Invited lecture

Presidential Symposium in the 40th Annual Scientific Meeting of the Japanese Society of Clinical Pharmacology and Therapeutics, 2019
International Collaborative Research and New Trends of Research Ethics

Declaration of Helsinki: Challenges and new trends ahead of us *1

Otmar Kloiber
Secretary General, World Medical Association

Organized & Chaired by:
Kazutaka Shimoda [1], Hiroshi Watanabe [2]
Discussant: Kyoko Imamura [3]
Organized by: Chieko Kurihara [4]

(Wednesday, December 4, 2019, Keio Plaza Hotel Tokyo, Japan)

*1 The symposium was held with the cooperation of the Mochida Memorial Foundation for Medical and Pharmaceutical Research and Rinsho Hyoka Kankokai Inc. (Clinical Evaluation). Japanese version is included in *Clinical Evaluation*. 2020; 48(1). Other related articles in this issue:
http://cont.o.oo7.jp/48_1/48_1contents_e.html

1 Professor & Chairman, Department of Psychiatry, Dokkyo Medical University School of Medicine; Meeting President of the 40th Annual Scientific Meeting of the JSCPT; Current President of the JSCPT

2 Professor, Executive Director / Vice President, Hamamatsu University School of Medicine; Immediate Past President of the JSCPT

3 Project Professor, Social Cooperation Program of IT Healthcare, The Graduate School of Pharmaceutical Sciences, The University of Tokyo

4 National Institutes for Quantum and Radiological Science and Technology

Abstract

In 1964 the World Medical Association Declaration of Helsinki (DoH) was the first international policy to set ethical principles for medical research with human subjects. The DoH demanded informed consent and later the authorization by ethics committees, the publication and sharing of results, the registration of clinical trials and many other groundbreaking elements of protection for all participants in research.

The success of the DoH has partly been due to being regularly updated taking into account new developments and trends in research when those pose new questions or challenges regarding ethical conduct. Having received major updates every 5 to 10 years, the last DoH revision in 2013 was complemented in 2016 by the Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks, which extended the ideas of subject protection to the world of virtual studies.

Current technological developments, but also the need for a better response to emergency situations, which may include the testing of new medicines (e.g. vaccines) or procedures, as well as the currently insufficient pre-clinical evaluation of medical products, raise questions about the comprehensiveness of the DoH. The WMA observes a trend towards branched studies using multiple arms and new designs, including the use of data sets from large patient groups as virtual control groups (“Real-World-Data”).

On the social side, the development of patient-driven research, the inclusion of vulnerable groups and the question of ownership of data and process may raise challenges to the principles laid down in the DoH. Is it time for the next revision?

Key words

medical ethics, human subject protection, research integrity, patient centricity, real world data

Rinsho Hyoka（*Clinical Evaluation*）. 2020；48(1)：W9-W27.［Epub ahead of the issue publication］

Dr. Otmar Kloiber, M.D., Ph.D.

After studying medicine at the University of Cologne, Otmar Kloiber joined the Department of Biochemistry at the University of Minnesota, Duluth in 1985. He continued as a research fellow at the Max-Planck-Institute for Neurological Research in Cologne until 1991 when he joined the German Medical Association (GMA). Between 1997 and 2005, he served as Secretary and finally Deputy Secretary General of the German Medical Association. During his tenure in GMA, he was appointed as Member of the Study Commission on the Law and Ethics of Modern Medicine of the German Bundestag (Parliament), 14th electoral term. He has intensely co-operated with the Standing Committee of European Doctors (CPME), the World Medical Association (WMA), and other national and international medical associations. Since 2005 he serves as Secretary General of the World Medical Association. He is interested in the development of deontology under the influence of health system organization and its relation to the provision of medical care. He provided advice to numerous governments and parliaments on medical ethics and socio-medical issues. His personal advocacy focus is on equitable access to quality health care for all people.

In 2006, he was awarded an honorary doctorate by the Victor Babes University for Medicine and Pharmaceutics, Timisoara, Romania. He was appointed Clinical Professor in Health Administration at the Brooks College of Health, University of North Florida from 2009 to 2013.

1. Introduction

First let me just make one thing clear: I am here to report to you about what we are doing, but more important, to learn from you. I am sure most of you sitting in this room have much numerous ideas about research conduct and the changes that will be necessary in research ethics in the coming years, than I have. This presentation is been thought as the start of a dialogue with you, which I would like to continue.

2. Deontological work of the WMA

Before I come to the questions of possibly renewing the Declaration of Helsinki (DoH), let me give you a brief overview on the general deontological work that the World Medical Association (WMA) has done (Table 1). In 1948, one year after its foundation the WMA started with the Declaration of Geneva, which is kind of a renewed Hippocratic Oath. This finally has been up-dated most recently 2017, in Chicago. One year after the initial Geneva Declaration in 1949 the WMA published the International Code of Medical Ethics. These two policies, the Declaration of Geneva and the International Code of Medical Ethics, are the core

documents of medical deontology. It's not the Declaration of Helsinki which came much later and is dedicated to research ethics, but it is those two documents which describe the basis of medical ethics nowadays.

There are some other documents I would like to mention: The Declaration of Tokyo, 1975, prohibiting physicians' involvement in Torture. Related to this is the Declaration of Malta on Hunger Strikers, in 1991, which says that doctors must not force-feed hunger strikers. These are very prominent papers which during the past years have played a very important role in dealing with Human Rights violations. There is the Declaration of Lisbon on the Rights of the Patients, which the WMA published in 1982, long before many others started to think about patient rights. Very recently 2016 the Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks, supplemented the Declaration of Helsinki extending ethical rules into the world of virtual research.

We have now close to 200 policies, and I would like to just mention these core policies because of their importance.

3. What is the Declaration of Helsinki?

The Declaration of Helsinki of 1964 is the first international document on research ethics and principles for medical research (Fig. 1). Since 1964, it has been updated several times. The Declaration of Helsinki aims to protect the subjects in a study, those patients or persons who are helping us as research subjects to study a certain question in medicine. It's not only about clinical trials, the Declaration of Helsinki sets rules for any medical experiment that is being done involving human subjects. It serves also to facilitate medical research, to make it easier to do research with human beings, by building trust in medical research.

Table 1　General deontology

Declaration of Geneva 1948 / 2017
https://www.wma.net/policies-post/wma-declaration-of-geneva/

International Code of Medical Ethics 1948 / 2006
https://www.wma.net/policies-post/wma-international-code-of-medical-ethics/

Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects 1964 / 2013
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

Declaration of Tokyo
Guidelines for Physicians Concerning Torture and other Cruel, Inhuman or Degrading Treatment or Punishment in Relation to Detention and Imprisonment 1975 / 2016
https://www.wma.net/policies-post/wma-declaration-of-tokyo-guidelines-for-physicians-concerning-torture-and-other-cruel-inhuman-or-degrading-treatment-or-punishment-in-relation-to-detention-and-imprisonment/

Declaration of Lisbon on the Rights of the Patient 1982 / 2015
https://www.wma.net/policies-post/wma-declaration-of-lisbon-on-the-rights-of-the-patient/

Declaration of Malta on Hunger Strikers 1991 / 2017
https://www.wma.net/policies-post/wma-declaration-of-malta-on-hunger-strikers/

Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks 2002 / 2016
https://www.wma.net/policies-post/wma-declaration-of-taipei-on-ethical-considerations-regarding-health-databases-and-biobanks/

Fig. 1 Aims and mechanisms of the Declaration of Helsinki

Aims
- Facilitate medical research involving humans
- Protecting study subjects
- against dangerous experiments and exploitation
  - Mechanisms:
    - Ethical and methodological correctness
    - Informed Consent
    - Advices and permission by ethics committees
    - Obligation to make public (study as such and results)

Photograph: Courtesy of the Finnish Medical Association

The key mechanisms in the Declaration of Helsinki are the ethical and methodological correctness of a study that is being demanded, the informed consent, first time in an international document research policy, the advice and permission by ethics committees and the obligation to publish and share findings. The Declaration of Helsinki was the first international document which asked for those safeguards. None of this has been invented by the WMA. It all had been there before in one place or another, but it never has been brought to an international consensus before.

4. Origin and current development of the Declaration of Helsinki

The Declaration of Helsinki developed in several steps (Table 2). There were two preceding documents before 1964, a resolution in 1954, and a draft document on research ethics in 1961. Since then, in the Declaration of Helsinki, received further important amendments in the ‘90s about placebo use and then later on, in 2000, on post-trial access to care. The latter needed clarifications as the wording turned out to be unclear. In 2008, we corrected this with the version of Seoul and we developed further the Declaration of Helsinki to a now current version adopted 2013 in Fortaleza.

Table 2 Declaration of Helsinki: historical development

1954	Resolution on experiments with humans: Principals for researchers
1961	Draft Ethics Codex for research in humans by the World Medical Association Medical Ethics Committee
1964	**Declaration of Helsinki adopted (informed consent)**
1975	Tokyo (ethics committees)
1996	Somerset West (placebos use limited)
2000	Edinburgh (placebo use, post trial access to care, vulnerable populations)
2002	Note of clarification (Placebos)
2004	Note of clarification (post-trial access to care)
2008	Seoul (opening of the placebo use/post trial access)
2013	Fortaleza (new structure, higher subject protection)

Table 3　Importance of the Declaration of Helsinki

Referenced by

- EU GCP Directive /Regulations
- European Medicines Agency
- US Food and Drug Administration (withdrawal after the Edinburgh version)
- Japanese GCP/Research Guidelines
- CIOMS (Council for International Organizations of Medical Sciences)
- WHO (World Health Organization)
- ICH (International Conference for Harmonization)
- Numerous national laws and regulations

The importance of the Declaration of Helsinki is documented by being referenced by many organizations (Table 3). It has made it into several laws and international treaties. It is by far the most recited document when it comes to research ethics in human beings.

5. The 2013 Fortaleza version of the Declaration of Helsinki

What is different with the 2013, the current version of the Declaration of Helsinki (Table 4)? First of all, we restructured the document so that it now allows a better reading, especially by means of including sub-headings. We are convinced it offers a higher protection for vulnerable groups as for participants in general, i.e. by including the issue of compensation for damage done by a trial. There are more clear requirements for post-study arrangements, to better avoid exploitation of persons taking part in a study. We have a more systematic approach now for placebo use without weakening our demands for safeguards.

Nevertheless, when we adopted the last version of the Declaration of Helsinki in 2013 it was already clear that we had left a gap. This was at that time called the “secondary use of research data”. What should you observe, what should you keep in mind when you want to re-use the data which you have won from a clinical study or from any other experiment?

Table 4　The 2013 “Fortaleza”-Version of the Declaration of Helsinki

What is different?

- Better readability by reorganising and restructuring the document with sub-headings.
- Higher protection for vulnerable groups.
- Higher protection for participants by including the issue of compensation for the first time.
- More precise and specific requirements for post-study arrangements.
- A more systematic approach to the use of placebos, but no weakening of the ethics of placebo use.

Open question: A practical solution for research using the identifiable data and material in bio and data banks on a regular basis.

6. Opportunities and threats with big data

This brings us to the question of how to use big data? We are sure, the problems we already see occurring with the use of big data, but also the chances are just the tip of the iceberg. There is much more to come in good things we can do with big data. There is much more to come in dangers with big data.

7. Informed consent and broad consent

Based on the Declaration of Helsinki as the core document on research ethics, we found that a one-time broad consent which had been proposed by some to use the data repeatedly or to use generally clinical data for research was not acceptable. Such a broad consent for later (re-)use of data practically voids the concept of informed consent (Table 5). The concept of informed consent is one of the biggest achievements in research ethics and patient rights in the last century. We don't want to give that up just because we now can use big data and bio-banks.

Table 5 Initial conclusions

- Broad or one-time consent alone is not acceptable as it practically voids informed consent.
- Stringent use of informed consent is unrealistic.
- A specific solution only for research is neither practicable nor desirable.
- However, other than in classical study situations the holder of the data or material is often different from the user/researcher.

However, a stringent use of informed consent is unrealistic when doing research with big data because databases may be used multiple times, for changing and sometimes unforeseeable purposes. It is not possible to ask every patient who has given you data every time whether they consent to this or that use. We need a new solution, allowing the frequent use of research data and at the same time providing a level of protection being equal or similar to the informed consent.

8. Ethics of health database and biobanks

We also found that it is not only research the data may be used for. There may be other questions directed to such a pool of health data. In the end we found that the differentiation between research and non-research is no longer realistic. However, there are also chances by having a data base of biobank as a repository, because you can give the repository a governance structure and you can separate between those who are holding data in a database or bio-bank and those who are using it. At some point that may make things a little bit easier to provide for correct ethical use.

The solution we found and which finally constitutes the WMA Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks is a stepped concept (Fig. 2). It starts with an ethical review of the justification for a database or biobank, which means you have to explain why you collect data or samples of a person. Then there has to be a consent procedure which gives information, not about a concrete research project, because you don't know that yet, but how this data will be governed and protected, how access will be allowed and what happens for instance, if there are incidental findings with this data.

Then when it comes to the use of the data there has to be an ethical review of any proposed use. The ethical review may then tell the user or researcher that the initial consent which had been given at the time of collec-

Fig. 2　A Solution: Declaration of Taipei

- Ethical review of the justification for the database or biobank
- Consent with Information about purpose and procedures (as far as known and protection mechanisms install)
- Ethical review with any use of the database or biobank
- Determination if additional consent is necessary

tion is enough, because there will be no danger for the data or specimen donor foreseeable or that there will have to be additional safeguards like anonymization and aggregation or the ethics committee may advise to ask each person for informed consent, because there are potential dangers to the donor by using this data or specimens. Such may derive from a potential stigmatization, from incidental findings, or something else that comes up.

9. WMA Strategic Plan

The WMA has a strategic plan (Fig. 3). In the strategic plan, if you look to the first section you find our focus on medical ethics. One of the priorities is to maintain active ownership of the Declaration of Helsinki and the Declaration of Taipei. Practically that means we have to go out and ask the question, is the Declaration of Helsinki still relevant? This is why I am speaking to you and what I would like to find out with your help.

10. Pending questions

As the stewards of the Declaration we constantly have to ask certain questions such as: Is the underlying value concept of the Declaration of Helsinki still valid? Are those values still protected by the Declaration of Helsinki? Are there new developments in science, in society which may have an effect on research conduct? Are there developments that question the relevance of the Declaration of Helsinki? Are there other developments outside the Declaration of Helsinki that we have to consider or observe in order to protect research subjects or research participants in general?

Now, let me try to group those questions (Table 6). The first two, on the values, whether they are still correct and protected by the Declaration - we will for the moment simply will take them as a given, until they are seriously challenged. But then comes a group of questions where we really have to deal with now, even so we are not yet in a formal process of revision. Are there societal or scientific developments relevant to the Declaration of Helsinki? Are there developments which may undermine the relevance of the Declaration of Helsinki? There may be more questions of such type which we will have to address at a later point. Finally,

Fig. 3　WMA Strategic Plan 2020-2025

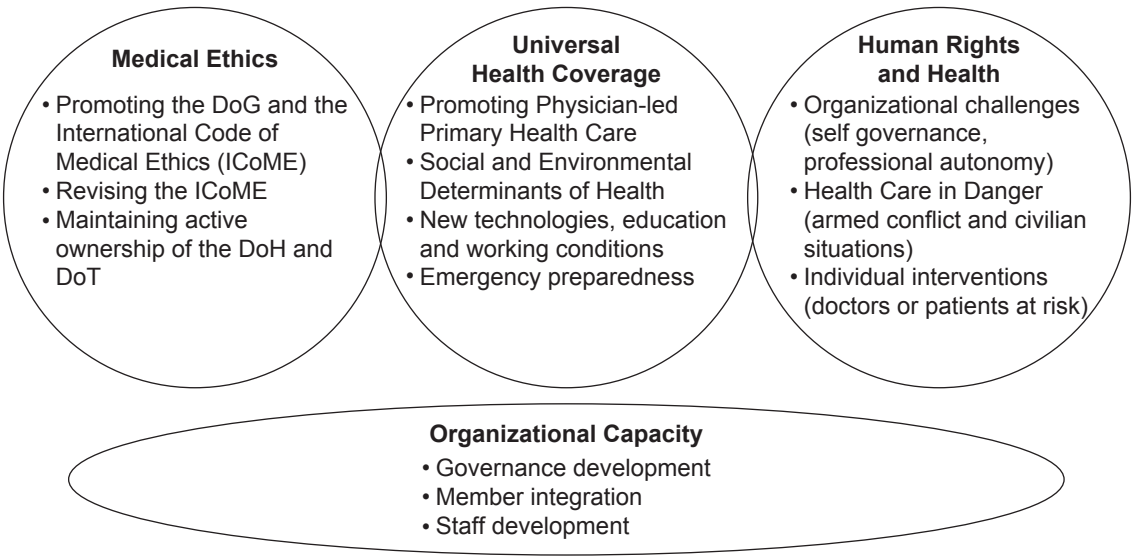

Table 6 Declaration of Helsinki: Pending questions

• Is the underlying value concept still valid? • If yes, is it still protected by the DoH?
• Are there scientific or societal developments that the current DoH does not cover? • A there developments that question the relevance of the DoH?
• Are other actions outside the DoH necessary to protect research subjects and research integrity?

are there developments outside the current frame of the Declaration of Helsinki which nevertheless the WMA has to look into, when caring for the Declaration of Helsinki? Let me concentrate on the questions in the middle.

11. New developments relevant to the Declaration of Helsinki

For the new developments, I see a not exhaustive number of areas, which to me appear necessary to be reconsidered or at least to be discussed in the context of the Declaration of Helsinki (Table 7). That does not mean that such discussion or consideration must necessarily lead to amending the Declaration of Helsinki, but we have to put them on our radar. Number one, patient centricity, number two, new study designs, number three, new requirements for ethics committees, the big data problem, new reasoning approaches for measuring research and research results, the question of informed consents, its methods and validity; new concepts for key groups, study benefits in prevention research and so on.

Table 7　New developments

- Patient Centricity
- New study designs (adaptive)
- New requirements for ethics committees
- Big Data availability
- New reasoning approaches
- Informed consent – methods and validity
- New concepts for key groups
- Study benefits in prevention research

12. The concept of patient centricity (Table 8)

You probably all have experienced that there is a much stronger involvement of patients and communities, which on one hand leads to a better acceptance of studies in the research cohort or in affected communities. This may lead to more patient-relevant designs because we can learn from the study participants and from our patients. There may be a higher intensity of contribution by patients through self-collected and patient-owned data. I must mention the Internet of Things (IoT), sensors, smart watches, fitness apps and wearables collecting data from patients and which are already being used for health studies at this moment.

On the other hand, there are also downsides which we have to discuss: The power of patient groups may extend to an influence that is deforming research protocols and methodology. And last but not least, there is the question about the independence of patient groups.

Table 8 Patient centricity

↗	Better acceptance of studies
↗	More relevant designs
↗	Higher intensity of contribution by patient owned and collected data (Internet of Things)
↘	Power of patient groups on forcing research items
↘	Independence of patient groups
↘	Interference with study protocols
↘	Interference with subject selection and randomization
↘	Legitimization of patient representatives

There is a big group, PatientsLikeMe, which presented itself as a patient organization and then very suddenly in summer this year (2019) it turned out that this organization is not by patients - for patients but it had a big Chinese investor. The United States (U.S.) authorities last year raised concerns because the group is dealing with highly sensitive, confidential, patient data. They finally had to change the investor [1]. The new investor is one of the big insurance companies in the U.S., United Healthcare. I as a patient, would have doubts whether these are the hands in which I would like to give my patient data in for research. A lot of skepticism remains with such a model.

13. Patient groups

There are several questions regarding patient groups and organizations.

First there is the question of the independence of patient groups. Does their financing produce a conflict of interest?

There may be interference with study protocols, which I have learned from colleagues in clinical trials. Patients are telling researchers how they have to structure or restructure their research protocols. That may on one side be valid and justified and part of patient-driven research. On the other hand, it raises questions about the scientific validity of studies and protocols. There may be interference with subject selection and randomization. There have been notions about patients pressuring entry into studies which messes up randomization and group allocation.

Then there is also the question of legitimization of patient representatives and what is their mandate? Who are the leaders of those groups and bringing the information from patients to us?

Again, their participation can be very positive and helpful, but on the other hand, it must be allowed to ask how patient representatives are legitimized and whom do they really speak for.

14. New study designs (Table 9)

The developments in technology, study design and big data use during the past decade have been extremely

1) Matthew Herper M. PatientsLikeMe, forced by U.S. to ditch Chinese investor, sold to UnitedHealth Group. *STAT*. June 24, 2019. https://www.statnews.com/2019/06/24/patientslikeme-forced-by-u-s-to-ditch-chinese-investor-sold-to-unitedhealth-group/

rapid and they show us new avenues in dealing with the results from trials and to develop new methods. Just to mention germ-line therapies, which are in theory possible now. We already have heard about experiments where CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) technology has been applied to embryos. What does that mean for the design of an experiment, if you can't ask the person that is your research subject, that you have to care for after an experiment, potentially a new human being that will be there for whole life. What will be the observation period for that human being,? Will it be a couple of months, will it be a couple of years, will it be the whole life for that? We have no answers so far – just questions.

There are already multiple arm trials departing from our classical design of having a control group and a verum group in the past. There are adaptive study designs, which may change, which may develop during the course of experimentation. There are so called double dummy trials, which we hadn't seen years before, and there are now real-world-data controls coming to application.

Table 9　New study designs, big data availability, new reasoning approaches

- Germline therapies
- Multiple arm trials
- Adaptive study designs
- Double dummy trials
- Real world data controls
- Bayesian reasoning
- Data driven studies

Just 2 days ago, in *Wired*, a popular data science journal, the author conclude "the end of placeboes is in sight" [2]. That is a little bit premature, but it shows that we are about to use controls with real-world-data instead of using placebo or other control groups. This generates a lot of questions. Can we really compare groups in a study with the real-world-data? What does its use mean for our ethical standards, ownership of results and the ethical standards for research.

15. New reasoning approaches

There are new reasoning approaches which we haven't been using before in clinical trials, e.g. big data or real-world-data combined with Bayesian reasoning approaches. There are new approaches in better comparing study results with historical data all extending the classical comparisons which we have been using for decades. There will be data-driven studies arriving in completely new research arrangements which are no longer be inductive as we are doing them now for the last century. They will be deductive, and they will be derived from the data in which we may observe patterns to study. In other words: we will get answers for which we have to find the questions. New ways to find solutions for the problems we would like to solve.

16. New requirements for Research Ethics Committees (Table 10)

All of this leads to the question whether there should be new requirements for research ethics committees. The monitoring requirements for ethics committees which we have right now are weak, to put it friendly. The research ethics committee has the right to monitor. With new study designs like e.g. adaptive trials, should monitoring not be a requirement? At the moment this is a question, we don't have an answer yet. And then, if required, should monitoring reports be a prerequisite for publication? Should it be an obligation that whenever a study is being submitted for publication that there has to be obligatory monitoring report to make sure that the ethical requirements have been fulfilled? Can we leave it to ethics committees which nowadays for most of it take a decision and then forget about the studies. I am convinced that there are developments in the

Table 10 Ethics committee and informed consent

New requirements for research ethics committees
• Monitoring requirements – to be made obligatory
• Monitoring reports as prerequisite for publication
• Adaptive study designs
Informed consent – methods and validity
• Understandable?
• Complexity and usefulness
• Layered information
• Avatar use?

2) Chapman M. The end of placebos is in sight. 02 Dec 2019. *WIRED*. https://www.wired.co.uk/article/end-of-placebo-trials

research landscape which will force ethics committees to change their procedures in the future.

17. Pragmatic informed consent (Table 10)

Let me come back to the question of informed consent. Again, the informed consent is one of the biggest achievements in patient protection of the last century. However, you all know the forms that patients have to sign in order to give informed consent. Pages over pages with small print, and let's face it, most people don't read it and probably even more people don't understand it. That cannot be an informed consent. An informed consent has to be meaningful, has to be understandable, and has to be perceivable in a reasonable time. A 30-page document you get there which you have to sign when you are suffering and when you are in need of a medical treatment is not what I would consider helpful. We have to look into the complexity and the usefulness of the informed consent and the information we are giving.

There may be ways of doing layered information. Such information can point to more and deeper information, if patients wants to see it before giving informed consent, and for the rest it is restricted to the most important. We have to come to a less complex process and something that is really understandable and workable and at the same time provide complete information, if desired. Some colleagues would like to work with avatars. Avatars could enter into a dialogue with the patient. Patients could ask questions and avatars could give answers. A dialog which may take minutes or hours before an operation, or before an experiment that is being done, with hundreds or thousands of participants. New technology from hypertext to avatars may be the answer to provider of layered information on patient demand in order to really improve informed consent and at the same time to make it more feasible.

18. New concepts for key groups

We have to think about new concepts for key groups (Table 11). For instance HIV prevention research. Some groups like men having sex with men, drug users, and transsexual persons, have in the past often being excluded from research studies as they had been classified as "vulnerable groups". Such groups should receive special protection, as studies that can be done in other groups should not be done in such vulnerable groups. On the other hand, these groups rightfully underline that they have the highest danger of transmissions. In recent discussion with UNAIDS and WHO some demanded not to be labelled as a "vulnerable group", but as an "affected group". They demand not be excluded from research, but to be the target of research. The same can be asked for other groups, like, for instance, women in childbearing age. There are valid questions about the concept of vulnerability which we have to re-ask, especially before the background of prevention research. Are we wronging some groups from the point of distributive justice by labelling them as "vulnerable"?

That does not mean that I pledge for giving up the concept of vulnerable groups, but the question is whether for a specific research purposes, we have to redefine group status as some communities are demanding. We also have to ask whether just offering participation in a study can be an unethical inducement, be it a preventive study or be it a therapeutic study, if otherwise treatment is not accessible in a specific country or situation. Personally, I don't believe that it is, but those are questions which are coming up again and for

Table 11 New concepts for key groups: study benefits in prevention research

- Inclusion of children, seniors and women in reproductive age
- Vulnerable populations or "affected" populations
- Distributive Justice
- Benefit of study participation – undue incentive?

which, we have to give firm answers in the future.

19. Conclusions

With all the questions that are before us now, we have to consider a next revision of the Declaration of Helsinki (Table 12). New methodological approaches entering the research environment at rapid speed, are changing the research landscape. They are going far beyond the scenarios which we have had in minds when we made the previous versions of the Declaration of Helsinki.

These developments at least demand from us that we rethink the Declaration. That does not necessarily mean to amend it. Big data, the Internet of Things, new study designs, new reasoning methods and new statistical methods raise the question whether we should update requirements to study designs, researchers and ethics committees. We have to expect and to appreciate growing influence by the communities. We have new areas of research, such as prevention research, germline therapy or health system research where. Do they pertain to the Declaration of Helsinki and do the need to be addressed more clearly or discretely?

I have collected these ideas from different discussions and from different groups of experts, patients and regulators. I hope that I get more impressions, more ideas from you, from the discussion today and tomorrow. That all will help to maintain the value of the Declaration of Helsinki and to demonstrate our engagement for ethical research.

Table 12 Conclusions

A new review of the Declaration of Helsinki becomes more than likely as:

- The research methodology is continuing to change at a rapid speed – methods have developed beyond the scenarios that were known at the time of the last revision;
- Among other developments big data and the IoT allow new study designs and new reasoning approaches and bring a much stronger patient (and community) involvement;
- New areas of research, such as prevention research and health systems research bring about new challenges to research ethics.

＜Q&A＞

Kyoko Imamura, Discussant
Project Professor, Social Cooperation Program of IT Healthcare, The Graduate School of Pharmaceutical Sciences, The University of Tokyo

Kyoko Imamura　I am glad to learn that the planned revision of the Declaration of Helsinki may be in the next few years. Regarding patient centricity, human research should be based on full understanding of the patients participating in the study, but in fact, take an example, the institutional review board discussions involving patients and laypersons as discussant. We often see that they may not have a good understanding of what the trial is aimed toward and what ethical challenges they may face if they participate in that clinical trial in question. Over the years, in Europe and also America, there are a lot of community efforts to develop patient's knowledge and expertise related to clinical trial design teaching them how the drug is made into the world, how they are tested, and how they are delivered to the patients. The European and American organizations have been working to provide educational opportunity to the patient so that they can learn before they participate in the IRB discussions. This is not always the case in Japan.

We decided to start patient and public involvement consortium in Japan, trying to lead the activities nationwide to catch up with the patient centricity focus overseas. It is of paramount importance, especially in the days of big data and bio-samplings going out of the country without recognizing its potential risks or benefits. It will be nice to hear how the WMA is going to enforce patient centricity in action, not only in those well-developed western societies but also resource-limited regions where discussion is still immature and patients themselves are not aware of their rights.

Kloiber　Let me start with the first remark about the capacity of the ethics committees. We have to acknowledge that even not all the scientific members of ethics committees, will be always be capable of understanding all of the aspects of a trial. Trial protocols come from completely different fields of research, of medicine. It may encompass methods that even the scientific experts in the committee have never used or may even not know. So, all members in an ethics committee nowadays face challenges when it comes to their capability of comprehending proposed studies. There has to be a professionalization of ethics committees. Members of ethics committees should have qualified staff support. Some of the ethics committees already have scientific staff which helps them to understand the complexity of studies and can prepare them. I see this more or less as a requirement for a good functioning ethics committee in the future.

The involvement of patient groups has upsides and downsides. It is very good to have the involvement in order to prepare for a study to make it more meaningful for patients, to get acceptance for a study, to collect data from patient groups. This is especially important, if we are talking about real world data and Internet of Things (IoT). There are downsides when patient groups try to dictate what to do. There will be a real problem

when the pressure of patient groups would distort the scientific basis of studies. Another problem is: Who speaks for patients, who has the legitimacy to represent patients. Are we listening to the right ones?

As the WMA, we are not enforcing a community involvement. What we would like to do is to facilitate community involvement. Like with patient involvement: It is up to the patient themselves to decide whether they want to be part of it. We have started with outreach for instance in communities which are usually difficult to reach, for instance, illiterate communities. We have used so called speaking books, which are illustrated books that can speak a given text. In the future such communities may be better reached by mobile technology.

Q You have talked about issue in big data. Are you ready to provide new way to get informed consent in the revision of the Declaration of Helsinki?

Kloiber Yes, the answer lies in the Declaration of Taipei. In the Declaration of Helsinki, the informed consent is structured to serve a very classical research environment. We have one research question, one protocol, with a clear idea about benefits and risks that we can explain. When we collect sample data or sample specimens for future research, we cannot tell the people this is the risk and this is the benefit you can get, because we don't know, which research will be done. The differentiation has to be done by governance and due process. The first is an initial consent that is given to store and use samples or data. This should be given after receiving information on how the database or the biobank will be governed. What do they do with it? How do they give the data away? Who is the watchdog? What happens if something is being found out? What are the benefits you get back if there is a finding, for instance an incidental finding? So, the first step is a consent based on the trust in the governance of a database or biobank. Each research protocol (or other plan of use) will have to be seen by an ethics committee, which then will decide whether more safeguards have to be taken or not. Those can range from accepting the initial consent to the data collection as sufficient or to demand seeking a full informed consent, if the study may have negative effects on the donor of data or specimens. We think that the Declaration of Taipei gives a very workable method on one side to protect individuals for not having their data being abused and on the other hand to facilitate research and the use of the data.

Q Researcher often discuss about the importance of data sharing, especially for enhanced clinical trials for orphan diseases. This is easier said than done. There are many ethical concerns that we should overcome.

Kloiber Yes, we have been some of the first advocates on the data sharing, starting with the demand for registration of clinical trials and for the publication of the clinical trials data. On the other hand, we see ourselves as the guardians of confidentiality and patient privacy. Data sharing finds its limits where the individual autonomy and integrity of the person who gave the data is at question. This is a border that can only be crossed if the individual gives you permission to use the data. Data sharing is a valid strategy to avoid unnecessary trials and unnecessary repetition of trials. It will also allow data-driven research, but it needs the safe guards of a proper consent procedure and governance.

(Published May 7, 2020)