating 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).

7. 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.

8. 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.

Day 1 (August 5, 2024)

Experience of CONEP to facilitate Ethical Research

Laís Alves de Souza Bonilha
Coordinator, National Research Ethics Commission (CONEP)
Member National Health Council (CNS) 2024

1. Introduction

I would like to thank and congratulate the organizers for the importance of this topic and the need to discuss changes in bioethics and specifically in research ethics due to the multiple interests involved and the risks, especially for vulnerable populations as in Brazil, as Fernando mentioned earlier.

I have no conflict of interest in this presentation. I am a physiotherapist and professor in the field of public health.at a public university in Mato Grosso do Sul, in central region of Brazil.,

I am currently the Coordinator of the National Research Ethics Commission (CONEP) and a Counselor of the National Health Council (CNS). I also underline that I am a potential research participant, reminding us to defend our rights so that research can develop, since there is no adequate participation in insecure conditions. I am also a Brazilian citizen, which is important to mention given Brazil's severe inequality and the push to increase research. As it has been mentioned, Brazil's vulnerable population increases my commitment to my people.

2. Conep/CEP System

The CNS was created with the Brazilian Unified Health System (SUS) and is guaranteed by the Constitution. CNS advisors have 19 specific committees, including the CONEP. CONEP is composed of CNS members and those nominated by ethics committees, with representatives from different knowledge areas and research participants. It is now mandatory to have at least two representatives, but the new law reduces this to one—just one example of the losses we face in Brazil.

CNS created CONEP through two resolutions, establishing regional research ethics committees, our CEPs. This CEP/CONEP system supervises all research involving human subjects. CONEP is one of CNS's 19 committees. CNS is composed of 38 full members and substitutes representing national health boards, professionals, service providers, social movements using SUS, and federal government representatives. To balance interests, 50% are SUS users, 25% are workers, and 25% are service providers and managers.

Table 1 Conep/CEP System

National Health Council (CNS), Guaranteed by the 1988 Brazilian Federal Constitution
The CNS created the National Research Ethics Commission (CONEP) by Resolution 196/1996, succeeded by Resolutions 466/2012, which established regional research ethics committees (CEPs). This CEP/CONEP System is responsible for the ethical supervision of all research projects involving human subjects in Brazil
CNS Commissions 1. Health Care for People with Pathologies 2. Primary Health Care 3. Health Care in Life Cycles - Child, Adolescent, Adult and Elderly 4. Attention to the Health of People with Disabilities 5. Food and Nutrition Science 6. Technology and Pharmaceutical Assistance **7. National Research Ethics Commission (Conep)** 8. Permanent Education for SUS Societal Control 9. Budget and Financing Equity Promotion Policies 10. Promotion, Protection, Integrative and Complementary Practices in Health 11. Human Resources and Labor Relations 12. Indigenous people's Health 13. Women's Health 14. Mental Health 15. Worker's Health 16. Supplementary Health in the SUS 17. Health Surveillance 18. Oral Health

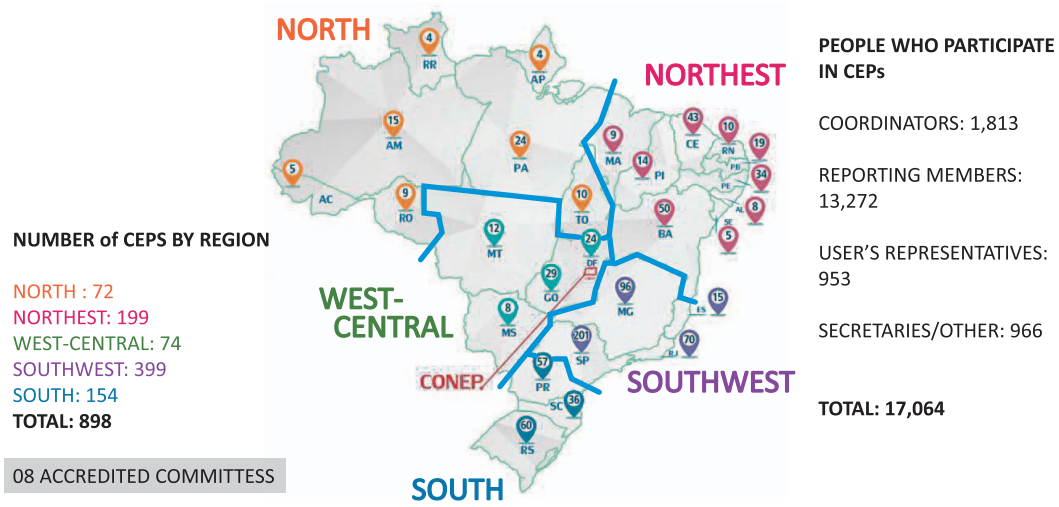
CONEP and the CEPs form a system responsible for the ethical review of research with humans. CONEP oversees projects involving greater individual risk, those of national interest, or those receiving foreign funding. It also registers and monitors 898 ethics committees.

CONEP has 34 members, five alternates, 17 ad hoc members, and two secretaries. There are 878 CEPs spread throughout the country, most concentrated in the southeast. Eight accredited CEPs share the function with CONEP for higher-risk projects, but new law changes will require more CEPs outside this region as CONEP will no longer review projects.

A recent national meeting of ethics committees had over 700 in-person attendees and 5,000 online. The government financed 200 participants to attend in person.

Since 2012, the site "Brazil platform" (Plataforma Brasil) has been used for communication between research institutions, research ethics committes (REC) , and CONEP, although it's an old system that needs updating.

Fig. 1　National Research Ethics Commission (CONEP) and Research Ethics Committees (CEP)



898 Research Ethics Committees
1,137,275 registered uses on System (the Brazil Platform)
946,166 research projects registered on the Brazil Platform (since 2011)
32,249 institutions registered on the Brazil Platform
33,641 Brazilian, 1,856 foreign
89 approved biobank

3. CONEP's role and change of the system

CONEP's current role is to check documents, analyze protocols, assess risks, the research's social value, researchers' competence, monitor RECs, investigate complaints, and update standards. All of this ensures protection for participants.

New ethical research laws, approved May 28, 2024, bring significant changes, reducing CONEP's authority to analyze higher-risk projects, which weakens the system. RECs will now handle medium and low-risk projects, with CONEP as the appeals body.

Risks from the new law include reduced social control of CONEP, increased conflicts of interest, limitations on post-trial access to treatment, and more flexible standards for sending biological material abroad.

In Brazil, the use of placebo is limited to situations where there is no effective and safe control, and a proposal to expand its use has been removed from the law. A presidential decree will provide further details, and we hope it will reduce risks of to research participants.

Current Role of Conep

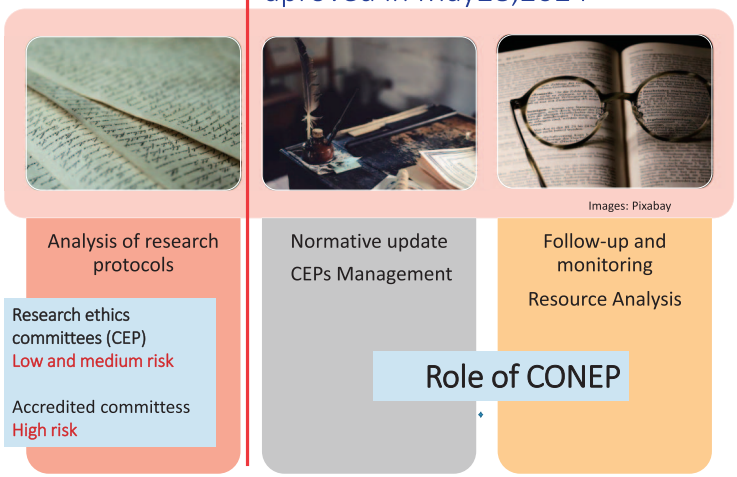
Current characteristics
Multi-professional composition and various áreas of knowledge

Restricted use of placebo, strictly when there is no effective and safe treatment

Post-study access for an indefinite period and under the responsibility of the sponsor

Limits for sending biological material abroad

Modifications included in the new research ethics law aproved in May28,2024



Other risk of the law:

- CONEP to be established outside of social control, with increased risks of conflicts of interests
- Limitations on the right to post-study access to medication/treatment
- More flexible standards for sending biological material outside the country

Day 1 (August 5, 2024)

Discussion

Dirceu Greco
Professor Emeritus of Infectious Diseases and Bioethics, School of Medicine, Federal University of Minas Gerais, Brazil

Chieko Kurihara
Specially-appointed Professor, Kanagawa Dental University

Diego Zanella
Professor of Bioethics, Universidade Franciscana, Brazil

Fernando Hellmann
Department of Public Health at the Federal University of Santa Catarina, Brazil

Greco　What I want to underline is the feeling of déjà vu because what happened in Brazil in the last years in the discussion of the new law mentioned by Dr. Lais Bonilha is exactly what happened with the Declaration of Helsinki after 2000. There was a lot of pressure, especially from the pharmaceutical industry to lower some rights of the participants. Can you imagine we have almost 900 research ethics committees throughout Brazil? This system started in 1996 and it is well-established system linked to the National Health Council. It is made up of so many people from different backgrounds with the inclusion of research participant representatives.

With this new law, the government takes over, and one of its secretaries, who usually have substantial changes every three to six months, will be responsible for handling the system and CONEP's role is being reduced. Many conflicts of interest are likely to occur. An example is that from now on multicenter studies will be analysed and approved by one REC, which will simply communicate the results to the other centers. What will happen is that the pharmaceutical industry will be able to choose which research ethics committee to send its projects to. Local pressure will be needed to ensure that each REC will analyse the local specificities of a project. Another point is the reduction of research participants' involvement. Regarding post-trial access, the current guidelines states that the research project must guarantee all participants free access, for as long as needed, to the best diagnostic and therapeutic methods proven effective at end of the study. Furthermore, access must be granted between the end of individual participation and the conclusion of the study. This can be done through an extension study based on a justified analysis by the doctor assisting the participants.

Due to intense pressures from many stakeholders, post-trial access remains, but the law limits it to five years, or until the drug is incorporated into the National Health System (SUS). SUS covers almost 210 million people, and this will increase costs for the system. It's a bad situation. We tried to maintain the previous directives, discussing it with politicians before the law was passed. We thought they were convinced, but at the time of voting that was not the case. We are now looking for ways to reduce the damage.

Kurihara　Thank you for informing us of the very serious situation with the CONEP system. I think the

CONEP system is great because most of the audience doesn't know much about it. Not only does CONEP handle policymaking and accreditation, but it also analyzes each protocol and provides opinions, such as on placebo use or post-trial access. Professor Greco previously explained that with this system, you can argue to the sponsor company if the protocol is not good. Then, the company may change the protocol based on CONEP's advice. Is that correct?

Greco Yes, that's how it was. When we decided on the resolution with these two aspects, placebo and access, many said it would lower the number of research projects in Brazil because pharma companies wouldn't like it. But that didn't happen [1]. They have specific projects for Brazil, including placebo use and post-trial access. Now, they're happy because they couldn't change Brazil, but removing post-trial access and social control is their goal. We're facing a difficult situation. To answer directly, all high-risk projects were first evaluated locally, then sent to CONEP for dual evaluation.

Zanella I think Laís clearly explained the situation in Brazil, and Dirceu commented well. This new law has reduced the protection of research participants. However, CONEP is fighting to minimize the damage.

Greco I completely agree with Diego, and yesterday I spoke with Laís Bonilha, and she reminded me that perhaps we should help create an association of research participants, like in Japan. Actually, there's one in Brazil, but we must help them—not empower them but help them emancipate and be the reason for change.

As Diego said, our role will be harm reduction. Before this law, we had no formal law on research ethics, but the existing directive worked well for 27 years. It is now fixed in a law that is difficult to change. We could still try to introduce amendments, but it is worth remembering that it took almost 17 years to pass this law! The Brazilian Society of Bioethics, led by Elda Bussinguer is discussing how we can support and protect research participants.

As Laís pointed out, we are all potential research participants. We must work together and share our role.

Kurihara I would like to address Takeo's question regarding the three declarations from Latin American countries, two from 2008 and one from 2013. I invited Fernando because in a book to describe Latin American situation [2] mentions that in 2008 at the WMA General Assembly, the Brazilian Medical Association expressed strong disappointment with the 2008 version of the Declaration of Helsinki. This is recorded in the Declaration's history and is very important. Latin American countries issued declarations rejecting the Declaration of Helsinki due to the weakened placebo clause and post-trial access. These strong objections are historically significant. What is the current agreement among Latin American organizations?

Greco One of the most important positions was the decision of the Latin American and Caribbean Bioethics Network (REDBioethics), known as the 2008 Cordoba Declaration, issued immediately after the approval of the 2008 version of the Helsinki Declaration. It proposed rejecting this version and adhering to the principles of UNESCO's Universal Declaration of Bioethics and Human Rights as an ethical reference

1) Greco D, Invited lecturer. Kimura R, Special guest. Victoria Perottino M, Guest Discussant. Saio T, Kurihara C, Organizers & Discussants. Ethics of international collaborative research: Perspectives from Brazil: Part 1 Selected notes on Paulo Freire: Part 2 Access, Compulsory license, Case Study. *Clin Eval*. 2020; 48(1): 273-301. http://cont.o.oo7.jp/48_1/w95-w123.pdf

2) Homedes N, Ugalde A, editors. *Clinical trials in Latin America: where ethics and business clash.*Springer International Publishing Swizerland. 2014.

mark. In the same direction, the Brazilian CNS and CONEP maintained what was established in the 2000 DoH, regarding placebo and post-trial access. This occurred shortly before the approval of the 2008 version, as it was expected that the two notes of clarification would be included in it. And this actually happened. Let's remember, the Declaration of Helsinki is not a law, countries have no obligation to follow it. So why are we still discussing this? We have been discussing it for almost 25 years. There is no doubt that the Declaration of Helsinki has a global impact, but it is worth mentioning that 2005, Peter Lurie and I published an article in The Lancet criticizing the US FDA decision to remove it from their requirements [3]. It was not the new version, but the one from 1975. The FDA decided that research projects outside the U.S. must follow the Good Clinical Practices (GCP), which is not an ethical document.

That's where we are. We need to stay united. This entire process was described in the chapters of our Springer-published book, on placebo [4] and post-trial access [5].

Kurihara　Fernando, do you have any opinion on this kind of historical analysis on the Brazilian situation?

Hellmann　We always need to consider the politics. For example, in 2008, the National Council of Medicine was more progressive, but now they are denialist. Back then, they were against the Declaration of Helsinki, but not the Brazilian Medical Association, which changed its members.

When Dirceu Greco was representing us, we were pleased because he fought for participants' best interests. However, with the change in leadership, such as the current Vice President of CONFEMEL, who previously opposed the Declaration of Helsinki's placebo and post-trial access flexibilities, politics has shifted. Now, the situation may have changed due to political influences and financial interests.

Our institutions also change with leadership, reflecting different viewpoints. The Brazilian Medical Association was progressive in 2000, 2002, and 2004, but shifted its stance afterward. The World Medical Association's 2013 meetings in Brazil influenced our National Health Research Council to uphold stronger placebo and post-trial access principles. We need to pay more attention to politics and the social environment.

Greco　I remember in 2013, when the WMA GA was held Fortaleza, Brazil, I was invited but not CONEP. I declined the invitation because I didn't think it was right not to include CONEP, the largest research ethics committee in the country. In 2008, the pressure on the Brazilian Medical Association was so intense that they agreed with our position against the changes. We have written about this and for countries like Brazil, Argentina, and other South American nations, we face significant challenges.

Kurihara　I would like to ask Fernando one more question. You mentioned the highest standard versus the minimum requirement. Currently, many believe the Declaration of Helsinki is the highest standard, but it

3) Lurie P, Greco DB. US exceptionalism comes to research ethics. *Lancet.* 2005 Mar 26-Apr 1;365(9465):1117-9.

4) Kurihara C, Greco D, Dhai A, Saio T, Tsubaki H. Ethics of placebo-controlled trials: historical analysis including experiences during the COVID-19 pandemic. In: Kurihara C, Greco D, Dhai A, editors. *Ethical innovation for global health: pandemic, democracy and ethics in research.* Springer; 2023. p. 195-224.

5) Kurihara C, Greco D, Dhai A. Post-trial access: historical analysis considering the experience of COVID-19 pandemic. In: Kurihara C, Greco D, Dhai A, editors. *Ethical innovation for global health: pandemic, democracy and ethics in research.* Springer; 2023. p.225-41.

seems to be evolving into a minimum requirement. I bring this up because I recently presented to the National University Hospital about the proposed revision of the Declaration of Helsinki. The organizer was surprised to learn that Japanese guidelines are considered higher than the Declaration of Helsinki. At present, the Declaration of Helsinki has little impact in Japan, except the inclusion of the Declaration of Taipei. This reaction was unexpected and surprising also for me. What are your thoughts on this?

Hellmann The historical lack of consensus among different associations often leads to ethical guidelines that reflect the lowest common denominator rather than the highest standards. For instance, early drafts of the Declaration of Helsinki did not address specific vulnerable groups like orphans or prisoners, and initially had weaker emphasis on informed consent.

The Declaration of Helsinki should not be considered the highest ethical standard but rather a minimal consensus among diverse international viewpoints. While it has introduced important elements like ethics committee review and post-trial access, it is often more about accommodating varying needs than setting the highest bar for ethical standards.

Historically, institutions like the American Medical Association have adjusted their guidelines to be more accommodating, potentially at the expense of higher ethical standards. Recent changes by bodies like the FDA further reflect this trend.

The Declaration of Helsinki remains crucial, but it's important to recognize it as a baseline rather than the pinnacle of ethical standards. The ongoing efforts to promote higher ethical values, as discussed by experts like Dirceu Greco and Chieko Kurihara, are essential. This includes ensuring that principles like social value are preserved and strengthened in future revisions of the Declaration.

The World Medical Association's challenge is to harmonize diverse and often conflicting perspectives, resulting in guidelines that reflect the minimal common ground rather than the highest ethical standards.

Kurihara Your reflections on the evolving ethical standards and the current state of the Declaration of Helsinki highlight the complexity of maintaining high ethical standards in the face of global pressures and institutional challenges. It's crucial that as a community, we continue to advocate for the highest possible ethical standards while recognizing the practical realities and limitations faced by different stakeholders. Your efforts to align with members of organizations like IFAPP and to navigate the ethical landscape in collaboration with global pharmaceutical entities are commendable. The balance between maintaining high ethical standards and adapting to the realities of regulatory and industry practices is indeed a challenging one.

Now closing time is coming, I would like to request Prof. Dirceu Greco for your closing remarks.

Greco I just want to thank everyone and thank, again, the organizers. Being part of this is very good for Brazil. The presence of the Brazilian Society of Bioethics is notable, especially remembering that during the pandemic and the right-wing government, the Brazilian society of Bioethics played a strong role in the protection of human rights. It's very good to be here with all of you.

I've summarized what the presenters showed. I don't need to add anything because I have already praised them. They were fantastic in their presentations. I particularly liked the highlights by the research participants. I think that's a very good point. Of course, it is important to have IFAPP with us, since this is not the usual position of many research doctors in Brazil. It's nice to have this example. We talked about this before, and IFAPP position was clear and intense, very similar to ours.

It is an honor for me to represent today the Brazilian Society of Bioethics. As I said before, unfortunately,

our President Elda Bussinguer could not come today and has sent her apologies. She will be here on the 26th. I'm glad to have so many people together in these three hours, at different times around the world. This reinforces that, our role is to be together, fight together, and add more participants everywhere. Remember what happened with the AIDS epidemic: in national and international meetings, there are people living with HIV participating in all discussions. It's the same as we mentioned in relation to the essential involvement of research participants.

Our goal is to be modest enough to recognize that we don't know many things and that we need to stand together. Although the Declaration of Helsinki now seems to be the lowest common denominator of ethics, we must modify it reach the highest achievable standard. Each country can and should establish more stringent and protective guidelines than the Declaration of Helsinki. We have to keep this in mind. It's not a war but a tabula rasa, as they say in Latin. We need to put the truly necessary discussions on the table.

Day 2 (August 26, 2024)

Welcome Remarks from the representatives of organizers

Varvara Baroutsou
President of the International Federation of Associations of Pharmaceutical Physicians & Pharmaceutical Medicine (IFAPP)
Consultant in Internal Medicine and in Pharmaceutical Medicine, Athens

Elda Coelho Azevedo Bussinguer
Full Professor at the Faculty of Law of Vitoria (FDV, Brazil)
President of the Brazilian Society of Bioethics (SBB)

Dirceu Greco
Professor Emeritus of Infectious Diseases and Bioethics at the School of Medicine, Federal University of Minas Gerais, Brazil
Member of the UNESCO International Bioethics Committee
Associate Member of the World Medical Association

Varvara Baroutsou Hello everyone. It is my great pleasure to welcome you all to today's webinar, which will certainly enrich our perspectives and discourse. I would like to express my special thanks to the organising committee for their great efforts. I owe a big thank you to all the distinguished speakers, and I would also like to thank each and every participant.

This webinar is very important. It is the second of the series in August, and the topic is of course so timely and important in light of the ongoing revision of the Declaration of Helsinki. I feel that we all have a role to play in contributing our input, because there is a potential for actionable influence on the ongoing discussion. Actionable change is a possibility, and so I invite everyone to speak up, and the input will be very much appreciated.

This is a precious moment, and without further ado I invite everyone to stimulate the dialogue and the debate, to inspire each other, so that we can have some great concluding remarks and proposals. Thank you for the invitation and I look forward to the discussion.

Elda Coelho Azevedo Bussinguer Hello, everyone. It's a pleasure to be here with the Brazilian Society of Bioethics. I send my best regards to the organization and this meeting. You've done a great job, and I'm happy to represent the Society.

The far-right is rising globally, threatening human rights and bioethics progress. We must stand together—Brazil, Japan, and all participants. United, we can counter negative trends.

Brazil faces challenges, even with the new president. The far-right is positioning itself for the upcoming elections. They may reverse recent advances, and this is happening globally. Being together gives us a chance to make a difference in human rights and bioethics research.

We must remain united to confront challenges. Scientific advancement cannot happen without respecting

human rights and dignity. That's why we're here.

The Brazilian Society of Bioethics is with you. We will stand by your side, fighting for necessary changes. Even if we can't make those changes, we will still be here, ensuring we make things better.

(Spoken in mother language and interpreted in English by Dirceu Greco. Same hereafter.)

Dirceu Greco　Hello, everyone. I am from Belo Horizonte, Brazil. I'm honored to co-organize the second day of this webinar. Today, I share the opening remarks with Elda Bussinguer, President of the Brazilian Society of Bioethics, and Varvara Baroutsou, President of the International Federation of Associations of Pharmaceutical Physicians & Pharmaceutical Medicine (IFAPP). As you know, this event is co-organized by many important entities. I'm not going to list them because they are in the program.

We are meeting at a special moment. There are two months left until the General Assembly (GA) of the World Medical Association where the new version of the DoH will be discussed and approved. The GA will be held in Helsinki, Finland on October 19th. The Declaration of Helsinki, first approved in 1964, will be celebrated for its 60th anniversary. It is a globally respected document in human research ethics. Its guidelines must reflect the need for unequivocal support for human rights and the protection of research participants. I hope we will have a productive and comprehensive debate on these important topics.

Day 2 (August 26, 2024)

Participation in WMA meeting in Washington DC: Taking forward bioethics and human rights, maximizing the impact of the NEW DoH

Chieko Kurihara
Specially-appointed Professor, Kanagawa Dental University
Member of the Japan Association for Bioethics
Member of Ethics Working Group of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)

1. Introduction

I will briefly report my participation in World Medical Association (WMA) meeting in Washington DC. My talk is for "taking forward bioethics and human rights", objective of this webinar. And for "maximizing the impact of the NEW DoH", which is the objective of my session at WMA's meeting.

Today we invited Peter Lurie as a guest commentator. We met at the venue of the WMA meeting in Washington DC, although he did not attend the WMA meeting. I wish to introduce his achievement as background of placebo debate.

2. Historical background

Just a bit about historical issue. During the HIV/AIDS pandemic, Prof. Dirceu Greco took a role of principal investigator of vaccine trial and there is a good example of community engagement to improve study protocol while negative image of mass media against "human experimentation". He has been also engaged in governmental HIV program as well as clinical practice.

One big event was establishment of the best-proven intervention to prevent perinatal transmission. After the establishment of the best proven intervention, in 1997, Peter opened the international debates on injustice of placebo-controlled trials, sponsored by developed countries and performed in developing countries, which could not be performed in rich countries. In 2005, his paper with Greco criticized the FDA to abandon the requirement for adhering the Declaration of Helsinki (DoH) for clinical trials outside US, replacing it with the ICH-GCP [1].

1) Lurie P, Greco DB. US exceptionalism comes to research ethics. *Lancet.* 2005 Mar 26-Apr 1;365(9465):1117-9.

3. Crisis of the Declaration of Helsinki

This is my rapid response[2] to a BMJ paper, expressing objection to the DoH 2002 Note of Clarification to permit high risk placebo-controlled trials, which is as if a Guidance for Industry. Such text in the DoH is still now continuing.

4. Webinar to discuss placebo, access during COVID-19 pandemic, June 2021

We also discussed injustice of placebo studies and importance of post-trial access during the COVID-19 pandemic. This led to the proceedings[3] and Springer book publication[4].

5. Discrepancy between DoH and CIOMS

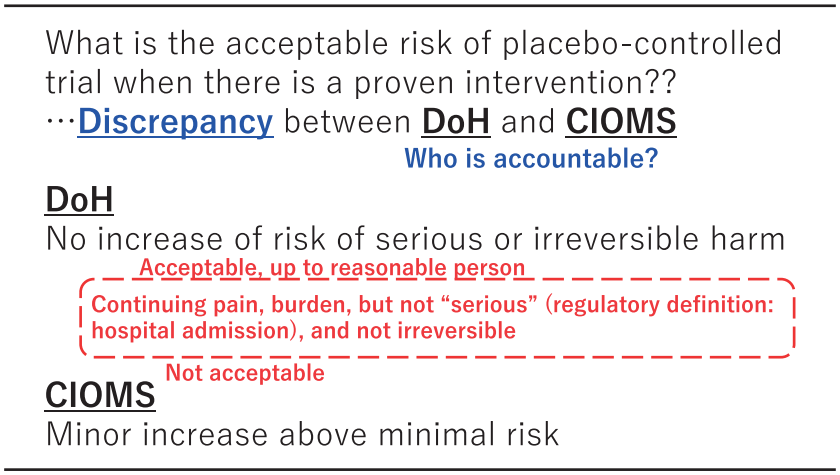
What is the acceptable risk of placebo-controlled trial when there is a proven intervention? There is **Discrepancy** between **DoH** and **CIOMS** (Table 1).

DoH states: No increase of risk of serious or irreversible harm

CIOMS states: Minor increase above minimal risk

Between these two, there are risks of continuing pain, burden, but not "serious" (regulatory definition: hospital admission), and not irreversible. These are acceptable for the DoH, but not acceptable for COMS.

Table 1　Discrepancy between the DoH and CIOMS of the acceptable risk of placebo



2) Kurihara C, Mitsuishi T, Nudeshima J. Rapid response: Crisis of the Declaration of Helsinki becoming a guidance for industries. 2003 Sep 25. thebmj. https://www.bmj.com/rapid-response/2011/10/30/crisis-declaration-helsinki-becoming-guidance-industries

3) http://cont.o.oo7.jp/49sup38/49sup38contents_e.html

4) Kurihara C, Greco D, Dhai A., editors. *Ethical innovation for global health: pandemic, democracy and ethics in research.* Springer; 2023.

6. North American regional meeting on the Declaration of Helsinki, held by AMA and WMA

Next I will introduce the discussion at the Washington DC meeting held by the WMA to discuss about the revision of the DoH, which is the final occasion where external stakeholders can participate. There are several topics to be discussed.

Just about some impressive discussions.

There were unanimous voices supporting inclusiveness of vulnerable people.

"Social value" was once included but deleted in the second draft. Still now it does not come back.

It was surprising that all the US government representatives, FDA, OHRP, NIH, CDC, argued to deregulate the DoH, core principle to prioritize patient interest to goal of research; disregard Taipei Declaration and post-trial access. Korean bioethicist and I expressed objections to defend these core principles in the DoH.

The last session was for maximizing impact of the New DoH, where I argued the importance of these principles.

7. Maximizing the impact of the DoH

The session of my participation was titled "Maximizing impact: Communication, advocacy and implementation". The moderator was the current president of the WMA, Speakers are Secretary General of the WMA, immediate past president of CIOMS, who are WG chair of the research guidelines, and representative from patient organizations, and I represented IFAPP, but talked a personal opinion.

I introduced discussions on the DoH and Springer book in which patient and public expressed their opinions on the DoH.

The book got a lot of readers worldwide and we are planning NEXT book to discuss on the New DoH. I argued that this book could maximize the impact of the NEW DoH, including debates during the revision process, which will improve the actual practice of clinical research.

8. What is the value of the NEW DoH?: Key concepts missing in the new DoH

The question is whether the DoH is highest ethical standard or minimum requirements.

This Table shows how key concepts are missing in the proposed draft (Table 2). Most of these items are in CIOMS, opinions form patient groups, IFAPP; Japanese guidelines already incorporated many of these items, but missing in the New DoH. It is surprising because Japanese people believe that the DoH is No. 1.

Table 2　Established key concepts missing in the proposed draft of the revision of the DoH

Protection items	DoH	CIOMS*1	Patient group	IFAPP*2	GL Japan	GCP (R3)	Brazil	
Social value	–	◎	◎	○	◎	–		
Community Engagement/Patient Public Involvement	△incomprehensible	◎	◎	◎	–	◎		
Benefit Sharing	–	◎	◎	○	–	–		
Avoid Discrimination/Stigmatization (risk to target group)	–	◎	◎	–	○	–		
Consider Future Generations/Sustainability	△	–	◎	–	–	–		
Inclusiveness of the vulnerable	–	◎	○	◎	–	–		
Right to know/not to know the result (including incidental findings up to the status of information)	– (△)	◎	◎	◎	◎	–		
Broad informed consent/dynamic consent	–	◎*1	◎	◎	○	–		
Fairness of REC/Patient Public Involvement (democracy)	–	◎	◎	◎	○	○		

*1: “Dynamic consent” is not in health research guidelines but in Report XI for patient engagement.
*2: Not official opinions of IFAPP, but of some members of IFAPP.
◎Strongly argued ○medium △weak or not explicit

Protection items	DoH	CIOMS *1	Patient group	IFAPP *2	GL Japan	GCP (R3)	Brazil	
Best proven/risk minimization in comparative arms	–	◎	◎	◎	–	–		
Post-trial access for participant (informed consent form), community (for those most in need globally)	△	○	◎	◎	△	–		
Publication ethics (research integrity) items	DoH	CIOMS	Patient group	IFAPP	GL Japan	GCP (R3)		
Open Access (to result published in journal)*3	△	–	◎	–	–	–		
Result publication in public database	△	◎	○	◎	◎	◎		
Individual participant data (IPD) sharing (Open Science)	–	◎	○	◎	△*5	–		
Clinical use of unproven intervention*4	**DoH**	**CIOMS**	**Patient group**	**IFAPP**	**GL Japan**	**GCP (R3)**		
Data accumulation	–	–	○	△	–	–		
Safety/efficacy monitoring	–	–	○	△	–	–		

*3: Open Access (to full rext) is coming to be mandated for public-funded studies in US, EU, Japan but not yet included in human research guidelines.
*4: Points missing in the DoH comparing with WHO-MEURI were discussed in patient and public group.
*5: Not in ethical research guidelines for non-interventional studies/surgical study etc. but in Clinical Research Act and GCP for clinical trial of medicinal products in Japan.
◎Strongly argued ○medium △weak or not explicit

9. My proposal

This is my proposal at the end of my talk. First, missing items in the Table 2 should be filled, according to CIOMS.

Second, placebo-controlled trial, risk should be minimized according to CIOMS. “serious or irreversible harm” such terminology as guidance for industry should be deleted. It is not for the Declaration of Helsinki, which is Ethical Principles.

Third, Post-trial access should be assured for all who need it. The proposed draft states “Exceptional case must be approved by ethics committee” such kind of excuse is not necessary, should be deleted. Post-trial access should be assured for study participant; trial host community, and finally those most in need world-wide.

10. Actions for the future

Continuing expression of objections and clarifying missing items in respectful matter would be important for the improvement of the impact of the New DoH.

Continuing collaboration with the WMA to fill the missing items and caring for contested opinions would contribute to **better protections of research participants**. It would be achieved by:

- Publications of books, papers;
- Webinars; In-person meetings;
- Actual research practice, ethics committee reviews, etc.

Let’s start preparation for the **next 10 years**!

11. Meet at Helsinki!

The new DoH will be adopted at the General Assembly of the WMA in October.

Some of us will have a web/in-person meeting, so we wish you to join.

We hope that you visit these websites to upload continuous discussions [5].

5) http://cont.o.oo7.jp/sympo/eigh.html

Day 2 (August 26, 2024)

Collaboration with the WMA and the IFAPP's perspective

Varvara Baroutsou
President of International Federation of Associations of Pharmaceutical Physicians & Pharmaceutical Medicine (IFAPP)
Consultant in Internal Medicine and in Pharmaceutical Medicine, Athens

1. Introduction

I will share my personal views, literature data and our work within the International Federation of Associations of Pharmaceutical Physicians & Pharmaceutical Medicine (IFAPP). I appreciate the contributions of the members of our Ethics Working Group to our community efforts.

I am a physician, President of IFAPP and a member of the Executive Committee of the Council for International Organisations of Medical Sciences (CIOMS). I work with academia in Greece. I'm a graduate of the Stavros Niarchos Foundation Bioethics Academy and member of the IFAPP Ethics Working Group. I have no conflict of interest to declare, and being part of the IFAPP Ethics Working Group and of the IFAPP Board is a great experience.

I hope to contribute some useful data or views to the discussion.

First, I'd like to mention my expectations of the Declaration of Helsinki as a physician and former clinical investigator. I want this new version to be clear and to protect human participants. I want benefits and risks to be shared fairly. I want more care and concern for vulnerable patients and poor, low/middle income countries with few resources. I have modern expectations about current ethical challenges, such as new technologies, artificial intelligence and advanced genetic tools. I hope we'll overcome the placebo problem in the era of accelerating artificial intelligence and genetic tools and inventions.

The World Medical Association (WMA) has launched a major consultation process. We tried to participate in all the public comment periods and attended most of the regional meetings. Global openness and cooperation are important. We hope that all voices and suggestions will be heard, even at the last moment. I felt we had to contribute and participate in these periods.

Recently, there have been interesting and intriguing publications commenting on the Declaration of Helsinki [1, 2], which have sparked debates in various countries. I'm sure you're aware of them, and the titles indicate the challenges that need to be addressed.

1) Menikoff J. Protecting Participants Is Not the Top Priority in Clinical Research. *JAMA.* 2024 Jul 16;332(3):195-196. doi: 10.1001/jama.2024.7677.
2) Hellmann F, Marceau E, Cruz R. 60th anniversary of the Declaration of Helsinki: ethical challenges in the 10th amendment. *J R Soc Med.* 2024 Aug 20:1410768241261758. doi: 10.1177/01410768241261758. Epub ahead of print. PMID: 39163296.

2. IFAPP Ethical Journey

As IFAPP, the International Federation of Pharmaceutical Associations, we're a purpose-driven organisation that promotes ethical and innovative leadership in Pharmaceutical Medicine. Our primary value is to offer benefits to our members. We emphasise the empowerment of our members in terms of ethics and competencies so that they adhere to the highest professional standards, including ethical standards. We seek to network with key stakeholders in medical research and R&D to present our views and proposals. We want to maintain an open dialogue with our communities and external stakeholders.

This is why we have our IFAPP TODAY journal, IFAPP LinkedIn, we post all our activities on our website and run webinars on ethics. We invite participation and discussion on ethical issues at our flagship event, the International Conference of Pharmacovigilance Medicine (ICPM), which will take place in Amsterdam in April 2025, where we will have a roundtable on the new revision of the Declaration of Helsinki.

I'd like to briefly go through the IFAPP's ethics journey and explain what we do for ethics, what we have done so far for the current revision, and what we will continue to do.

In terms of internal rules, we have a code of conduct for all our members and the board. This is part of the IFAPP constitution. We also have an ethical framework for our members, mainly doctors but also other health-related biomedical professionals. Externally, we try to present our ideas through public consultations, peer review requests and opportunities to talk about ethics in our webinars.

In terms of the ethics framework for our professionals and IFAPP members, we're currently discussing moving to a new edition, the third one. We need to streamline priorities and core principles to update and introduce them to our members.

In terms of our regular activities, the Ethics Working Group is the most active, prominent and internationally involved working group. I'm proud of all the members. It's a hard-working group, with monthly meetings, events, and I'm proud of all the team members. The Ethics working group has, constructive agenda, and peer review papers, major contributions to our journal IFAPP TODAY, close collaboration and meetings with WMA, joint projects such as the extraordinary book "Ethical Innovation for Global Health", and more to come.

We're closely associated with CIOMS, supporting working groups and specific papers. A recent one was on research governance. We also contributed to the Real World Data booklet published this summer.

3. Collaboration with the WMA

With WMA we have a systematic collaboration, a Memorandum of Understanding, and we work together on all projects of common interest. The WMA Declaration of Helsinki is a top priority for both IFAPP and WMA. We've had several meetings between us. In 2019, we submitted our opinions to WMA, which were later reported in IFAPP TODAY [3, 4]. In 2021 we collaborated on the webinar on placebo and post-trial access during COVID-19 [5]. In 2022, when we had the session with WMA during our International Congress, ICPM in Athens [6].

Then we met with WMA representatives at our IFAPP regional meeting in Amsterdam [7]. We didn't miss

any opportunity to attend WMA meetings. Chieko Kurihara has been to Tel Aviv, Sao Paulo [8] and most recently Washington DC. I was in Copenhagen [9]. And at the WMA General Assembly in Helsinki, Chieko Kurihara, Kotone Matsuyama and I will send a strong signal from the IFAPP.

I'm sharing the evidence of the meetings and the publications related to the meetings for your information. They refer to the activities of 2022 and 2023.

Here I present the 12 proposals (Table 1) that I made in Copenhagen last year, items that we felt should be updated or included in the ongoing revision. We didn't succeed in all of them, but we will continue to try.

Table 1　Twelve proposals from IFAPP: items for update in the ongoing revision of the Declaration of Helsinki

1. Connection of Declaration of Helsinki (DoH) & Declaration of Taipei (DoT)
2. Ethical approval & consent for secondary use of data
3. Incidental findings
4. Registration of "data sharing plan" and study results in public databases
5. Shared responsibility
6. Patient & Public involvement plan
7. Diversity of membership & qualified experience of Research Ethics Committees (REC)
8. Terminology aspects of human subjects & humans, participants, etc.
9. Medical research for common nomenclature between organisations
10. Placebo use wording & alignment of wording CIOMS &WMA (paragraph 33 DoH)
11. Vulnerable population
12. Post trials access

3) Kurihara C, Baroutsou V, Becker S, Brun J, Franke-Bray B, Carlesi R, Chan A, Collia L, Kerpel-Fronius S, Kleist P, Laranjeira LF, Matsuyama K, Naseem S, Schenk J, Silva H. A proposal for the Revision of the Declaration of Helsinki to promote data-driven science and strengthening human subject protection. *IFAPP TODAY.* 2021; Nov/Dec (19): 13-5. https://ifapp.org/wp-content/uploads/2021/12/IFAPP-TODAY-19-2021.pdf

4) Kurihara C. IFAPP Recommendations for the Revision of the Declaration of Helsinki, Version 2013. *IFAPP TODAY.* 2022; Jan (20): 3-7. https://ifapp.org/wp-content/uploads/2022/01/IFAPP-TODAY-20-2022.pdf

5) Kurihara C. Webinar COVID-19 and Bioethics - Pandemic and Research Ethics: Democracy, Placebo and Post-Trial Access. *IFAPP TODAY.* 2021; Jul/Aug (16): 4-7. https://ifapp.org/wp-content/uploads/2021/07/IFAPP-TODAY-16-2021.pdf

6) Kurihara C, Crawley FP. Future revision of the Declaration of Helsinki: Dialogue with WMA in Athens. *IFAPP TODAY.* 2022; Nov/Dec (29): 5-8. https://ifapp.org/wp-content/uploads/2022/11/IFAPP-TODAY-29-2022.pdf

7) Kurihara C. Discussion in Amsterdam on Data-driven Research and the WMA Declaration of Helsinki. *IFAPP TODAY.* 2023; Sept (37):5-9. https://ifapp.org/wp-content/uploads/2023/09/IFAPP-TODAY-SEPTEMBER-2023-37.pdf

8) Kurihara C. Discussions for the Next Revision of the Declaration of Helsinki: Meetings of the WMA and IFAPP. *IFAPP TODAY.* 2023; May (34):8-12. https://ifapp.org/wp-content/uploads/2023/05/IFAPP-TODAY-34-2023.pdf

9) Baroutsou V. Exploring New and Emerging Trial Designs Considering the Revision of the Declaration of Helsinki. *IFAPP TODAY.* 2023; Nov/Dec (39): 14-17. https://ifapp.org/wp-content/uploads/2023/11/IFAPP-TODAY-39-2023.pdf

4. Continuous discussions in meetings, articles, peer-reviewed papers

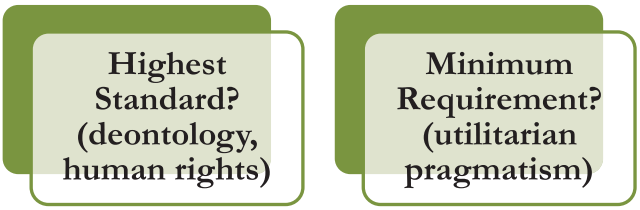
IFAPP doesn't hesitate, and we ask ourselves: are we aiming for the highest standard or the minimum? (Fig. 1) Let's see what we have done (Table 2).

We started at the beginning of 2020 with a peer review paper proposing to link the Declaration of Helsinki with the Declaration of Taipei because of the data-driven research and biobanks that are a key feature of medical research [10]. I think the link between the Helsinki and Taipei Declarations is well known. I commented that we need to clarify this, especially for the use of secondary data. The link will be very helpful.

In April 2024, we published the "Declaration of Helsinki ethical norm in pursuit of common goals" [11]. In our paper, we discussed data-driven research, broad consent, dynamic consent, participants' rights, sharing of individual patient data, open science, social value, minimising risk in placebo-controlled trials, post-trial access to best proven interventions, and co-creation with stakeholders of future-oriented research frameworks.

Another article on vulnerability, social value, placebo and post-trial access is in final review and should be published soon [12]. In the last submission, we tried to address the issue of vulnerable trial participants and promote diversity. We have emphasised social value as a prerequisite for everyone, especially vulnerable people, and continue to debate and challenge placebo-controlled trials. We believe that ethics reform to achieve social value and equitable global health is obvious and common sense because medical research aims to improve human health.

Fig. 1 A question about the revision of the Declaration of Helsinki



10) 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

11) 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.

12) Kurihara C, Greco D, Dhai A, Matsuyama K and 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

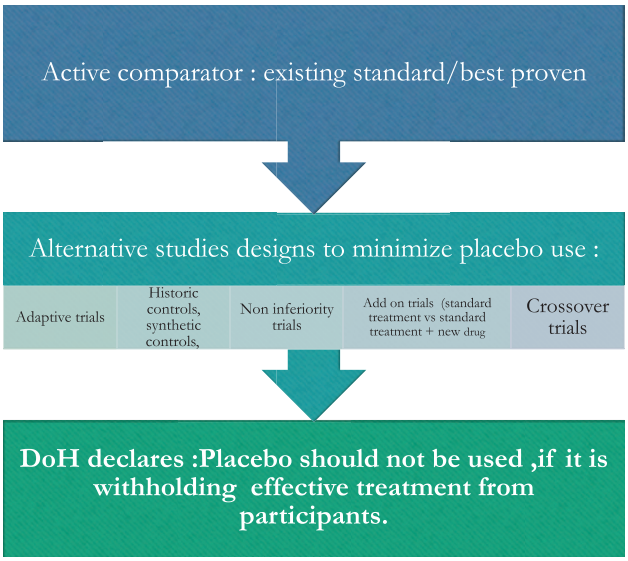
Table 2　Continuous discussions in meetings, articles, peer-reviewed papers for the revision of the Declaration of Helsinki

Meetings		
Sessions with WMA at IFAPP meetings		
Year, Month *Meeting venue*	*Title of the session*	*Speakers invited from the WMA*
2022 October ICPM Athens	IFAPP Workshop on the future revision of the Declaration of Helsinki: Dialogue with the WMA	Hybrid, Jack Resneck, Workgroup chair for DoH, Otmar Kloiber, Secretary General of the WMA, online invited
2023 June IFAPP Regional Meeting Amsterdam	IFAPP & WMA Workshop on the Revision of the Declaration of Helsinki focusing on Data-Driven Research	Hybrid, Daniel Fu-Chang Tsai, WG member for DoH, Jeppe Berggreen Høj, advisor of the WMA, online invited
Sessions with IFAPP at WMA Regional Meetings, General Assembly		
Year, month *Meeting venue*	*Topics*	*Participants from the IFAPP*
2022 December Tel-Aviv	General Data-driven research	Chieko Kurihara, EWG of the IFAPP, participated
2023 February Sao Paulo	Placebo-controlled trial	Chieko Kurihara, EWG of the IFAPP, participated
2023 September Copenhagen	Emerging trial design	Varvara Baroutsou, President of the IFAPP, invited as a speaker
2024 August Washington DC	General Maximizing impact of the DoH	Chieko Kurihara, EWG of the IFAPP, invited as a speaker
2024 October, Helsinki, General Assembly	Adoption of the 2024 revision of the DoH	Varvara Baroutsou, Chieko Kurihara, and Kotone Matsuyama, EWG Chair of the IFAPP will participate
IFAPP TODAY articles		
Year, Month, *No. pages*	*Title, Topics*	
2021 Jul/Aug No. 16: 4-7	Webinar on COVID-19 and Bioethics: Pandemic and Research Ethics: Democracy, Placebo, and Post-Trial Access.	
2021 Nov/Dc No. 19: 13-15	A proposal for the Revision of the Declaration of Helsinki to promote data-driven science and strengthening human subject protection.	
2022 Jan No. 20: 3-7	IFAPP Recommendations for the Revision of the Declaration of Helsinki, Version 2013 • General, whole the construction of the DoH	
2022 Nov/Dec No. 29: 5-7	Future Revision of the Declaration of Helsinki: Dialogue with the WMA in Athens. • General, whole the construction of the DoH	
2023 May No. 34: 8-12	Next Revision of the Declaration of Helsinki: Meetings of the WMA and IFAPP. *IFAPP TODAY.* • General, whole the construction of the DoH (Tel Aviv) • Placebo-controlled trial (Sao Paulo)	
2023 Sep No 37: 5-8	Discussion in Amsterdam on Data-driven Research and the WMA Declaration of Helsinki.	
2023 Nov/Dec No 39, 15-17	Exploring New and Emerging Trial Designs Considering the Revision of the Declaration of Helsinki	
Book, peer-reviewed papers		
Year, Month	*Title, topics*	
2020 Jul	Linking the Declarations of Helsinki and of Taipei: Critical Challenges of Future- Oriented Research Ethics.	
2023 Nov	Ethical innovation for global health: pandemic, democracy and ethics in research. Springer (Several number of chapters are contributed from the members of the IFAPP)	
2024 Apr	Declaration of Helsinki: ethical norm in pursuit of common global goals • Data-driven research • Broad consent, Dynamic consent • Participants' rights, Individual patient data sharing • Open science • Social value • Risk minimization in placebo-controlled trials • Post-trial access with best proven intervention Co-creation with stakeholders in future-oriented research frameworks	
2024 Sep	Vulnerability, social value and the equitable sharing of benefits from research: beyond the placebo and access debates	

5. Placebo-controlled trials (Fig. 2)

Regarding placebo-controlled trials, I wonder how we can still discuss placebo when there are so many alternatives that even regulatory authorities are suggesting [13]. We can use active comparators, existing standards and best proven treatments. There are many drugs available today, but I can't believe that there is nothing we can use as a reliable comparator, an active comparator.

Fig. 2 Placebo-controlled trials and considerations on alternatives



We also have neutral designs such as adaptive trials. We can use historical or external controls by using real-world data, non-inferiority trials, add-on trials, crossover trials. We still insist that we should not deprive patients of effective treatments.

Now, I would like to respond to how the Declaration of Helsinki is seen or received by regulatory authorities. A paper published in 2018 [14], based on a questionnaire with international regulatory authorities, including FDA, EMA, Japan and Korea, found that they consider the Declaration of Helsinki to be the minimum ethical standard. The use of the most current effective treatment as a comparator is preferred to avoid the abuse of placebo-controlled trials, which are ambiguous and open to different interpretations.

Recently, we have a lot of scientific evidence and regulatory guidance that will allow us to work with

13) Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Oncology Center of Excellence. Guidance document (draft). Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. February 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products

14) Skierka AS, Michels KB. Ethical principles and placebo-controlled trials - interpretation and implementation of the Declaration of Helsinki's placebo paragraph in medical research. *BMC Med Ethics.* 2018 Mar 15;19(1):24. doi: 10.1186/s12910-018-0262-9.

model-based drug development and in silico trials going forward.

We're in an era of artificial intelligence, which is accepted in Europe and the US for medical devices, clinical trials and research and discovery of new medicines. We have an AI law in the EU and need to focus on other important and challenging technologies to ensure they're safe for patient use.

6. Final recommendations for the DoH revision

If I can summarise the recommendations (please see Table 3), I think we should be guided by the highest ethical standards to use the best proven intervention in the world. Personally, I can say that in reviewing the literature, I see that most active comparators in clinical trials may not even be the best, for various prominent reasons. Drugs that don't use the best proven intervention may be held back by health technology assessment committees that don't want to invest in them. We have many reasons, beyond science, technology and affordability, to choose the best proven intervention.

Table 3　Final recommendation for the revision of the Declaration of Helsinki

- Be our guide of "**highest ethical standards**"
    - DoH to ensure consistency with CIOMS
- **Best-proven intervention in the world must be assured in any comparative** arms and risk should be minimized (as in CIOMS)
    - Ethics committee excuse in post-trial access paragraph should be deleted.
    - **Leaving the placebo paragraph open to various interpretations will continue the controversy**
    - **Post trial access** should be assured in protocol/consent form to:
        - study participants
        - host community
        - those most in need worldwide

Post-trial access is something we cannot stress enough. It's important for trial participants, for the community in which the trial takes place, and for all those in need around the world.

Next, we will continue to base our proposals on our core ethical principles: autonomy, beneficence, non-maleficence and justice. We believe that ethical considerations are important determinants of the design and conduct of research studies, and we will continue to do so.

In parallel, we need to initiate debates on issues related to new genetic technologies, genetic privacy and data security, artificial intelligence in research and development, equity and access to genetic therapies, pricing, and so on.

Discussion

Chieko Kurihara　I would like to confirm the placebo language of the Declaration of Helsinki, from the view point of your professional expertise engaged in design and conduct of clinical trial. There is a controversy, at least a discrepancy between CIOMS and the DOH of the language of acceptable risk of placebo-controlled trial when there is a proven intervention. Do you think it is possible to change the language from

DoH to CIOMS without losing valuable, and necessary studies to improve individual or public health?

Baroutsou From Copenhagen discussions, I understood that WMA aims to produce a high-level principles document. They don't see their work as detailed. They simply refer to principles. CIOMS translates these principles into actionable guidelines that are hopefully adopted by ICH and regulatory authorities. This is the implementation pathway.

I propose using these three documents synergistically. Follow the highest standards in each of these three fundamental documents in real life. Regulatory authorities screen and scrutinize protocols. EMA is stricter than FDA, and research ethics committees should do their proper job.

We can think we're in a synergistically working system. With WMA, I have to say what I heard there. I respect that they're the high-level principles organization that gives the direction. The direction should be translated into guidelines and legal binding documents by regulators for application.

However, given that the Declaration of Helsinki is considered the top principle organization on medical research and is respected by regulatory authorities, as mentioned in the 2018 study, we should try to convey the message to the Declaration of Helsinki Working Group and WMA that their intervention will be critical worldwide for increasing the level of ethics in research.

Kurihara I agree we should use the Declaration of Helsinki and CIOMS documents together. I heard WMA and CIOMS people say the DOH should be the highest ethical standard, not detailed. However, the placebo paragraph is too detailed. It's not the language of ethical principle. It's strange they say the DOH should be the highest ethical standard but leave the placebo paragraph as it is. It's too much detailed guidance for industry. This is my argument, but it's not argued to you. I have to continuously tell the WMA this issue.

Dirceu Greco We need to discuss this in depth and before the Helsinki meeting. The Declaration of Helsinki has changed over the years, getting worse. In 2000, it was very clear on the limits to placebo use and on the right to post-trial access. After that, it changed for the worse. And then we have the CIOMS guidelines.

I was part of the working group for the 2016 CIOMS guidelines. The placebo issue was contentious. We were 12 members arguing about what to do. None of these documents are binding, especially not the Declaration of Helsinki. There are possible solutions. As I mentioned before Brazil decided in 2004 not to follow the Declaration of Helsinki. It kept the requirements included in the 2000 version. We should not expect anything to improve at the next meeting in October.

For many reasons, we have tried to propose changes. We have sent many proposals over the last few months, but none have been included. The worst didn't even mention social value. To discuss with our students, I think we need to set the bar very high. What's the real need for a clinical trial? It must have social value, respect people, and have post-trial access.

My opinion is that the placebo shouldn't be used when there is a proven intervention. I liked what you proposed, which is the same as us. There are many alternative designs. Maybe with this we can continue to respect each other. I respect what the WMA have been doing for 60 years, but not for the current situation.

After 2002, the notes of clarification watered down everything that it was achieved in 2000. I will say that again in my presentation. I think it's a discussion for all of us, what can we do as individuals, participants, and researchers.

Day 2 (August 26, 2024)

Access and equity in research: Justice, vulnerability and low-resource settings

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South African Medical Association

Introduction

I'll talk about access and equity in research, focusing on justice, vulnerability, and low-resource settings. I've included all world regions because low-resource settings aren't limited to low- and middle-income countries. High-income countries also have low-resource settings.

The South African Medical Association is a member of the World Medical Association Working Group on the revision of the Declaration of Helsinki. I'm Vice Chair of the Board of the South African Medical Association. I won't refer to the Declaration of Helsinki in my talk.

Here's the outline of my talk. Here are my priority resources [1~3].

Equity in health and research

Let's unpack equity in health and research. They're closely related. Health equity means everyone has equal opportunities and resources to access health. This aligns with the WHO 2018 definition of health equity, which is "the absence of avoidable or remedial differences amongst groups of people, whether those groups are defined socially, economically, demographically, or geographically." This notion of health equity is based on the concept of social justice, making it ethically immoral and unjustifiable to have differences in access to health.

How does this translate to research equity? Let's draw from the definition of health equity to look at the definition of research equity. It boils down to those affected by research or who can benefit from its outcomes

1) 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/
2) Council for International Organizations of Medical Sciences. Clinical research in resource-limited settings. 2021. https://cioms.ch/publications/product/clinical-research-in-low-resource-settings/#description
3) United Nations Educational, Scientific and Cultural Organization. Universal Declaration on Bioethics and Human Rights. 19 October 2005. Available at: https://www.unesco.org/en/legal-affairs/universal-declaration-bioethics-and-human-rights?hub=66535

having equal opportunities to contribute to it and benefit from it. Research equity includes those absent or silent in research, those deliberately left out. If we have research on everyone who needs help, research equity is an important means of addressing health equity.

In terms of the CIOMS 2016 Guidelines, Guideline 3 is important for the equitable distribution of benefits and burdens in selecting individuals and groups of research participants in research. This means no group or class of persons should bear more than their fair share of risks or burdens from research participation. Equitable distribution would allow participants to be drawn from the qualifying population in geographical areas of study where the results can be applied. There should be no unfair discrimination regarding inclusion and exclusion criteria, based on various issues like privileged disadvantage, race, sex, etcetera. If there's underrepresentation in research, health disparities will be perpetuated.

Research benefits must address the diverse needs across different classes or groups of people. It's unjust to selectively include disadvantaged individuals or groups. They already have risks and burdens. Selectively including them for the benefit of a privileged few exposes them to even more risks and burdens.

They can be overused in research. They're most likely to be excluded from research benefits or have difficulty accessing them, especially when there isn't a commitment to post-trial access. Broader inclusion of different social groups will help ensure research is conducted in a socially and ethically acceptable manner.

Social value

I want to look at Guideline 1, of the CIOMS Guidelines, which talks about scientific and social value and respect for rights, especially considering social value is no longer included in the revision of the Declaration of Helsinki.

Why do we need social value? The information the study produces must be able to promote individual or public health. The research would have social value if the endpoints are related to clinical decision-making and if clinicians, policymakers, and others are likely to alter their practice based on study findings. Only if the research has social value can we justify the associated risks, costs, and burdens of the research in that particular locale or setting. It's disappointing that this has been left out.

Research conducted in low-resource settings

Guideline 2 is specific to research conducted in low-resource settings. These guidelines highlight that where there are low resources, there is vulnerability to exploitation. If we're going to be doing research in low-resource settings, local social value must be created. There must be a critical benefit. They also highlight that the responsiveness of research to help needs and priorities is important to provide social value to communities and populations. There has got to be a shared responsibility in terms of providing social value. This shared responsibility would be shared by sponsors, funders, researchers, governments, etcetera.

There definitely has to be post-trial availability. The best way to work out this post-trial availability is not only on interventions developed but also in terms of the knowledge generated by the research. This knowledge needs to be disseminated, whether it's a low-income setting or a high-income setting. This knowledge needs to be generated equitably as well. It's best to engage with communities to find out how best to get this

done. If we conduct ourselves this way, we will counter the horrible notion of ethics dumping.

CIOMS went further and in 2021 published its consensus study on clinical research in resource-limited settings. It was specific to resource-limited settings. Some of you on the panel were part of this working group.

In terms of the guideline, it starts with clearly stating that the highest burden of preventable diseases globally is in lower- and middle-income countries. It stresses that there is still the global health divide. Most research and development is focused on diseases in high-income countries still in today's day and age, and this is because there is so much infrastructure already available. This infrastructure is so costly and not freely accessible in low-income countries.

Sustainable Development Goals (SDGs) and clinical research

We have the Sustainable Development Goals (SDGs), and one of them is ensuring healthy lives and promoting well-being for all, with universal access to needed medicines and vaccines. But for us to reach these SDGs and realize this SDG, we require good quality research to identify and address unmet need, and therefore, we need to have access to this type of research for all.

Clinical research drives healthcare advancement. Without clinical research in low-resource settings, entire populations miss out on these advancements. These guidelines recognize that there are challenges, mostly regulatory and administrative, but we shouldn't use them to ignore ethics. We need to develop strategies to overcome these impediments for access and equity in research and healthcare.

Non-communicable diseases have fallen since 1990 but remain high. There's a divide between low- and high-income countries. Although most diseases are infectious, non-communicable diseases are prevalent in low-income countries. We need research in non-communicable diseases in low-income countries. Non-communicable diseases are almost as prevalent in low-income countries as in high-income countries.

To improve public health, we need health research and view it as a social responsibility. A well-developed healthcare system offering substantial benefits for all is essential. We can implement a healthcare system, but it can't be limited to providing available therapies. It must include strategies and tools to improve healthcare, ensuring unmet health needs are covered and effective, safe, and evidence-based care is delivered.

Strategies must include clinical studies to increase knowledge of health problems, develop medicines and health products targeting these problems, study medicines locally, and optimize their accessibility and use. Pragmatic disease management trials provide evidence on how to improve healthcare by comparing different approaches to disease management or mechanisms to improve patient adherence to therapy and improve outcomes.

Considering vulnerability

Trust is essential as there are a number of ethical guidelines and clinical regulations, and they keep on advancing in terms of their guidance. Clinical research in resource-limited settings is crucial. However, local populations often don't understand the aim and nature of such research. Some see research as exploitative, with researchers from high-income countries taking advantage of low-cost and underregulated environments

in LMICs. When entering these sites and building collaborations, we must start with a foundation of trust.

It's important to include special and vulnerable populations. In the past, certain physiologically special or populations with medical and pathological problems were excluded from research. Recently, we've seen a movement from exclusion to inclusion. But we need to look beyond physiological differences, as poverty and socioeconomic situations in low-income settings can also render research participants vulnerable.

While unnecessary research with vulnerable populations should be avoided, it's essential that vulnerable persons, like any other societal group, are included in research. This shows how they can be treated with the medicine safely and effectively, including those in low-resource settings.

UNESCO Declaration on Bioethics and Human Rights and benefit sharing

The UNESCO Universal Declaration on Bioethics and Human Rights, 2005, emphasizes that human vulnerability must be considered in applying and advancing scientific knowledge, medical practice, and associated technologies. People must be protected and their personal integrity respected.

A very important principle in Article 13 is solidarity and cooperation. If there was solidarity and international cooperation, we wouldn't be discussing access and equity in research and healthcare.

When we look at Article 15 of UNESCO, sharing of benefits, and the number of benefits that could be shared, it's an issue of justice. This is similar to the CIOMS Guidelines of 2016, which also focus on benefit sharing.

CIOMS highlights the importance of avoiding exploitative research, especially in partnerships between high-income and low-income countries. Exploitative and unethical research practices can occur. For example, a study in a low-resource country might fail to consider the need for such research, plans to make products and services available locally, or conflicts of interest affecting participant safety or research validity.

A controversial example

I'll talk about a controversial example in CIOMS Report on research in resource-limited settings: cervical cancer screening in India. This happened some years ago but is relevant to our placebo discussions. The international standard for early detection of precancerous lesions is periodic Pap smears or cytology screening, which require infrastructure not available in all low- and middle-income countries. Three clinical trials were conducted in India with funding from the US and France to investigate the effectiveness of alternative screening methods. These were primarily visual inspection with acetic acid in high-risk women from socially disadvantaged backgrounds. The study protocols were reviewed and approved by local institutional research ethics committees in India. Two studies were also approved by the International Agency for Research on Cancer, which is the specialized cancer agency of WHO. All participants were educated about cervical cancer and alternative screening methods. They were randomly assigned to receive either screening (200,000 women) or standard of care (140,000 women). 294 women from the screen group and 254 women from the control group died of cervical cancer during the long-term follow-up.

An American physician complained to the US government's Office of Human Research Protections (OHRP) stating the research was pointless and offering no screening to the women in the control group

resulted in unnecessary deaths. The OHRP investigated the study but only the one with US government funding because it had no jurisdiction over the other two studies. They found gaps in translated materials informing about the available screening methods to the participants and irregularities in the research ethics committee functioning. Importantly, they did not determine that the no-screening control groups were unethical.

Question about local or global standard

During discussion, questions arose about the need for a more locally feasible screening method in India. Researchers said yes, while the complainant said no, as Pap screening is feasible anywhere. The complainant argued that the no-screening control group exposed participants to increased risks, while researchers disagreed.

The complainant quoted, "*I do acknowledge that I have harbored for many years that I care to count an evolving sense of anger in the face of what I have perceived as meaningless unavoidable harm and death visited on desperately vulnerable women.*"

Regarding the necessity of withholding or delaying screening, researchers said no methodological issues were raised in the protocol review. The complainant argued that IARC should not have approved the study protocols.

Were women informed of the benefits and risks? Researchers said yes, with initial problems addressed. They quoted, "*Our studies were explained in the local language to all eligible women and written informed consent was obtained from each participant*."

The complainant disagreed, saying women were not informed. They suggested Indian women were unimaginably stupid to knowingly consent to more death. Enrolling and sustaining the unscreened control groups required withholding critical information from all participants regarding the predictable health benefits of cervical screening.

Day 2 (August 26, 2024)

Ethical reflections by the Brazilian Society of Bioethics on research ethics

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*Presentation

I would like to inform you that my presentation today does not have any conflicts of interest. My speech has been coordinated with Elda Bussinguer, the President of the Brazilian Society of Bioethics. The views and positions I will express here represent those of the Brazilian Society of Bioethics and do not generate any conflict of interest in relation to my own positions.

The Brazilian Society of Bioethics was founded in 1995 with a mission to promote ethical standards in research and healthcare. From its inception, the Society has been deeply involved in addressing ethical issues in research, advocating for the responsible conduct of scientific studies, and ensuring the protection of human participants.

Although bioethics emerged late in Brazil, dating from the late 1980s and early 1990s [1], during this period, bioethics was already present in Brazil and some people were already working with bioethics, but there was not yet a convergence of these individuals [2]. So, the creation of a national entity was a significant milestone for the convergence of people with interests in bioethics and for its dissemination.

> It seems to have been important for the implementation and development of bioethics in Brazil that, since the first administration, one of the main goals was to bring together all individuals from various fields of knowledge who were interested in bioethics [3].

The Society has played a pivotal role in fostering dialogue and collaboration among professionals from various fields, including medicine, philosophy, law, and social sciences. By organizing conferences, work-

1) Cf. DINIZ, Debora; GUILHEM, Dirce Bellezi; GARRAFA, Volnei. Bioethics in Brazil. *Bioethics,* v. 13, n. 3-4, 1999, p. 246.
2) Cf. HOSSNE, William Saad; ALBUQUERQUE, Maria Clara; GOLDIM, José Roberto. Nascimento e desenvolvimento da bioética no Brasil. In: ANJOS, Márcio Fabri dos; SIQUEIRA, José Eduardo de (orgs.). *Bioética no Brasil: tendências e perspectivas.* Aparecida, SP: Ideias & Letras, 2007, p. 148; cf. CREMESP. *Revista Ser Médico, edição* 71, abril de 2015. Seção Debate: Ética e Bioética. Entrevista com William Saad Hossne e Regina Ribeiro Parizi Carvalho.
3) HOSSNE, William Saad; ALBUQUERQUE, Maria Clara; GOLDIM, José Roberto. Nascimento e desenvolvimento da bioética no Brasil. In: ANJOS, Márcio Fabri dos; SIQUEIRA, José Eduardo de (orgs.). *Bioética no Brasil: tendências e perspectivas.* Aparecida, SP: Ideias & Letras, 2007, p. 148.

shops, and educational activities, the Brazilian Society of Bioethics continues to contribute significantly to the advancement of bioethical standards in Brazil and beyond.

The Brazilian Society of Bioethics actively participated in the improvement of research ethics in Brazil, especially in the process of revising Resolution No. 1, dated June 13, 1988, of the National Health Council (CNS) [4]. This revision process, which took place during the I Brazilian Congress of Bioethics from June 26 to 28, 1996, and in several other meetings with this purpose, culminated in the presentation of Resolution No. 196, dated October 10, 1996, of the National Health Council (CNS) [5]. This resolution created the Brazilian research ethics system, namely, the Research Ethics Committees (CEP) and the National Research Ethics Commission (CONEP), known as the CEP/CONEP System.

The history of research ethics in Brazil is a narrative of progressive development influenced by both national and international contexts and which was initiated in 1988. The framework of ethical research in Brazil has evolved considerably over the past few decades, with significant milestones marking its growth.

In the mid-second half of the last century, Brazil, like many other countries, had limited formal structures for research ethics. Ethical considerations were often handled on an ad-hoc basis, relying on the discretion of individual researchers and institutions. However, as scientific research expanded, the need for more systematic oversight became evident.

The global awareness of ethical standards in research was significantly influenced by historical events such as the Nuremberg Trials and the subsequent Declaration of Helsinki, which emphasized the need for ethical principles in medical research involving human participants. These international milestones resonated within the Brazilian scientific community, prompting discussions and actions towards more formalized ethical guidelines.

A pivotal moment in Brazil's history of research ethics came in 1996 with the publication of Resolution No. 196/1996 by the National Health Council (CNS). This resolution laid the foundation for ethical standards in research involving human participants in Brazil. It outlined the need for informed consent, the protection of vulnerable populations, and the establishment of Institutional Review Boards (IRBs), known in Brazil as Research Ethics Committees (RECs).

Following Resolution No. 196/1996, Brazil continued to refine its ethical guidelines. The establishment of the National Commission for Research Ethics (CONEP) further strengthened the oversight of research ethics. National Commission for Research Ethics plays a crucial role in coordinating the activities of Research Ethics Committees across the country and ensuring compliance with national and international ethical standards.

In 2012, Resolution No. 466 replaced Resolution No. 196/1996, providing updated guidelines that reflect the evolving landscape of research ethics. This resolution takes into consideration other international documents on research ethics and human rights, such as Nuremberg Code, from 1947; the Universal Declaration of Human Rights, from 1948; the Declaration of Helsinki, adopted in 1964 and its versions from 1975, 1983, 1989, 1996 and 2000; the International Pact regarding Economic, Social and Cultural Rights, from 1966; the International Pact regarding Civil and Political Laws, from 1966; the Universal Declaration regarding Human

4) Cf. BRASIL. *Resolução CNS nº 1,* de 13 de junho de 1988.
5) BRASIL. *Resolução CNS nº 196,* de 10 de outubro de 1996.

Genome and Human Rights, from 1997; the International Declaration regarding Human Genes Data, from 2003; and the Universal Declaration regarding Bioethics and Human Rights, from 2005.

Brazil continues to evolve its research ethics landscape, responding to new challenges and advancements in science and technology. The country is committed to ensuring that ethical considerations keep pace with scientific progress, safeguarding the rights and well-being of research participants.

The history of research ethics in Brazil is marked by significant progress and a commitment to upholding the highest ethical standards. Through continuous refinement of guidelines and the establishment of robust oversight mechanisms, Brazil has developed a comprehensive framework that ensures the ethical conduct of research involving human participants.

It is true, not everything is rosy in the development of research ethics in Brazil. Recently, the National Congress approved a law on research ethics, namely, Law No. 14,874, dated May 28, 2024, which will come into effect in two days.

Since the inception of research ethics in Brazil in 1988, 36 years ago, much has been done for the development of bioethics and research ethics in Brazil. And the instances of social control have played a prominent role. Social control presupposes the effective participation of society, not only in overseeing the application of public resources but also in the formulation and monitoring of policy implementation [6].

However, there are attempts to interfere to minimize the role of social control [7]. This is the case with the new research ethics law approved in Brazil, namely, the Law No. 14,874, dated May 28, 2024, which provides for research involving human beings and establishes the National System of Ethics in Research with Human Beings.

The problem here is that Brazil already has a national system of research ethics, namely, the CEP/CONEP System, which the mentioned law does not even mention. The National Research Ethics Commission (CONEP) and the National Health Council (CNS) have responsibilities to ensure the protection of participants in clinical research. In this sense, the changes proposed by the mentioned law may remove autonomy from the National Research Ethics Commission (CONEP), weaken the security of research participants, and favor commercial interests without considering ethical aspects. In the national and international scenario of clinical research, as pointed out in the Clinical Research Action Plan in Brazil:

> Brazil has the potential to attract clinical research due to its large and diverse population; the existence of a public health system, which facilitates patient recruitment and follow-up; the high incidence of the most prevalent diseases in developed countries; the existence of ethical research standards compatible with other countries, qualified professionals, and a good infrastructure of hospitals and reference centers for phase III clinical trials [8].

6) Cf. SALGUEIRO, Jennifer Braathen; FREITAS, Corina Bontempo Duca de. Regulamentação ética da pesquisa no Brasil: pepel do controle social. *Revista Bioética,* v. 30, n. 2, 2022, p. 239-240.

7) Cf. FONSECA, Claudia. Situando os comitês de ética em pesquisa: o sistema CEP (Brasil) em perspectiva. *Horizontes antropológicos,* v. 21, n. 44, 2015.

8) BRASIL. Ministério da Saúde. Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde. Departamento de Ciência e Tecnologia. *Plano de ação de pesquisa clínica no Brasil.* Brasília: Ministério da Saúde, 2020, p. 20.

Thus, it can be observed that Brazil is an important destination for multicenter clinical research due to its mixed-race population with great genetic diversity. This characteristic is important for phase III studies, as the objective of this phase is to test the drug or vaccine on the largest number of people with different characteristics to analyze its efficacy and possible variables.

Phase III studies are often portrayed as the gold standard in clinical research, yet a critical examination reveals that many of these trials function less as genuine scientific inquiries and more as a service to the global pharmaceutical industry. Rather than being driven by a quest for new knowledge or the desire to address significant public health needs, these studies frequently prioritize the commercial interests of pharmaceutical companies. This is evident in the design and conduct of many Phase III trials, which are often tailored to meet regulatory requirements and market demands rather than to answer essential scientific questions. The focus on large-scale, multi-center trials also reflects a tendency to produce data that supports market approval rather than advancing medical science. Consequently, the integrity of the research process is compromised, as these studies become tools for profit generation rather than true endeavors in scientific discovery. This blurring of the line between research and service provision undermines the credibility of the entire clinical trial process, calling into question the validity of the findings and their contribution to the broader scientific community.

Returning to the context of research in Brazil, the process of conducting a clinical study begins currently with the approval of the research protocol by the CEP/CONEP System. The system operates independently of the Federal Government to protect the rights of research participants, always guided by ethical values. The system is also an international reference due to the comprehensiveness and robustness of its regulations. It is worth noting that the CEP/CONEP System performs the ethical analysis of research protocols involving human participation. The National Health Surveillance Agency (ANVISA) is responsible for authorizing experimental drugs for use in research and operates with different timelines from the CEP/CONEP System.

It is undeniable that there is a need for greater investment in clinical research. However, this development should not occur to the detriment of research participants. As stipulated in the Clinical Research Action Plan in Brazil, all actions presented on ethical regulation have been executed by the National Research Ethics Commission (CONEP), with the aim of improving the system and everyone involved [9]. This demonstrates that the ethical regulation sector of clinical research in Brazil is constantly striving to improve itself to contribute to the development of clinical research in the country. Moreover, it is also concerned with protecting and maintaining the guarantees for research participants that have been secured since the creation of the CEP/CONEP System in 1996.

Increasing the volume of clinical research in Brazil is unattainable among the growing weakening of research ethics guidelines. Robust and unwavering ethical standards are the cornerstone of credible and humane research practices. As such, any erosion of these standards undermines not only the integrity of the research but also the trust and safety of its participants.

It is imperative to thoroughly qualify researchers in the ethics of human being research. Without a deep understanding and commitment to ethical principles, researchers may inadvertently cause harm or fail to

9) Cf. BRASIL. Ministério da Saúde. Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde. Departamento de Ciência e Tecnologia. *Plano de ação de pesquisa clínica no Brasil.* Brasília: Ministério da Saúde, 2020, p. 32.

protect the rights and well-being of participants. Comprehensive ethics training ensures that researchers are equipped to navigate the complex moral landscape of clinical studies, balancing scientific advancement with the respect and dignity owed to each participant.

Moreover, clear communication about rights and guarantees is crucial for research participants in experimental trials. Participants must be fully informed of their rights, the nature of the study, potential risks, and the measures in place to protect them. This transparency fosters trust and empowers participants, allowing them to make informed decisions about their involvement.

Furthermore, the provision of post-trial access to treatments is a critical ethical consideration, particularly for chronic diseases. Recent legislative proposals to limit this obligation undermine the ethical responsibility of researchers and sponsors to continue providing effective treatments discovered during trials. Such changes threaten to reduce participant trust and could deter individuals from participating in future research, thereby stifling scientific progress.

Investing in the development of clinical research in Brazil also necessitates adequate infrastructure and funding. This includes ensuring that research facilities are well-equipped and that there is sufficient financial support for both the operational aspects of trials and the long-term follow-up of participants.

Finally, fostering a culture of ethical research requires continuous oversight and public engagement. Independent bodies such as the CEP/CONEP System must remain vigilant and autonomous, ensuring that all research complies with ethical standards. Public awareness campaigns can also play a role in educating potential participants about their rights and the importance of ethical standards in research.

In conclusion, the potential for expanding clinical research in Brazil hinges on maintaining and strengthening ethical guidelines, providing comprehensive ethics education for researchers, ensuring transparent communication with participants, and investing in robust research infrastructure. Only through such measures can Brazil emerge as a leader in ethical clinical research, attracting global partnerships and contributing significantly to medical advancements.

Day 2 (August 26, 2024)

Ethics of placebo-controlled trials and post-trial access: International health research as a stepping-stone to universal public health care access

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1. Introduction

I declare no conflict of interest. My opinions are based on my expertise as a physician in Infectious Diseases and Bioethics. I hold a professorship at the Federal University of Minas Gerais in Belo Horizonte, Brazil.

The ethics of placebo have been extensively documented, in documents such as the UNESCO Universal Declaration on Bioethics and Human Rights [1], CIOMS research ethics guidelines [2], UNAIDS [3], Declaration of Helsinki [4] Brazilian Research Ethics Commission Resolution [5]. It must be included the 2021 CIOMS document on research in resource-limited settings [6]. My focus today is on the 2000 Declaration of Helsinki and its 2013 revision.

2. Benefit sharing in UNESCO Declaration, 2005 [1]

While many documents exist, I find the 2005 UNESCO Declaration concise and comprehensive. However, Article 15 could be improved. It states the options of "benefit sharing", including "*provision of new diagnos-*

1) United Nations Educational, Scientific and Cultural Organization. Universal Declaration on Bioethics and Human Rights. 19 October 2005. Available at: https://www.unesco.org/en/legal-affairs/universal-declaration-bioethics-and-human-rights?hub=66535
2) 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/
3) Joint United Nations Programme on HIV/AIDS (UNAIDS) 2007. Ethical considerations in biomedical HIV prevention trials: Guidance Document. 2007
4) World Medical Association. WMA Declaration of Helsinki: Ethical principles for medical research involving human subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and last amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.
5) Brazilian Research Ethics Commission Resolution 466/2012, which succeeded Resolution 404/2008.
6) Council for International Organizations of Medical Sciences. Clinical research in resource-limited settings. 2021. https://cioms.ch/publications/product/clinical-research-in-low-resource-settings/#description

tic and therapeutic modalities or products stemming from research" but there are alternative possibilities, allowing "*other forms of benefit consistent with the principles set out in this Declaration*". This alternative, which has the potential to not provide post-trial access, better aligns better with the access principle advocated in the Declaration of Helsinki. In reality, post-trial access should include not only research participants but all those who might benefit from it.

3. Post-trial access and caring in CIOMS, 2016[2)]

On the other hand, t 2016 CIOMS document, while not strictly requiring it, emphasizes the need for research and sponsors to make plans for addressing the health needs of participants. This requirement, however, can be considered permissive. It's essential to ensure that plans are not simply drawn up but also executed effectively.

Another criticism of the 2016 CIOMS document is its provision that access ends after a set period or when the study intervention becomes available through the public health system. This effectively limits participant ´ s rights and puts an economic pressure on health systems, which are usually underfunded.

However, CIOMS general comments section is noteworthy. It recognizes the ongoing care needs of participants based on the principles of beneficence, reciprocity, and the duty of care. This requirement is not limited to research in resource-limited countries, but applies universally. While some argued that providing care during and after the trial could unduly influence participants, this is not actually true.

4. UNAIDS/WHO[3)]

The UNAIDS/WHO guidance document of 2007 provides specific guidance on care and treatment for participants who acquire HIV infection during biomedical HIV prevention trials. It highlights the need for sponsors to ensure access to optimal treatment regimens. Although this document was revised in 2019 and became less protective, its original version was a strong advocate for the right to post-trial care and treatment.

5. Post-trial access in the Declaration of Helsinki[4)]

In 2008, in Seoul, South Korea, the Declaration of Helsinki underwent its first significant change since 2000. The Brazilian Medical Association and the Brazilian Medical Council advocated for maintaining the requirements of the 2000 Declaration of Helsinki which guaranteed access to the best proven prophylactic, diagnostic, and therapeutic methods for all study participants and the right to post-trial access.

From 2008 to 2013, the Declaration of Helsinki's requirements for clinical trial participants were weakened. Initially, sponsors and researchers were required to ensure post-trial access. However, this has been changed to a less stringent requirement stated as "make provisions" for participant needs. This trend continued in the 2024 draft, which only requires arrangements for the provision of health care.

The weakening of requirements to respect and protect clinical trial participants is of particular concern for phase III clinical trials conducted in in low-and-middle-income countries (LMIC). Furthermore, the 2024 draft places responsibility on RECs to approve to these requirements, which should be included in the initial

research proposal. It goes without saying that RECs can be subject to unfounded pressure from researchers and sponsors. This is a significant disadvantage of the proposed changes.

6. Placebo use in the Declaration of Helsinki[4)]

Regarding the use of placebos, in 2008 the proposal to maintain the 2000 declaration's strict criteria was defeated. In 2013, the declaration was amended to allow for the use of placebos in certain circumstances, even when there is a proven intervention. This change is considered harmful as it allows the use of potentially harmful interventions in a placebo-controlled trial.

Although the 2013 DoH includes a statement about avoiding the abuse of including placebo as a control, this is insufficient. A more direct and specific requirement is needed. Unfortunately, the 2024 draft is likely to maintain the 2008 approach.

The Declaration of Helsinki has undergone significant changes since 2000, with a general trend towards weakening requirements for the protection of participants. These changes, particularly regarding post-trial access and the use of placebos, have raised disagreements among many experts. It is essential to advocate for stronger protections for research participants in future revisions of the declaration.

I want to revisit Diego's question about countries ´ position vis-à-vis the DoH. It should be remembered that its requirements are not binding and that it has become less and less protective over time. Therefore, countries can independently make decisions on these and other items.

7. Brazilian Research Ethics Commission (CONEP and the Code of Ethics of the Brazilian Medical Council[5)]

Brazil responded to these questions in an interesting way. The Brazilian Research Ethics Commission adopted in their requirements a position similar to the 2000 DoH. It states that in biomedical research, the use of placebo must be fully justified and all trials must be compared to the best current prophylactic, diagnostic, and therapeutic methods. Placebo use is not acceptable when an active comparator exists.

Second, a more important point is that at the end of the study, sponsors must ensure all participants have free access to the best proven prophylactic, diagnostic, and treatment methods for as long as needed. In specific cases, an extension might be permitted based on the attending physician's analysis.

This decision taken in the latest Research Ethics requirements issued in 2012 was based on a 2008 resolution in which Brazil decided to act independently of the Declaration of Helsinki. This approach is likely unique, and has met resistance from some pharmaceutical companies. However, Brazil's position has demonstrated that it is possible to implement such measures with the necessary will, independence and commitment to human rights and bioethics.

The 2029 Brazilian Medical Council Code of Medical Ethics prohibits physicians from participating in clinical trials using placebo as a control when effective treatments exist for the disease in question. There are two relevant documents to be consulted: one that outlines the directives modified by the 2024 Brazilian law cited by Diego, and the Brazilian Code of Ethics, which all physicians must comply with.

8. Comparison

A slide presented by Chieko Kurihara raised the question of whether the proposed draft of the DoH adheres to high standards (Table 1). It does not, as it still allows the use of placebo when there is a proven intervention except when there is a risk of serious or irreversible harm to participants, remaining far below the standards set by 2016 CIOMS Guideline eight: in exceptional circumstance placebo may be used as a comparator only if a minor increase above minimal risk can occur. Furthermore, the DoH draft retains "post-trial access", but dilutes responsibilities by stating that sponsors, researchers, the healthcare system, or host country governments must provide it. Publications on this topic are available in our book [7].

I use here a very nice table kindly provided by Chieko, which contains key points, many of which must be non-negotiable. The first point, which I find crucial, is the "social value". Research is not ethical if it does not have social value. This is significant because, if applied, many phase III trials would not progress, as they often lack social value, being just repetitive trials with no scientific value.

The second point includes several crucial aspects, and I highlighted Brazil's strong position on social value, benefit sharing, avoidance of discrimination, best proven in comparison arms, and right to post-trial access for all. Brazil is close to CIOMS in some areas and is aligned with the patient group proposals in the

Table 1 Established key concepts missing in the proposed draft of the revision of the DoH-Comparison with Brazil

Protection items	DoH	CIOMS *1	Patient group	CONEP Brazil	IFAPP*2	GL Japan	GCP (R3)
Social value	—	◎	◎	◎	○	◎	—
Community Engagement/Patient Public Involvement	△incomprehensible	◎	◎	○	◎	—	◎
Benefit Sharing	—	◎	◎	◎	○	—	—
Avoid Discrimination/Stigmatization (risk to target group)	—	◎	◎	◎	—	○	—
Consider Future Generations/Sustainability	—	—	◎	--	—	—	—
Inclusiveness for vulnerable people	—	◎	○	○	◎	◎	—
Right to know/not to know the result (including incidental findings up to the status of information)	— (△)	◎	◎	△	◎	◎	—
Broad informed consent/dynamic consent	—	◎*1	◎	○	◎	○	—
Fairness of REC/Patient Public Involvement(democracy)	—	◎	◎	○	◎	○	○
Best proven/risk minimization in comparative arms	—	○	◎	◎	◎	—	—
Post-trial access for participant (informed consent form), community (for those most in need globally)	△	○	◎	◎	◎	△	—

◎Strongly argued ○medium △weak or not explicit

*1: "Dynamic consent" is not in health research guidelines but in Report XI for patient engagement.
*2: Not official opinions of IFAPP, but of some members of IFAPP.

Modified from Chieko Kurihara

7) Kurihara C, Greco D, Dhai A., editors. *Ethical innovation for global health: pandemic, democracy and ethics in research*. Springer; 2023.

presentation of August 5. This advocates for adequate research ethics, clinical trials, and protection of participant rights.

9. Fundamentals of human rights

I quote several times an important Italian philosopher Norberto Bobbio who in 1964 wrote in Fundamentals of Human Rights: "*The gravest problem of our times, in relation to human rights, is not anymore to set its foundations, but to protect them*." This is in line with our view.

There are many documents, and it is worrying that people can choose what they prefer, whether pragmatic approach of the United States or the more protective points of view coming from Latin America or Africa.

10. Conclusion-1

In conclusion, it is time to globalize ethical requirements. Research with humans must be scientifically sound and have social value. Clinical trials should be performed where vulnerability is low, and successful outcomes must be shared globally. International ethical guidelines are necessary, but they should be harmonized and approved by global institutions such as the UN, WHO, and UNESCO, which represents most countries, unlike the WMA, which only represents physicians.

In clinical trials, the best proven preventive, diagnostic, and therapeutic methods must be provided without double standards. Participants have the right to post-trial access to treatments that have been shown to be safe and effective. The use of placebo is only acceptable when there is no comparator. Lowering ethical standards makes it difficult to raise them again, as seen with the Declaration of Helsinki which became more permissive after 2000.

Researchers from developed and developing countries should be involved in all phase of the study, from protocol development to applying results, and participants' representatives should be equally engaged. This ensures research isn't dictated from above but includes the voices of participants.

11. Conclusion-2

Other conclusions include the need to address access to care and treatment in research. The debate over participants' rights to post-trial access should be replaced with the goal of ensuring universal access to all effective research products in public health. Ames highlighted this in the SDGs, and I believe these conclusions are part of that framework.

Universal access to current and future research products must be guaranteed internationally. The status quo of inequality should not be accepted as an immutable fact. We must advocate for universal access to healthcare, recognized as a human right, not an economic commodity.

Finally, we must prepare for upcoming ethical challenges, and provide guidance for difficult decisions regarding preparedness for new pandemics, technological advancements, and issues such as, overcoming inequalities, access, costs, and artificial intelligence.

12. Three examples of access in public health

These are three examples of access in public health:

The first is UNESCO Article 15 of the UDBHR, which emphasizes social responsibility and health. It states that health promotion is a central duty of governments and society, recognizing health as a fundamental right for all, regardless of race, religion, or economic status. It underlines the importance of progress of science and technology, with particular attention to the health of women and children, considering health as a social and human good.

The second example is taken from the 2010 WHO Guidance on ethics of TB prevention, care, and control [8]. It emphasizes that research should benefit the population in the places where it is conducted and that technological transfer is vital. This has been a significant issue during the development, production and distribution of the COVID-19 vaccine, which also raised the need for global access to technology, particularly in the Global South. A broader discussion must also include redesigning the TRIPS Agreement to ensure fair access to medical technologies.

The third example is the 1988 constitution of Brazil, which enshrines health as a universal right and duty of the state, leading to the creation of the Brazilian Universal Health System (SUS). Covering 210 million people, SUS ensures universal and equitable access to health services, in stark contrast to northern countries, such as the U.S., where many lack access to public health care.

13. From empowerment to emancipation

I conclude with a powerful quote from Thucydides, in his book on the Peloponnesian war According to him:

"*Justice will only come when those who do not suffer injustice are as indignant as those who do*." This is about "empowerment".

In my opinion, Justice will prevail when those affected and outraged by injustice are able to fight for their rights. This is about "emancipation". It highlights the need for collective action, not just empowerment but true emancipation, where people fight for their rights.

8) Guidance on ethics of tuberculosis prevention, care and control. 15 February 2010. https://www.who.int/publications/i/item/9789241500531

Day 2 (August 26, 2024)

Invited comment-1

Peter Lurie
Center for Science in the Public Interest, United States

1. Placebo clause and the issue of double standard

Well, good morning everybody or good afternoon or good evening, depending on where you are. I thank the organizers for inviting me. Attending a meeting like this after a quarter of a century is on the one hand quite saddening, in that it seems as if very much the same issues are being debated that were being debated 25 years ago, that the consensus in favor of human rights has still not been reached. On the other hand, it's encouraging, in that we have a whole new generation of people who have picked up the ball and run with it.

I want to emphasize that the issue may be old, but the issue is still current. Prof. Ames Dhai gave an interesting example about the Pap smear study in India which is fairly recent. But as hinted at occasionally by some of the other speakers, we did face this once more over COVID-19 vaccines in which a WHO directive established the idea or sought to establish the idea that after there was a first effective COVID-19 vaccine that it would still be acceptable to test subsequent vaccines against placebo in countries that didn't have access to the first one.

Now, as to the kind of rival versions of the language on placebo, and I am going to focus on that only, as has been noticed several times in the course of this day, the Declaration of Helsinki at present argues for "no increase of risk of serious or irreversible harm." I would look at that as a ceiling in terms of risk. It basically establishes a level above which you cannot go, and it provides license for one to engage in a degree of risk up to and until that ceiling, and that's worrying. Obviously, the definition of serious or irreversible harm is in the eye of the beholder.

I think that that approach, especially this negative language, "no increase" in effect will be less protective than the more positive language that is in the CIOMS which I think can be thought of as a floor. There, the language is "minor increase above minimal risk". I think that establishes a floor of protection for human subjects.

In my mind at least, it creates an opportunity for some placebo-controlled trials that I wouldn't find troubling. For example, the study of an allergy medicine, I am not personally troubled by the use of the placebo. But the CIOMS allows for that, while at the same time creating a much clearer definition of what acceptable risk is, in part because it's a floor, but also because it uses positive language, not this negative language, "no increase" that you see in the Declaration of Helsinki.

I was thinking when I was hearing all of these presentations about what might be an effective way to argue considering that the people who actually control the WMA are mostly from developed countries.

I think that at least one way of doing this is that there are inequities even within developed countries that

if the logic of the so-called local standard of care is to be applied will ultimately be applied within those countries and logically that could happen.

2. A study of needle exchange program

I just want to give one example. I used to have a lot of involvement in what are called needle exchange programs, programs for drug users in which a used syringe is exchanged for a clean one, and at a certain point in time, every public health organization in the world, including WHO itself, had said that these were effective and should be part of any comprehensive package to prevent HIV among drug users and by extension their sex partners and their children.

I was asked to be part of a study in about 1966 in which drug users in Anchorage, which is in the American state of Alaska, would have been randomized to either get a needle exchange program, or if they showed up at the needle exchange program, but had not been randomized to it, they would have been given information about how to buy syringes at a pharmacy, something which on the one hand as drug users they already knew about, but on the other hand was illegal in Anchorage anyway.

The idea was to randomize these two groups and establish once and for all where the needle exchange worked. We made the argument that there was a standard of care even within America and certainly internationally that needle exchange programs were effective and that withholding it and in this case literally blocking people at the door, literally turning them away from the needle exchange that held the syringes that could save their lives and sending them elsewhere which they may never do was very much the same as the kinds of other examples that we had encountered in the developing world.

Interestingly, the way that they were establishing the effectiveness of this program, if the study had ever really happened, which it didn't really in the end, but the project sort of died of its own inconsistencies, but there is not enough HIV up in Anchorage then or now to actually be able to measure the incidence of new infection.

I pointed this out to the principal investigator who said that they were going to measure hepatitis B infection instead at which point I asked him if he had ever heard of the vaccine, he said he had, but there was no real obligation to provide that either.

When we filed a complaint with the National Institutes of Health, they ultimately mostly did not side with us. They thought that the trial was ethically designed. But very interestingly, the head of the National Institutes of Health at the time, Harold Varmus, turned around to the committee that had said that this whole study was fine and said, "Don't you think it's important that in an NIH-funded study that we have the highest possible standards?" With that, he ordered them to provide hepatitis B vaccine, which they didn't do very well, mind you, perhaps because they had a conflict of interest.

3. Global and domestic inequities

But the point I want to make then in addition to my point about this idea that the standard of care argument will eventually be used in countries, especially like the United States where there are huge inequities even today, is that there ought to be an argument that the standards in research should not sink to what is provided

as a standard of care in countries that don't have enough to provide the care that they would love to provide, but are unable to for financial reasons. Rather, research should be based on the highest aspirations that we have, and that if there is any artificiality within a clinical trial, it should be in favor of providing what science demands and not what economics or the desires of researchers for data demand.

Those are a couple of arguments that I am sure you've heard before, but I do think those are potentially ways to argue with the WMA when the time comes. But in the meantime, I am just here to say how much I appreciate that you'll be there and that you're carrying the ball forward on this.

Day 2 (August 26, 2024)

Invited comment-2
Revising the Declaration of Helsinki: Three suggestions for improvement

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1. Introduction of Universities Allied for Essential Medicines

As a medicine student and Ph.D. student at the University of Amsterdam, I am part of Universities Allied for Essential Medicines (UAEM). We focus on access issues and the intersection with the Helsinki Declaration and clinical trials. Our organization began during the HIV/AIDS crisis when universities held key patents on 25% of HIV/AIDS drugs from 1988 to 2005 and therefore had a key role to play also in ensuring access and affordability of these drugs [1]. We believe universities should contribute to public health by doing medical innovation in the public interest and ensuring access to essential medicines and other health technologies.

We emphasize research equity, focusing on whether research addresses diseases with significant public health needs, the allocation of funding, and the terms of research sharing. Our main focus is on equitable technology transfer, examining legal aspects and advocating for fair terms with private sector.

2. Public consultation on the Declaration of Helsinki

● Improvement of trial results reporting

In our public consultation on the Declaration of Helsinki, we suggested improvements. One suggestion is clear rules for trial results reporting. Ethical obligations include sharing results with participants and the public in a timely manner. Universities are often worse than commercial entities in reporting results. For example, in the UK, university clinical trial results for CTIMPs were on the EUCTR, improved from 29% to 91% after three years due to political and concerted efforts. We recommend a 12-month deadline for reporting results on public registers, similar to the WHO Joint Statement of 2019.

● Creating accountability mechanisms

Another suggestion is creating accountability mechanisms for researchers. Ethics committees and funders should ensure that researchers with previous violations of Helsinki Declaration principles are not approved

1) Kapczynski, A., Crone, E. T., & Merson, M. (2003). Global Health and University Patents. *Science.* 301, 5640. https://doi.org/10.1126/science.301.5640.1629

or funded for new studies. This is not currently addressed in the declaration or practice.

●Post-trial access

Lastly, the term “post-trial provisions” should be replaced with “post-trial access” to emphasize the importance of accessibility, affordability, and timely access. During the COVID-19 pandemic, trials in countries like South Africa and Brazil raised concerns about access and technology transfer. Engaging with South African students at the University of Oxford revealed inequities where vaccines developed at their own university was inaccessible to their families. Universities and funders must address these access issues more thoroughly, but as the next generation we wish to be part of these conversations.

Day 2 (August 26, 2024)

Discussion and Closing Remarks

Varvara Baroutsou
President of International Federation of Associations of Pharmaceutical Physicians & Pharmaceutical Medicine (IFAPP)

Dirceu Greco
Professor Emeritus of Infectious Diseases and Bioethics, School of Medicine, Federal University of Minas Gerais, Brazil

Elda Coelho Azevedo Bussinguer
Full Professor at the Faculty of Law of Vitoria (FDV, Brazil)

Diego Zanella
Professor of Bioethics, Universidade Franciscana, Brazil

Ames Dhai
Professor Bioethics, School of Clinical Medicine, University of the Witwatersrand, Johannesburg, South Africa

Chieko Kurihara
Specially-appointed Professor, Kanagawa Dental University

Peter Lurie
Center for Science in the Public Interest, United States

Sarai Keestra
National Committee for Universities Allied for Essential Medicines (UAEM) Netherlands, Europe

Baroutsou The Declaration of Helsinki has not evolved to meet current needs, scientific advancements, and ethical standards, remaining a controversial document with minimal changes. There is a clear lack of consensus on the concept of social value, which is disappointing, and efforts are needed to strengthen this aspect. Equity issues are also unresolved, despite various proposals and examples presented. Additionally, the use of placebo controls requires better regulation; placebo should only be used when no treatment or intervention exists for the condition being studied.

The increasing economization of medical research is concerning. Approximately 25-27% of currently used medicines originate from research by universities or public institutions, while 75% come from industry. Revising industry practices may involve health technology assessment bodies evaluating not only scientific but also societal aspects. These bodies could influence the industry by rejecting new drugs or therapies that rely on problematic practices, such as placebo controls or inadequate post-trial access.

Positive aspects include the passion and advocacy demonstrated by many in this field. It is encouraging to see committed individuals and groups pushing for better standards. Prioritizing non-placebo use when alter-

natives exist is crucial. In cases where there is no established treatment, alternative approaches should be considered. Although challenges remain, maintaining optimism and continuing efforts to improve research ethics and access to essential medicines is vital for progress in this area.

Dhai　It is crucial to have safeguards to protect vulnerable individuals and populations in all respects, including post-trial access and the use of placebos.

Upon reviewing the slides and comparisons presented, I asked myself, whether the Declaration of Helsinki, as the primary document for participant protection and the most used instrument, is truly fit for purpose and able to continue making these claims. I have significant concerns about this.

In my view, the Declaration of Helsinki in its current form will not facilitate the implementation of solidarity and international cooperation, which is fundamental for protecting research participants and ensuring access to healthcare. Consequently, it will not support the quest for research equity and access, and therefore global health equity.

Zanella　I wish we could have more discussions like this in the future. By sharing our views and engaging in constructive debate, we can contribute to the development of better ethical guidelines. We know there is no global consensus on these issues, but by sharing our positions, we can gradually improve this discussion. This is my final message.

Bussinguer　We were all happy to participate in this important discussion. We face several problems, especially in Brazil, including medical institutions' behavior during the pandemic. They opposed vaccinations and promoted unproven treatments.

Pressure from the pharmaceutical industry is another major problem. Their influence contributed to weakening CONEP's achievements. Diego's presentation on the Brazilian Society of Bioethics' position was valuable. We thank everyone for their participation.

Keestra　How progressive can the WMA be on ethical topics, or should a different governing body be responsible?

Greco　The WMA can be considered a kind of "social club" for physicians. It represents a significant proportion of physicians in many countries, but physicians are not obliged to be members of national medical associations. For this reason, a document from CIOMS, WHO, or UNESCO are more representative because these institutions are supposed to represent us all I also want to mention what Peter Lurie discussed, which was very interesting because he mentioned studies on allergy drugs. In 2000, at the WMA General Assembly, Robert Temple (representing the US FDA) used these examples to show that placebo could be used for allergy trial. According to him, allergic participants have sneezed all their life. Why not, receiving a placebo, sneeze a little more? That wasn't the point in the placebo discussion. Peter was very good in that. The bar applied by WMA is high at high. It's not protecting anyone.

The second thing is about the provision of providing clean needles for people who inject drugs. In Brazil, at the beginning of the AIDS epidemic, HIV infection among people who injected drugs was very high. A mayor of Santos, a large coastal city with high HIV rates, proposed to distribute clean needles and syringes and was almost arrested by in public court because they said he was promoting drug use.

Sarai raised the question, what kind of research should be done? I mentioned this too. Without social value, perhaps 75% of clinical trial research isn't worth it. It won't help anyone except the drug company, and it's interesting to have Varvara here because she has a similar position which is different from what's happening

in Brazil with many health professionals e working for pharmaceutical companies.

The last thing is that when we say that Brazil, South Africa and LMIC should have early access to vaccines, it's a good idea but not by negotiating separately for each country. In my opinion, this is not going to solve the problem and as examples I cite a new HIV drug, lenacapavir, an injectable drug lasting six months, costs $40,000/year. At this price it will never be available for the most vulnerable people in LMIC. If we continue this way, scientific progress will come but the cost will be impossible. The only way is to really discuss patents and their duration. The TRIPS Agreement allows for openings, but TRIPS Plus agreements, which are becoming frequent, block the opening provisions of the DOHA agreement for issuing compulsory licenses. This is another battle that young people like Sarai must carry on.

Returning to our webinar, I've outlined points to keep in mind as we expand the discussion. The social value is of the utmost importance and it is one of the most difficult because it touches on what the pharmaceutical industry fears—how much of these clinical trials should really be performed, as I said to Diego yesterday. And when people say Brazil is good for research, in my opinion, most international clinical trials coming to Brazil is not really research. The industry needs people to do the work. We have good researchers and resources, but many times they are just providing a service for big industry. This is something we must consider in any discussion on this issue.

Post-trial, access for all is essential. No participant should be left out. Peter Lurie's 1989 publication on unethical placebo use in mother-to-child transmission of HIV trials is relevant here. Brazil holds a strong position: placebo cannot be used if there is an effective and safe comparator. Fortunately, even with the new law, recently approved in Brazil, this requirement is maintained

Finally, the Declaration of Helsinki is not binding. In our countries, we have to decide what we want. Do we follow something that's not good if approved, or do we create something we can be proud of that respects researchers and participants? Brazil's position has been clear and will remain so.

Keestra How can we engage young researchers more with the Declaration of Helsinki and post-trial access issues? They often study these topics but quickly forget their importance.

Lurie I don't really know the answer, except to say the following. Listening to these presentations, I was amazed we're still having this conversation in the modern era, in two ways.

First, I firmly believe that in 10, 15, or 20 years, people will look back at what happened with perinatal HIV and realize it was a mistake. It often takes 30, 40, or 50 years for people to say, "I made a mistake." That's how long it took for people to understand what happened and for it to be addressed in Nuremberg or the Tuskegee study. Time is on our side, and history will judge this effort well.

Second, we live in an era with greater understanding of diversity, equity, and inclusion. The idea of a double standard like what's being proposed is remarkable in this day and age. History is moving in the other direction, with countries becoming more multinational and awareness of these issues increasing. It's amazing people are still pushing this because it feels outdated.

Young people understand this better than most. They're onboard with diversity movements and new racial consciousness. For a medical student, seeing an injustice like this, there are opportunities for organizing, and clearly, Sarai, you've caught the bug. There's an audience ready to hear your message.

Greco I just want to add that it is extremely important that young people are involved, and the organization that Sarai represents is crucial everywhere. In Brazil we have had many discussions with them, espe-

cially regarding patents, and it is essential to do this globally.

The second group that must be involved, as we discussed in the first seminar, are the participants. They must help ensure a strong voice, pushing those affected by the error to say, “You were wrong, and you will change this situation.” We should unite three groups: the older generation, the young generation, and the participants.

In Brazil, it’s difficult. Starting next year, we’ll graduate 40,000 doctors annually, many from poor institutions entering a non-functioning market. We must engage them. My real hope is with the participants. I talked to Chieko about the possibility of connecting participants from Brazil with Japan and to see if the Brazilian Society of Bioethics can include them as members, which would be very interesting.

Kurihara　Thank you for your participation. The Declaration of Helsinki has not changed significantly, but there have been changes among us. Since 2020, we started with patient and public group to discuss about the Declaration and patients and the public group have expressed strong opinions on the Declaration, which are more influential than those of research ethics experts. In the same way as this, I think the medical students will play a crucial role in addressing the challenges of research ethics.

Keestra　It still seems like a niche interest, but both clinical trial transparency and post-trial access, as mentioned before, make you wonder, “How has this not been resolved already? How can this injustice exist?”

I’m concerned that the ethical standards for all human research are being set by the WMA, which, if it’s true what was said earlier, is somewhat like a “social club”. They don’t represent all doctors or opinions globally, and it’s dangerous to let them decide ethical standards. I believe a UN organization like the WHO should set those standards, not the WMA.

The name “World Medical Association” sounds impressive, as if they represent medicine, but if they don’t, it’s dangerous for their standards to be the foundation for laws and ethics. There should be a push for WHO to establish a global ethical standard instead.

Greco　I completely agree. I will talk about it with Ames, who is also a member of UNESCO’s International Bioethics Committee. This topic will be addressed in our annual meeting in September 2024, and it is a pity that you will not be in Helsinki in October. We will talk about it there too.

Bussinguer　The Brazilian Society faces challenges due to the lack of engagement from a significant portion of the medical profession. However, there is resistance, as evidenced by the recent election for the Brazilian Medical Council.

To address this situation, it’s crucial to maintain partnerships and expand the Brazilian Society’s reach internally and regionally. Collaborating with research ethics groups and expanding work to Latin America will help counter the negative influence of those who oppose ethics and human rights. This will require building stronger connections within the Brazilian Society and fostering a more inclusive and engaged community.