Clinical Evaluation 2024 Vol.52
Preprint Online Publication on Oct 10, 2024

Patient Public Declaration of Research Ethics (1st edition) :

Research ethics of the people, by the people, for the people—Expanding the impact of the 2024 revision of the Declaration of Helsinki

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Background of the Patient and Public Declaration of Research Ethics

We are members of Bioethics Working Group of the Japanese Institute for Public Engagement (Ji4pe) and learning the systems of healthcare and drug development from the perspective of patients and the public. Among various agendas, we have been learning about since the year of 2020 the World Medical Association (WMA)'s Declaration of Helsinki (DoH)[1], the ethical principles for medical research involving humans, through monthly online meetings[2]. Patients and health people would first encounter the DoH in an informed consent documents when they are requested to participate in medical research. Meny of them would give consent to participate in research without knowing the contents of the DoH.

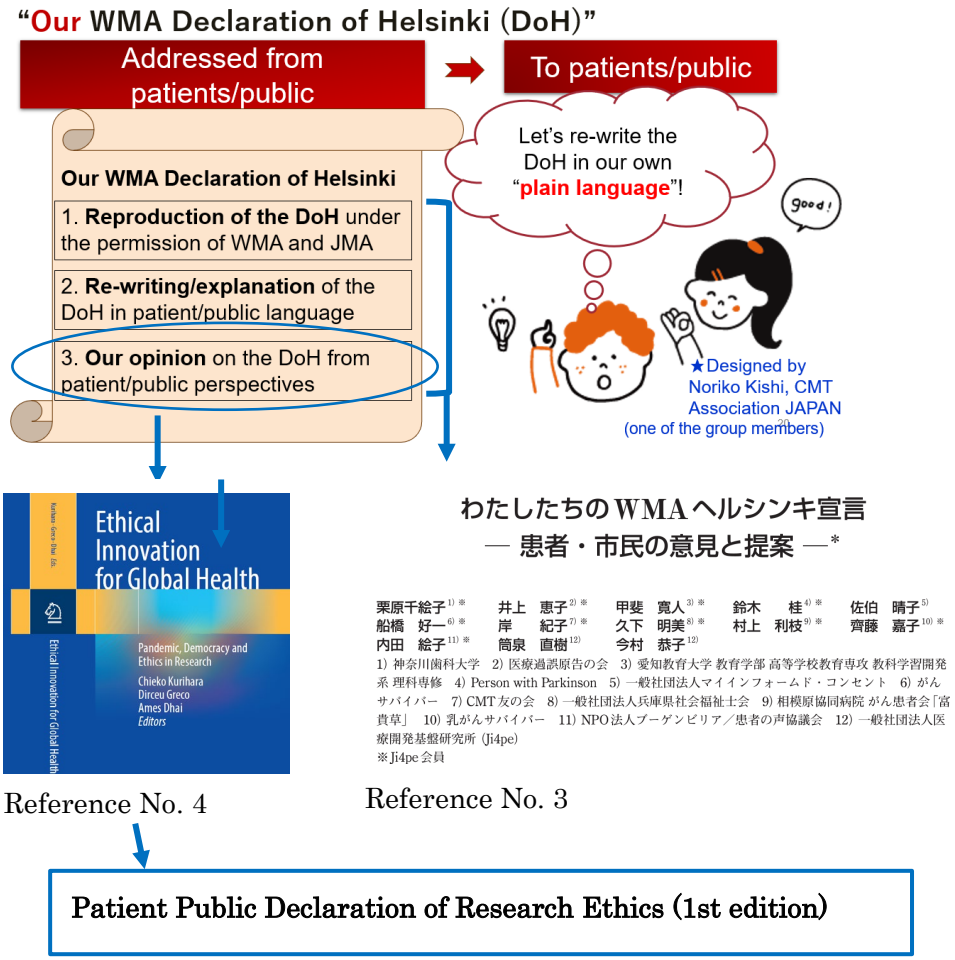
During the series of study meetings, a group member proposed that, as the texts of the DoH is difficult for the general public to understand, we should produce a document called "Our WMA Declaration of Helsinki"[3], which will be communicated in our own language to the people in the same position as we are. It consists of the following three

descriptions for each paragraph of the DoH.

(1) Reproduction of each paragraph of the DoH, using the Japanese translation of by the Japan Medical Association (JMA) (based on the permission of the WMA and JMA)

(2) Paraphrasing of each paragraph of the DoH in our own plain language

(3) Our opinions on each paragraph of the DoH



In the course of this activity, an extraction of the part (3) only was constructed in English manuscript and it was included as one chapter of a book published from an international publisher[4]. During a webinar to disseminate the publication of this book, Professor Ames Dhai, one of the editors of this book, acknowledged that the content of the opinions had important significance which is not found in the DoH, and encouraged us to issue a declaration of research ethics by patients and the public, from here in Japan. After the publication of this chapter of a book in English, we published a paper in Japanese "Our WMA Declaration of Helsinki", consisting of (1) to (3).

The DoH was first published in 1964 and the 2024 revision to the 2013 version is the

tenth and latest after eleven years interval. In February and July of 2024, we submitted our opinions to the draft revision of the DoH, responding to the two times of public consultations organised by the WMA.

While some of our opinions are reflected to the revision (we believe that there would be many other same/similar opinions), some are not. For this reason, we have decided to publish the Patient and Public Declaration on Research Ethics, in order to disseminate the 2024 revision of the DoH and expand the impact of it. Our Declaration is on the premise that the DoH will be adhered to, and with the hope that ethical principles not included in the DoH and we present here will become in future a universal common ethical principes.

This first edition is based on the agreement among the authors, however, we wish to update it collaborating with domestic international individuals and groups of patient and public.

Development of cutting-edge technologies and patient public involvement

The development of cutting-edge technologies is now being pursued in various forms, bridged from basic research to human applications, and then commercialisation. Development of technologies that can artificially create human life and mental activity is progressing, including artificial intelligence through the use of accumulated personal data, utilising information technology, manipulation of genetic information such as genome editing, technology to create eggs and sperm from iPS cells and fertilise them, and brain organoids. In order to consider the impact of these technologies on the human mind, society and future generations, as well as on ecosystems, it is necessary to involve patients and the public from the early stages of research and development and to continue thorough discussions.

Protecting health and well-being, living with and overcoming illness or disease is not an issue for individuals or families alone, but for the society as a whole, and it is necessary to consider social issues that emerge as technology continues to advance day by day from a bird's eye view, encompassing in inclusive way a diverse and changing society and ethical perspectives. In order to create new ethical norms responding to the emerging social issues, with a vision of what we should aim for in the future, we declare a research ethic that we should all respect for.

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Patient Public Declaration of Research Ethics[1]

1. Purpose and scope

The Patient and Public Declaration on Research Ethics is a declaration of ethical principles for research involving humans, of the patient and public, by the patient and public, for the patient and public. Our Declaration requires all those who conduct health research involving humans to adhere to the World Medical Association (WMA)'s Declaration of Helsinki (DoH) (Box 1).

Our Declaration covers health research involving not only living humans, but also research on prenatal embryos, foetuses, dead persons, and materials or data derived from humans.

On the premise that the DoH is adhered, we declare here some additional ethical principles, most of that are not included in the DoH, which was developed primarily by physicians. Our Declaration proclaims the principles with aspiration that they come to be recognized in future as world common norms, being addressed to all the patient and public, including those who are physicians and other experts.

Box 1 Principles of research ethics established until the 2013 revision of the Declaration of Helsinki (Summary. Key words are in bold.)

■Preamble
- The Declaration of Helsinki is an **ethical principle for medical research involving humans**.
- The Declaration covers research on not only **living persons** but also **individually identifiable human materials and data**.

■General principles
- **The rights and interests of research participants take precedence over the goal research to generate new knowledge**.
- Research must be conducted only by **qualified** individuals.
- **Harms resulting from participation in research** must be appropriately **compensated** and necessary **treatment** provided.

■Risks and benefit
- **Risks benefits assessment**, **risk minimization** and **risk management** are continuously required, and research may not be initiated or continued unless the **benefits outweigh the risks**, and must be discontinued if necessary.

■Research protocol and Research Ethics Committee approval

[1] A summary of the principles established by the 2013 version of the DoH is given in Box 1, and in the text of this Declaration, statements based on the new principles in the 2024 revision of the DoH are given with article numbers in the form of (§1) , and statements based on the principles already in the 2013 version of the DoH are given in the form of (§1, 2013), with the article number of 2024 version.

- Research may not be initiated or continued unless a **research protocol** describing the design and performance of the research has been approved by a **research ethics committee**.

■Informed consent

- Participation of individuals giving **informed consent** must be **voluntary**, after adequate necessary information is provided. For a potential participant **incapable of giving consent**, informed consent from **authorised representative** is required. In this case, **assent** from this individual must be sought.

■Placebo use and post-trial provisions

- The benefits, risks of a new intervention must be **tested against those of the best proven intervention**, if there is. Exceptional comparison with **placebo or no intervention** may be acceptable if there is **no additional risk of serious or irreversible harm** resulting from not receiving the existing best proven intervention.
- Provisions for **post-trial access** for participants who still need the tested interventions should be made in advance of starting clinical trial.

*Acceptable risk in this case described in the CIOMS guideline is "no more than a minor increase above minimal risk".

**There are opinions that post-trial access should be ensured to trial participants, not only making provision in advance, and to host community as well as those in need globally.

■Research registration and publication

- Research must be registered in a **publicly accessible database** before recruitment of the first participant. Results must be accurate and must be **published even if the results are not what is expected**.

■Unproven Interventions in Clinical Practice

- An **unproven intervention** may be used by a physician for a treatment of a patient, under some limited conditions, including **seeking for expert advice**, **obtaining informed consent** from a patient or representative. This intervention should **subsequently be made the object of research** to **evaluate its safety and efficacy**.

Source: Summarized from the World Medical Association's Declaration of Helsinki: Ethical principles for medical research involving human subjects, 2013 version, reference No. 1.

2. Fundamental principles

2.1 Research ethics principles in plain language

Research ethics principles must be described in plain language that can be shared among all.

2.2 Ethical principles based on universal human rights norms

This Declaration is based on internationally recognised norms of fundamental human rights[5678], patient rights[9], and principles of medical ethics[1011].

Both researchers and research participants should be aware of these basic norms.

2.3 Research ethics principle based on responsibility and awareness as "research

participants"

The rights of research participants （§1 and others）must be respected and assured.

On this premise, research participants will take a role of a collaborative partner to co-create research, having responsibility and awareness.

Furthermore, we wish to establish research ethics principles covering ethics of patient-initiated research.

2.4 Promotion of patient and public involvement

We will participate proactively in research and developments of medical products, and healthcare policy.

Additionally, we will advocate and support the participation of those who are unable to proactively express their wishes, and will deliberate together with them how their meaningful participation （§6）should take place.

2.5 Respect for human rights and welfare of research participants

The core principle of the DoH to state that the rights and interests of research participants take precedence over the goal of research（§7, 2013） must be upheld at all times.

2.6 Realising the value of research

The ultimate goal of medical research is to realise holistic healthcare through recognising the fundamental rights of patients, including diversity, and respecting the values of the communities of the research participants.

Everyone involved in research should share that such goal is the "value" of research.

2.7 Prevention of discrimination and stigmatization, and consideration of the impact on the environment, society and future generations.

Generating discrimination or stigmatisation from the conduct or result of research must be prevented.

All those who are engaged in research must consider about the impact on the human society, human mind, and on the future generation, as well as sustainability of ecosystem.

For this reason, patient and public involvement from the early stage of research and development program（§6） is required.

2.8 Advocate the rights and interests of the vulnerable and promote their participation in research

The participation of vulnerable people in research provides opportunities for their social inclusion, contribution to improving the future health and well-being of their community and all people, and creates value of the research for society as a whole.

The people who have particular difficulties in expressing and making decisions because of their physical or social conditions or power structure are more likely to be put at risk of research, and disadvantaged in the sharing of benefits from research, thus they must receive additional protection（§ 6 , 19, 20, 2013）.

Any form of exploitation in the name of research must be prohibited.

Self-advocacy of vulnerable people to express their views and make their own decisions, as well as advocacy on behalf of the rights and interests of them must be promoted.

2.9 Ensuring the scientific validity of research and animal welfare

Scientific validity and research integrity must be assured（§ 21, 22, 2013）, avoiding research waste（§ 21）, and strictly prohibiting research misconduct（§ 12）.

Animal experimentation must be accordance with the principles of 3Rs (Replacement, Reduction, Refinement) and animal welfare （§ 21, 2013）must be respected.

3. Research Ethics Committees

3.1. Diversity of Research Ethics Committees and patient public involvement

Diversity of Research Ethics Committee members must be assured and participation of members representing patients and the public must be promoted（§ 23）.

Members representing the patients and the public, should respect the perspectives of those who do not express their opinions, and will act taking responsibility for expressing opinions, asking questions if there is, and will participate in deliberations and voting.

3.2 Open recruitment for fairness

Research Ethics Committees must ensure transparency, independence （§ 23, 2013）and fairness in their establishment, membership and operation.

The selection of committee members must not be arbitrary, and there must be a system whereby motivated members who have achieved relevant systematic education program can make application and be assigned through open recruitment, be given training opportunities, and finally are replaced after serving a certain period of time, so that they can be followed by well-trained successors.

3.3 Assessment of advanced technology, impact on society and future generations

Research ethics review committees should have the function of deepening discussions on the impact of advanced medical technologies on society and future generations that emerge from the review of individual research protocols, presenting their views as supplementary opinions and encouraging discussions in society.

4. informed consent

4.1 Informed consent and shared decision-making

The decision of a person to participate in research must be based on fully informed understanding and the free and voluntary consent（§ 25, 2013）.

Explanations about the research must be given in a way that is understandable（§ 26） to candidate participant and that correctly conveys the nature of the research.

Research participants must be guaranteed the right to disagree, discontinue participation or withdraw consent without detriment（§ 26）.

In addition to the assurance of individual informed consent, shared decision-making should be promoted, on the premise of patient-centeredness, collaborating with the patient's family members, supporters, physicians and other multidisciplinary research team, discussing together on the treatment plan, including whether or not to participate in research, and reviewing the continuing participation as changing circumstances.

It is desirable to deepen the discussion on the impact on future generations, present views as ancillary opinions and have the ability to encourage society to discuss the issue.

4.2 Advocating decision-making for people without capacity to consent.

For a person who are not capable of giving informed consent, because of immaturity or physical or mental situations, a representative who is giving proxy informed consent must be a person who can most advocate the will, including previously expressed ones（§ 28）, and the best interest of the candidate participant.

In addition, advocate and support is required so that such a person can express an assent（§ 29, 2013）, an expression of willingness of participation in research, after receiving sufficient explanation is given according to the person's capacity to understand.

4.3 Dignity and rights of persons without capacity to consent and without relatives

The representation of decision-making of persons who do not have the capacity to consent, have no relatives and are unable to give their own or proxy consent even at a later date has not been adequately considered.

We wish to discuss from the perspective of patients and the public the rights and

conditions for participation in research of such persons, who would be the most vulnerable.

4.4 Broad informed consent and dynamic consent

The Declaration of Taipei for Health Databases and Biobanks[12] must be adhered where data or materials obtained in research may be subject to secondary use（§32）.

When a research participant gives consent to the secondary use of materials or data, the consent should be "broad informed consent" based on sufficient understanding of the information given as far as possible about the purpose, who could use, and the governance arrangement of possible future secondary uses. We request that how to access the secondary use information to be disclosed and the right of withdrawal of consent to be assured.

We wish to promote an emerging concept of "dynamic consent", which means giving continuing consent to the use of material or data, being informed about a new secondary use, progress of a research, as well as relevant important information generated from research, and the comprehensible way of how to access the secondary use information can, on the premise of assurance of right to refusal or withdrawal. We hope the development of social consensus for the methods and procedures for such type of consent and environment where participants can make adequate decision.

4.5 Right to know and right not to know

"Right to know" and "right not to know" of a research participant must be respected. Any information meaningful for an individual participant, including secondary findings, obtained from research, must be explained according to their wishes, based on due consideration of its scientific validity and its clinical significance in the treatment program.

5. Principles of controlled clinical trials and post-trial access

5.1 Controlled clinical trials

Clinical trials comparing treatments（§33, 2013） are conducted because it is not known which method is better.

We will be able to make decision whether or not to participate in placebo-controlled trial only when we are explained the significance and compelling reason.

When there is a safe, effective treatment, it is essential to compare with it. Nevertheless, if placebo-controlled trial is conducted in such setting, placebo-related risk

must be minimal.

We wish to be involved in the discussion on acceptable condition of the placebo use, from the perspectives of patients and the public.

5.2 Post-trial access

Research participants (patients) who still in need for a treatment proven to be safe and effective （§ 34, 2013） should be provided with it after the completion of the trial.

Research is co-creation involving patients and the public and the results of research are to be delivered to future society. To ensure that the results from research could be accessed from those who need them, we will work together with those involved in research to develop the infrastructure to realise post-trial access.

6. Publication of research results

6.1 Database registration of research

Outline information at the beginning （§ 35, 2013） and result information at the completion of the research must be registered in a publicly available database to make it freely accessible to all.

The results of the research should be released with a lay summary written in plain language understandable for the general public.

6.2 Journal publication of research

For the purpose to promote patient public involvement, “open access” of the report of research results in peer-reviewed journal should be facilitated so that everyone can read the full text through fair and equitable cost-sharing.

“Open science” should be also promoted so that the data supporting the research results can be disclosed to public or shared conditionally with those who need them. In addition, “citizen science” where patients and the public can make use of such data and participate in the research process should be also promoted.

7. Unproven treatments

The DoH state that physicians may use some unproven treatment for patient care under some conditions but recommends that it should be made objective of research to evaluate safety and efficacy （§ 37, 2013）.

When unproven intervention is used, relevant data should be accumulated and safety

and efficacy should be monitored.

8. The wishes of patients and the public

Both medicine and medical research depend on a trust between physicians/researchers and patients and the public.

The goal of medicine is not to pursue profit, but to move towards holistic care and realise the physical, mental and social well-being of humans.

Research is altruistic in nature and is supported by the altruism of all involved.

We all must always be aware that healthcare is based on research supported by such ethical foundation.

Conflict of interest

There is no conflict of interest to be declared related to this article.
KS is an employee of ASKA Pharmaceuticals.

Acknowledgment

We appreciate Ms. Midori Senoo, Managing Director, Myotonic Dystrophy Patients' Group of Japan (DM-family), and Ms. Konomi Wakasa (Patient's Association of Nesidioblastosis) who participated in some part of our series of web meetings and provided meaningful opinions. We also appreciate Prof. Dirceu Greco (Professor Emeritus of Infectious Diseases and Bioethics at the School of Medicine, Federal University of Minas Gerais, Brazil) and Prof. Ames Dhai (Professor Bioethics, School of Clinical Medicine, University of the Witwatersrand, South Africa), editors of the book which includes our chapter where our original ideas related to this declaration was expressed.

Author contribution

This article is a re-construction from the previous publications noted at the top page, and all the contents are constructed from the opinions expressed from authors whose positions are patient and public: YS、HK、YF、KI、NK、AK、TM、KS、EU, especially most critical re-construction was made by HK. KS is also an expert in drug development and AK is also a practitioner as a qualified psychiatric social worker. CK

took a role of editorial work to interpret the words expressed from authors with patient and public perspective into the terminologies of research ethics. KI gave advice as an expert of medicine and drug development. Contributions of all the authors are accordance with the recommendation of the International Committee of Medical Journal Editors.

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