

Round table discussion

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: Follow-up session ^{*1}

Part 1 General Discussion

(Thursday, December 5, 2019, Keio Plaza Hotel Tokyo, Japan)

Part 2 Post-trial access and post-trial care

(December 4 and 5, 2019, Keio Plaza Hotel Tokyo, Japan)

Invited lecturers

Otmar Kloiber, Secretary General, World Medical Association
Dirceu Greco, Professor Emeritus, Infectious Diseases and Bioethics,
Federal University of Minas Gerais

Discussants

Maria Victoria Perottino ¹⁾,
Hiroshi Watanabe ²⁾, **Kyoko Imamura** ³⁾, **Yoichi Yamamoto** ⁴⁾,
Kotone Matsuyama ⁵⁾, **Takeo Saio** ⁶⁾, **Chieko Kurihara** ⁷⁾

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- 2) Professor, Executive Director / Vice President, Hamamatsu University School of Medicine
- 3) Project Professor, Social Cooperation Program of IT Healthcare,
The Graduate School of Pharmaceutical Sciences, The University of Tokyo
- 4) Director, Academic Clinical Research Center of Osaka University Hospital
- 5) Professor, Department of Health Policy and Management, Nippon Medical School
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- 7) National Institutes for Quantum and Radiological Science and Technology

^{*1} The Part 1 of this article is a record of the round table discussion held on December 5, 2019, following the Presidential Symposium on December 4, and the transcription was edited including additional discussions with partial participation of discussants. The Part 2 was a record of the discussion with the two invited lecturers separately from the session recorded in Part 1. The Presidential 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

Abstract

The Part 1 of this article is a record of the round table, follow-up session held on December 5, 2019 with Dr. Otmar Kloiber, Secretary General of the World Medical Association and Dr. Dirceu Greco, Emeritus Professor of Federal University of Minas Gerais, both are the invited lecturers of the Presidential Symposium in the 40th Annual Scientific Meeting of the Japanese Society of Clinical Pharmacology and Therapeutics, held on December 4, 2019, at Tokyo, Japan. An invited guest discussant, Dr. Maria Victoria Perottino from Brazil, and other discussants from Japan, Hiroshi Watanabe, Kyoko Imamura, Yoichi Yamamoto, Kotone Matsuyama, Takeo Saio, Chieko Kurihara, introduced the topics of their interests and discussed issues ahead of us and future perspectives of research ethics, such as data-driven research and privacy protection; post-trial access and universal health system; patient public involvement and ethics committee; informed consent and paternalism; secondary use of research data and broad consent; phase 1 trial and post-trial care; conflict of interests; best-proven intervention and placebo control.

Important principles described in the international documents such as the Declaration of Helsinki (DoH), the Declaration of Taipei of the World Medical Association and the International Ethical Guidelines for Health-related Research Involving Humans by the Council for International Organizations of Medical Sciences (CIOMS) were discussed in depth.

The Part 2 is additional discussion with the guest lecturers at the separated occasion especially focusing the topics of “post-trial access” and “post-trial care”.

We hope this record of discussion could contribute to future development of research ethics.

Key words

clinical trial, real world data, human subject protection, medical ethics, right to health

Rinsho Hyoka (Clinical Evaluation). 2020 ; 48(1) : W55-W87. [Epub ahead of the issue publication]

Part 1 General Discussion

1. Opening remarks

Hiroshi Watanabe Today we wish to have an additional session to discuss about research ethics, following the yesterday's official, presidential symposium with Dr. Otmar Kloiber and Dr. Dirceu Greco. We are very much honored to welcome two of you here. All of us are deeply interested in future direction of research ethics, thus we wish to see how is the future direction of the World Medical Association (WMA)'s Declaration of Helsinki (DoH) after 2013 version and the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Health-related Research Involving Humans, which was revised in 2016, as both of these are very much important international documents.

At the beginning, both of the guests will provide short comments following yesterday's session. Next, there will be self-introduction by everyone here, and then question and answer or discussion. During this self-introduction session, all attendees can speak about their interests. I myself will provide a short presentation on my interest in research ethics and Chieko Kurihara will introduce some people who could not attend today but their activities are very much related to today's topics.

So we would like to start with short comments from Dr. Kloiber followed by Dr. Greco.

2. Comments following the symposium

Otmar Kloiber I would like to reflect once more on the Declaration of Helsinki and just remind us of what the Declaration of Helsinki is about and what it is not.

First of all, it is important to remember that the DoH is embedded in a set of general deontology for physicians. It is not standing alone. It is not free-floating, but it is anchored in a system of deontological requests to physicians that have been made before and still are the basis also for the DoH. The DoH addresses physicians, despite the document maybe of interest to others who are participating in research. However, we as a physician organization don't see it as our task to provide deontological advice to other professions. That is something those will have to do themselves, but everybody is invited to take note or to follow the DoH.

The DoH is a set of principles, not a law, and there is no enforcement from the side of the WMA, because we have no policing or controlling rights. The DoH also is not a menu to select from. All articles have to work together. It is not possible to select just some for certain circumstances or for certain situations.

It is first of all a document about the protection of subjects and second, about facilitating research. In the beginning in 1964, the emphasis may have been laid on facilitating research and only second on protection, but both is very closely linked together. Why? Because protection is number one for the subjects, it is against being wronged and it is against being in endangered or exploited. But the protection is also for researchers, it is against suspicion that they are doing something wrong or are exploiting patients or subjects. And very importantly, for the vulnerable populations a protection to be exploited as such.

We can clearly show that after 1964, the DoH has served this purpose in building trust in medical research.



**Otmar Kloiber, MD, PhD, Secretary General,
World Medical Association**

The mechanisms have evolved over time: In the beginning, it was a reliance on scientific methodological correctness, which is still developing and has become more complex over the years. The first big challenge here was the informed consent introduced with the first version of the DoH in 1964. In 1975 came the approval by ethics committees, and in later versions, requests or demands for information sharing and demanding justice. Demanding justice is one of the questions that we have for instance addressed with the question of post-trial access but also by addressing placebo use.

The DoH, although it is not restricted to clinical trials but addresses experimentation with human subjects in general, it is based on the idea of classical research settings for the past 100 years with identifiable individual subjects. Since the 2000 version it comes to include epidemiological research with identifiable data, but it does not cover health

system research. There is, of course, an overlap in what we now see as a development in prevention research, because prevention research has both aspects of population research and individual research.

Concerning the question, “will there be a next version of DoH”? I am sure there will be. But I cannot tell you is when it will be, but the time has come to start discussing now the next revision process. I am relatively confident that this will start during the next 2 years.

Dirceu Greco My position is a little bit different, because I am not representing CIOMS, as I was just a member of the working group of the latest (2016) revision. I can say that I wear at least two hats. The most important one is that I come from a developing country where I chair the Brazilian Bioethics Society. I have another hat that I have been wearing since 2018, as member of the International Bioethics Commission (IBC), United Nations Educational, Scientific and Cultural Organization (UNESCO). One of the reasons that I have been invited to this important venue is because in the past 3 years I have participated directly in the new version of the CIOMS document.

As for previous revision processes (between 2000 and 2008) of the Declaration of Helsinki (DoH), I have participated as a member of the Brazilian National Medical Council delegation. There were critical situations; one was during the approval of the 2000 version. Then, it was in 2004 that I met Dr. Kloiber in a complex meeting at the WMA headquarters, to discuss a note of clarification to the DoH. It was the first time that WMA added notes of clarifications (in 2002 and 2004), as response to what I considered as gains of the 2000 version (namely placebo restrictions and post-trial access). Then again, I was there in the 2008 revision (Seoul), with the Brazilian National Medical Council delegation.

But what I have been fighting in the last 35 years is for protection, is for access, and for justice. After finishing medical school and a residency in internal medicine I did a fellowship in clinical immunology outside

of Brazil (USA and UK) and came back to Brazil a few years later. Then, by early 1980s the HIV/AIDS epidemic hit Brazil. Being an immunologist, it was very clear that infectious disease was a very close specialty. To confront the epidemic, we opened at the Federal University of Minas Gerais, in Belo Horizonte, the second outpatient facility in the Brazil to receive people at risk or living with HIV/AIDS. That was in 1985. At this time, as we all remember, there was no effective drug against HIV. We had to be compassionate. We would treat the opportunistic infections that frequently affected individuals living with HIV. Until 1987 when AZT became available, the only thing we could do was to be compassionate. All of us do that all the time.

From that moment on, with all the complexities of receiving young people, living with a very difficult infection with all the discussion on mortality, on how you keep the secret of everything that they tell you, and the prejudice against specifically men who have sex with men. All this came at the same time as another historical moment for the country.

In 1985, the military dictatorship was just over in Brazil. We were in the verge of having something better, and we were talking again about justice, about access, about democracy, and that was concomitant with the arrival of the AIDS epidemic. Bioethics is an intrinsic part of all this. I still take care of many patients. Luckily now, I can tell my patients that being in a country where the State can provide you with everything that is needed for treatment and if you adhere to the treatment, you can expect to have a healthy and productive life as anyone without HIV.

This big change in relation to the treatment and care of people living with HIV did not happen as a gift. There was a lot of pressure from different groups (researchers, health professionals, NGOs) to achieve access to treatment. Many of the NGOs at that time were pressuring for fast availability of needed drugs. They have pressured the FDA in the United States and EMA in Europe and everywhere, trying to get drugs faster. Anyway, with all this in my mind, I got also involved in the ethics of research. Besides the involvement with the DoH, I took part in development of the UNAID/WHO Ethical Considerations in Biomedical HIV Prevention Trials (2007). By the way this guideline is in the process of being updated.

In 1996, just after the release of triple therapy for HIV, Brazil decided that everyone living with HIV should have by law, not by guideline, access to all drugs that could be useful for them. At that time, Brazil was going through an economic slump and even in that situation, the decision was that health is a right and not a commodity. Involved in bioethics, immunology and infectious diseases, in 2010 I became Director of the Brazilian AIDS Programme in Brasilia.



Dirceu Greco, MD, PhD, Professor Emeritus, Infectious Diseases and Bioethics, Federal University of Minas Gerais

Chair of the Brazilian Society for Bioethics (2019-2021); Member and Vice-chair of International Bioethics Committee of United Nations Educational, Scientific and Cultural Organization (UNESCO) (2018-2021)

My point now is if we consider that health is a right, we should make a way that after finishing any trial with a product that shows to be effective, it has to be made available and affordable. Availability itself is not a very good word, because the drug may be there but does not reach the most in need. What I mean is that everyone that need the developed product must have access, ideally through and financed by the public health system.

Thus, my rational is not the same as some people say that drugs should be available, period. Many times, there is no consideration on who is going to pay, how they are going really to get to the population in need. What I am telling you is what happens in a complex and dispar country as Brazil. Its Resolution 466 of December 2012 on research ethics makes it clear that post-trial access is an unquestionable right for the participant, and the products must be provided by the sponsor, free-of-charge for all needed time. This may be an example for other similar countries and for the world in general.

3. Justice principle and recent development of clinical science

Watanabe Thank you for important comments from both of you. So let me allow to introduce my position of interest in research ethics discussion. Here I would like to have a brief presentation about academic aspects of evidence generation through clinical trials.

First, I would like to start with this case. A 61-year-old male had a myocardial infarction 6 months ago. A 24-hour ECG monitoring revealed arrhythmia, but he had no symptoms relating to arrhythmia. How should we treat the patient? Several observational studies have demonstrated that the occurrence of ventricular premature contractions in survivors of myocardial infarction could be a risk factor for subsequent sudden death. Theoretical expectation led to hypothesis that anti-arrhythmic therapy might reduce the risk of sudden death in patients with myocardial infarctions with arrhythmia.

To answer this question, the Cardiac Arrhythmia Suppression Trial (CAST) was conducted. But, survival rate in the patients with active drugs, encainide or flecainide, is significantly lower than placebo group. Because of these results, the part of the trial involving encainide and flecainide was discontinued. We learned many things from CAST. CAST evaluated effect of anti-arrhythmic therapy in patients with myocardial infarction with arrhythmia. CAST trial terminated prematurely because the Class IC anti-arrhythmic drugs, encainide and flecainide, increased mortality. So, CAST led to the recommendation that Class IC drugs should not be used in patients with myocardial infarction. Before CAST, this type of treatment for such patient was a standard treatment, but after CAST, many lives have been saved by this finding.

We learned that rather than theoretical expectation, evidence derived from clinical research with scientific and ethical soundness is necessary. Scientific soundness is achieved by using several approaches to minimize bias such as randomization, blinding or masking and control of confounding factors. Such efforts to minimize bias is always very important, even if we use big data or real world data. We also have learned that clinical trials lead to answers for unsolved research questions and always yield very valuable information. There are no “negative results” even when the hypothesis is denied. We need to change investigators’ mind-set and also we need capacity building.

For capacity building, we should learn ethical principles including DoH or CIOMS, and also there is Belmont Report. Belmont Report has three principles, one of which is justice. Dr. Greco mentioned much

about justice, in yesterday's lecture. Justice asks us who ought to receive the benefits of research and where it is urgent. This is a question of justice in the sense of fairness in distribution of benefits and risks in research. It is not only the case between wealthy people and poor people and developed countries and developing countries. We always use medicines, medical devices, and those are the gift from previous clinical trials. If we receive the benefits of past clinical trials, we also should pay it forward through clinical trials for the future.

We also should learn what is happening now. The use of computers, mobile devices, wearables, and other biosensors that together store huge amounts of health-related data has been rapidly accelerating. Real-world data include electronic health records, claims and billing activities, product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health statuses such as mobile devices. Real world data hold potential to allow us to better design and conduct of clinical trials and study it in a healthcare setting to answer questions previously although invisible. In addition, with the development of sophisticated new analytical capabilities, we are better able to analyze these data and apply the results of our analysis to medical product development and approval.

ICH E6 and E8 are now in the "renovation" for modernization. Those documents approach product lifecycles. Different types of studies will be conducted with different objectives and designs. Depending on the study objectives and the position of the study in the overall development plan, the data sources may vary. Big data existing in real world has a great potential to indicate unexpected relationship by bio-informatics and that leads to finding new drug target in basic research. Now reverse translational research becomes very important. Not only translational research from bench to bedside, utilize findings in basic research to clinical practice, but it is also very important to cycling



Hiroshi Watanabe, MD, PhD,
Professor, Executive Director / Vice President,
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Immediate Past President of the Japanese Society
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Presentation on CAST study and justice principle,
future direction of research methodology.



Maria Victoria Perottino
Pharmacist; Specialist in Governance, Risks
and Compliance (Brazil)

Maria Victoria Perottino Thank you for your invitation to this valuable meeting. I am from Brazil. The right for privacy, many times forgotten by third parties, is the right of protecting one's innermost self and determining what he or she would permit to be seen or done with one self's personal information. Once it can pose threats to principles that are well defined by the Human Rights Declaration and by many countries Constitutions, the concern for people's privacy and the right to control one self's information is an ethical issue.

Yesterday during the presentation, the right to privacy came along the discussion. As a pharmacist working in a large private healthcare company in Brazil, I can't miss the opportunity to bring my concerns on the subject.

Personal data is widely used in researches such as in clinical trials, as well as on daily basis by a great variety of industries. Advances in technological areas such as AI (Artificial Intelligence) and the collection of data by these companies, is a reality. Many healthcare companies already own huge databanks with personal and sensitive information. Very important is to repeat that they own databanks (big data) but the data itself do not belong to them but to whoever provided them. The use of these databanks to create new products for health prevention programs or health policies is a reality, is necessary and cannot be prevented or avoided anymore. However, the crucial question is how to use the data collected in an ethical way, as most of the times they are used for researches done after data collection and this collection was done before even knowing what question we are looking to answer. This means that individuals do not know that their data are being used and for which objectives.

In Brazil, a new privacy law (Lei Geral de Proteção de Dados – LGPD) similar to the GDPR (General Data Protection Regulation) will enforce privacy as of August 2020. Yet, companies and the whole society are still

translational research and reverse translational research. Such cycling may generate new evidence. Real world data enables the development of two-way street: translational research and reverse translational research to generate new evidence. I really look forward to the development of research ethics respecting these scientific evolution.

4. Self-introduction by participants

Chieko Kurihara Thank you, Prof. Watanabe for your presentation to provide some scientific bases to discuss about ethical principles. Justice is very important principle related to many topics discussed here.

So next we wish to ask participants to introduce yourself mentioning topics which you are most interested in. First, Victoria, please introduce your interests as you are one of the guests.

not ready or aware of the impacts of this law. Personal data governance is a huge mystery and issue for many companies. The ethical and legal bases to justify the use of information in databanks after collection of personal and sensitive information is still not clear and the possibilities for individuals not to consent to use their data is a right. That's why I understand that this issue must be discussed on depth. This includes but it is not limited to: What are the possibilities and responsibilities and how to communicate clearly and previously; How to ascertain that the individual understands his or her rights; How to save and justify the use of personal and sensitive data long after collection; How to really protect privacy and avoid stigmatization?

Kurihara Thank you so much, GDPR is very important legal background situation to consider about ethics of data-driven clinical science. We have to consider the requirements coming from EU (European Union) when we discuss about the issue of broad consent, data sharing, etc. In Japan also, we have to consider it when our researchers share data with European group.

I am working at the National Institutes for Quantum and Radiological Science. My expertise is research ethics. I am working as a vice chair of research ethics committee of my institute. Also, I am engaged in quality assurance, monitoring and audit of medical research. Recently, I started work as a Specially-appointed Professor at Kanagawa Dental University to establish research governance framework. Reading Japanese research regulations as well as DoH is my everyday practice.

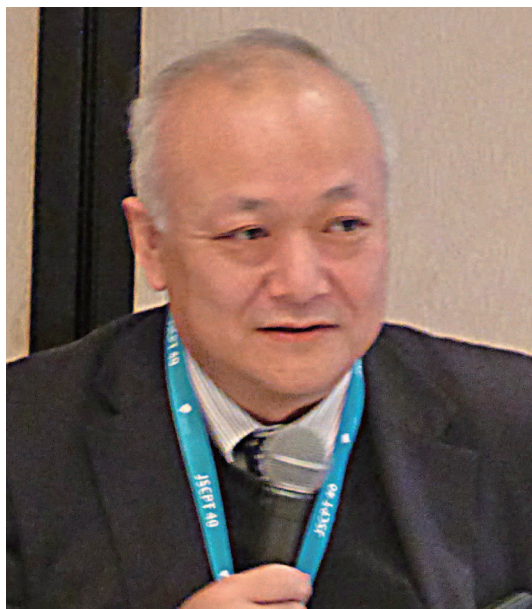
I would be probably only one person, or one of rare persons in Japan to continuously provide education to explain about the DoH and CIOMS. Because many of Japanese experts in research ethics have to educate very detailed procedural issues required by Japanese regulations. I also have to dedicate much time for that. CIOMS is not so well known in Japanese research community. The DoH is very much well known; however, many people don't know its contents but only the name. I am very much enthusiastic to explain so that people understand the principles and important essence of these international documents. I believe it far more important than just following Japanese procedural regulations. This is my motivation to organize this kind of session.

Kyoko Imamura I am orthopedic surgeon by training. I am currently Project Professor of the Social Cooperation Program of IT Healthcare at the University of Tokyo, aiming to facilitate patient-public involvement in clinical trial and utilization of mobile health in the context of drug development. I am now president of the IFAPP (International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical



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

President (2018-2020), International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)



**Yoichi Yamamoto, MD, PhD, Director,
Academic Clinical Research Center
of Osaka University Hospital**

expense this year (2019) should be reduced. The good news is that still the physicians get better pay than last year, but pharma companies should be receiving less. The government made a fine balance between the drug price and the physicians' payment. This is a regular scene of the public health claims which wins or which lose, but the pharmacist is increasingly expected in Japan to play more active role to make effective communication with the patient.

Increasingly, the government is encouraging to use more generic drugs. The cost of the drug is reducing quite rapidly, but the cost of management by the pharmacist is increasing. The Ministry of Health, Labour and Welfare (MHLW) in Japan and our School of Pharmaceutical Sciences try to educate more effective communication skill. Pharmacist should share the information with their prescribing physicians. That's something we can collaborate with not only working with the pharmaceutical physician groups but also extending collaboration with pharmacists or nurses or other care managers in the community.

One thing you need to know in Japan is that here new drugs are approved with health insurance reimbursement, generally, with some exceptional cases. In that sense, patients don't have to fight for post-trial access. But a cultural uniqueness in Japan is patient's position in this clinical practice. We don't have any patient's charter. We don't have any department or office of human research protection. Our GCP can protect them, so patients don't have to fight, but there is always a rule that they need to raise their voice effectively. But they don't know what to do since they don't know how the drug is manufactured, distributed, regulated in effectiveness and safety. So, we have a lot to do with the patient.

Yoichi Yamamoto I am Professor/Director of the Academic Clinical Research Center of Osaka University Hospital. I started my career as a clinical neurologist. For about 3 years, I studied basic neuroscience in

Medicine). In doing this support at the University of Tokyo in patients' education in clinical research and drug development, I feel the difference in the degree of understanding and sympathy about research ethics. Research ethics is always hot topics in professional societies, but it often leaves out the patient.

Patients and their families are important stakeholders. Most important is the society itself. Whenever we talk about post-trial access or patient involvement in decision making, it is important to have society's good understanding and support because after all, we need to finance these drugs and devices, not coming for free. We need to put more effort to expose the society to these kinds of discussions.

Also, my department is the graduate school of pharmaceutical sciences. Here in Japan, we are consuming a lot of pharmaceuticals. Just this week, the government made the deal that all health

France. After that, I came back to Japan and I tried to find new drugs for very difficult diseases, especially ALS, but at that moment, the infrastructure to develop new drug was quite fragile in Japan. My career changed from a basic researcher, a clinical neurologist to a manager to establish an excellent research center. I also had been director of the office for the Protection of Research Subjects until last year. I always think that we have to balance the promotion of the clinical research and also at the same time the protection of the human subjects, because this is quite important as these are quite closely related, but we have to do both things at the same time.

Kotone Matsuyama I am a professor of a private medical school, Nippon Medical School in Tokyo. I am a pharmacist. I am now the board member of the IFAPP (International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine). My major is in clinical pharmacology, but I am in the health policy management in the university. I am also the IRB manager and IRB representative in this university.

From the viewpoint of IRB manager, I am very interested in the problem of the broad consent, which may be needed in utilization of bio-samples or data. The Declaration of Taipei deals with bio-samples and data, nevertheless, how we should deal with broad consent in research context is not clear in the DoH, although it is discussed in the Declaration of Taipei. Between the two declarations, I am curious about the broad consent and the major problem in utilization of samples or data derived from human subject in clinical trials.

Takeo Saio I am practicing internal medicine and psychiatry, at hospitals, as well as occupational health at a private company. Medical ethics is my everyday practice and I am very much interested in how theory and principles can be applied to ordinary medical practice. I am one of the proponents of evidence-based medicine (EBM) movement in Japan. I have organized many times workshops and published books and papers in Japanese to promote EBM, mainly for users, practitioners, rather than for academic researchers. The reason why I am critical about ethics and science of research is because only ethical, scientific sound research results would be valuable for users, and could contribute to improvement of health care of our patients.

Kurihara There are some people who we wished to invite to participate in this session, but they could not because of some business. I would like to introduce four people.

This is **Professor Masanori Fukushima**, Professor Emeritus at Kyoto University. He worked so intensively for establishing university-oriented rigorous medical product development framework, under the Pharmaceutical and Medical Devices Act (PMD Act), to achieve “post-trial access”. Professor Fukushima is now Director of the Translational Research Center for Medical Innovation, Foundation for Biomedical



Kotone Matsuyama, Professor, Department of Health Policy and Management, Nippon Medical School
Board Member, Working Group on Ethics, IFAPP

Research and Innovation at Kobe. It is a very well-known center called TRI. Before appointed to the professor of Kyoto University, he struggled hard to establish the concept of informed consent, through law suit. It was 1990s when the concept of informed consent came in Japan. We are very latecomer. He also struggled with ethical issues of translational research. Now his achievement of university-oriented rigorous product development framework is for “post-trial access”. He does not say about this wording, “post-trial access”, which has been a hot topic of the DoH. He often says that if you start clinical trial, you must achieve product approval. Clinical research only for writing a paper is meaningless. Final goal of research must be cure of patient and disease control, this is his argument. This is the reason why I wish to introduce him.

Next is **Dr. Simon Croft**, Professor, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine. He is a member of establishment of Drugs for Neglected Disease *initiative* (DNDi), for which he was the first R&D director. Since 2011 he has been working for DNDi as a member of scientific committee. This is non-profit, non-government body to develop drugs for the people who need it but have been neglected. They have established the product development system called Product Development Partnerships (PDPs) worldwide networking the people from seeds discovery, non-clinical and clinical development until the product approval. They have very strong strategy of community involvement. It is a very good example when we think about post-trial access. I wish to introduce their work not being officially authorized by DNDi but because I am much engaged in editorial work of round table discussion with them.

Next is **Professor Hiroe Tsubaki**. He is the Director General of the Institute of Statistical Mathematics. This is a unique national research institute of statistical sciences in Japan. Last week I visited him for a different business. Then he told me that he has been engaged in education of clinical trial methodology at graduate school of health management and in his educational lecture he has been continuously discussing about the DoH focusing ethics of placebo-controlled clinical trial. He has a strong opinion on this topic. He says that historical progress in ethical norms has been always becoming more strengthening respect for person or individual rights. He is much engaged in both of clinical trial and environmental science. His opinion is that future effects of global environmental protection measures considering precautionary principles has more uncertainty compared to clinical research results; nevertheless, uncertain ethical considerations for future generations are gradually penetrating; thus it is historical inevitability that clinical research must require stricter human subject protection. Then he argues that the placebo provision of the DoH shows a very rare regression of ethical principle. He supports 2000 version of the DoH and respects CIOMS 2016 version. He is not an opponent of placebo trial. He has been working with clinical trial investigators since early days in Japan, and he has been involved in, as a statistician, design, control, or assessment of substantial number of placebo-controlled trials and facilitate it when necessary. He wishes to convey this message to the participants of this session.

Next, this is a very unique study group. A Japanese insurance company, Mitsui Sumitomo Insurance Co., Ltd., organizes **Clinical Research Risk Management Study Group**. MS&AD InterRisk Research & Consulting, Inc. is its secretariat. As one of the core members, I am engaged in research ethics discussion mainly compensation for research-related injury, as well as general issues of research ethics. They respect 2013 version of the DoH to define ethical obligation of compensation for harm resulting from the study. This is because they knows worst cases of injury of subject in long term experiences with company-sponsored clinical trials. As for investigator-initiated research, there is only limited information of monetary compensa-



Prof. Masanori Fukushima,

Professor Emeritus of Kyoto Univ., Director of the Translational Research Center for Medical Innovation (**TRI**), Foundation for Biomedical Research and Innovation at Kobe
He established “**informed consent**” through law suit in 1990s; struggled with ethical issues of translational research/medicine; now established **academia-oriented** rigorous product development framework under the Pharmaceutical and Medical Devices Act (PMD Act) to achieve “**post-trial access**” in Japan.

Fukushima M. Academia-originated Disruptive Innovations and Prospects for Disease Control. *Clin Eval*. 2019; 47Sup36: 25-46.



Prof. Simon L Croft, BSc PGCE PhD FRSB,

Professor of Parasitology in the Faculty of Infectious and Tropical Diseases at the London School of Hygiene & Tropical Medicine (LSHTM)

Discussion on development of **Drugs for Neglected Diseases** with **clear motivation** to achieve “**post-trial access**” establishing product development partnerships (**PDPs**) worldwide, with **community-involvement** strategy; Good example of compliance with DoH; CIOMS.

Croft SL, Yamada H, Kita K, et al. Round table discussion: The 2nd round table discussion on development of new medicines for neglected tropical diseases: From bench to bed, achievements and challenges – Partnerships, treatments and NTDs: 2005 to 2018, 13 years of change –.

Clin Eval. 2018; 46(2): 411-29.

http://cont.o.oo7.jp/46_2/w55-w73.pdf



Prof. Hiroe Tsubaki,

Director-General of the Institute of Statistical Mathematics, a **unique national institute of statistical sciences in Japan**.

He has continuously discussed about the DoH in his educational lecture, focusing on ethics of **placebo-controlled clinical trial**

“I support the 2000 version of the Declaration of Helsinki, and respect CIOMS 2016 version.”



Yuichi Niikawa, Mitsui Sumitomo Insurance Co., Ltd. (left);

Shinichi Okamoto, MS&AD InterRisk Research & Consulting, Inc. (right), They organize **Clinical Research Risk Management Study Group**.

Insurance company continuously supports discussion of ethics of clinical research.

They respect 2013 revision of the Declaration of Helsinki to define ethical obligation of **compensation for harm resulting from the study**.

Panel Discussion. *Clin Eval*. 2019; 47Sup36: 47-61.



Chieko Kurihara, National Institutes for Quantum and Radiological Science and Technology
Specially-appointed Professor,
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Takeo Saio, MD, Department of Internal Medicine and Psychiatry, Fuji Toranomon Orthopedic Hospital
K&S Consulting Office for Occupational Mental Health; An associate member of the World Medical Association

tion, but according to expanding awareness it seems to be increasing.

So we learned topics of interests of each other, now start discussion on any topic.

5. Post-trial access in Brazil and in Japan

Imamura I wish to ask Dr. Greco how you can achieve that success in winning the post-trial access of people to the product. You always had strong support in this type of discussion concerning international declarations or statement so that you can get global support for your actions. After all, you had to fight with the regulatory authority or pharma industry or the communities. How did you manage to do that?

Greco No, of course I have not managed all that by myself. What I have been doing as a physician, professor, citizen is to help in the fight to achieve it all. It's different. And one very interesting aspect you mentioned was that society has to be involved and it actually was. But society is not present here with us today, there are no community representatives. We are talking among ourselves. All of us, we are here to protect them, to help them to get drugs. I said yesterday and I repeat again, the real changes will happen when we together, including civil society, fight for them to happen. The AIDS movement is a good example. You see NGOs, such as ACT UP, that was one of the first one that started a very strong movement to get support against many of the cost of the drug companies.

But I was surprised to hear that any drug that comes to Japan and is approved, people have access.

Imamura So far so good. These days, the medicines for rare diseases, for example, just one tablet costs



millions of dollars, and people started to say that will make our insurance plan bankrupt.

Greco In this issue, in Brazil, it's in the federal constitution that health is a right of the people and should be provided by the government. Any new health related development, especially drugs, that gets to Brazil, people can get to the judiciary system with a prescription from a doctor, and they will probably get even these very expensive drugs for rare disease. The affected individual has this right, of course, but when you have a right that costs one thousand times more than what we are paying for most treatments, this may become a problem with difficult solution. And one of the mitigating possibilities is to pressure against the obscene cost of many patented drugs.

6. IRB/EC and informed consent

Yamamoto My question is, both the DoH and CIOMS are very ideal. It's necessary to evaluate whether each item is really effective or not. For example, the IRB is quite ideal, but most of the IRBs sometimes do not function well. Also, for example, when we get even informed consent form, most of the patients do not understand well. We have to start to evaluate how much these items really work well, and we have to start our feedback system. For each item, we should present a way how to evaluate and how to feedback to the real world.

Kloiber We don't know how much the DoH has been followed or not. We certainly expect the research journals to demand adherence to the DoH, but there are a lot of grey zones. Your request for monitoring development is correct, that is why we have versions of the DoH and why we change. For instance, after 2000 version, we added note of clarifications in 2002 and 2004. Because we have seen that things didn't work and was not realistic. Therefore, this has not been a regression, it has been a progression.

In many instances the informed consent has grown to what is now a bureaucratic monster and does no

longer really serve the purpose of understandable information in order to make an informed decision. What I am suggesting is to think about layered information. Nowadays, nearly everybody has access to internet. You can think, for instance, of a hypertext document which allows you to go deeper into questions you have so that you have a short structured information, which comprises the most important information of what is necessary to take a decision and then you are able as a patient to go into depth.

The point concerning the ethics committees is also very correct. There are serious doubts about the competency of all the ethics committees. I am very much in favor of recommending to all of the ethics committee to have a scientific staff that helps them to go through the process and that supports the committee members really to take decisions. That would allow the individual members of ethics committees who may not have a scientific education to be able to better comprehend what is going on in this process.

The other aspect which I also would like to mention and which I am critical about is the independence of ethics committees. I have serious doubt about commercial ethics committees. I am not sure whether they can really be independent if they are profit generating. But I also would like to mention the fact that some of the countries have what they call institutional review boards, which are ethics committees directly at the institutions which do the research. Since major universities nowadays are kind of living from research, I see the independence of those boards also in question.

Those are significant questions which we have to raise and which I hope that they are being addressed in the revision process of the DoH and hopefully they can be resolved. Again, the DoH is a document of principles, and it's not that much document that gives you technical direction. For that, we have CIOMS, we have ICH, and we have the silver book of WHO which describes the constitution of ethics committees and how they should work. But we certainly have those questions on our radar.

Kurihara I would like to ask one question about Research Ethics Committee. In the DoH, there are wordings about “independency”, which can include conflict of interest management of the committee; “qualification”, well-educated and trained members along with scientific staff, as well as “transparency”. However, there is no description about the “diversity” (multiple perspectives) of the members. Is there any discussion previously?

Kloiher No, there has not been. That may be because we have different understandings about the role of the ethics committee. It very much depends in the thinking of what is an ethics committee and what is the role and responsibility of the ethics committee. For us, as a physician body, the ethics committee is a way of sharing responsibility within the physician community. If you take this understanding, an ethics committee is a physician body. That is the original understanding where it comes from.

The understanding by other parts of society is that an ethics committee is a justification or controlling body. If you come from this side, then you probably would desire a much stronger influence from patient groups, society in general. The original idea would lead you to consider an inclusion of other experts like ethicists, lawyers, theologians in ethics. In the latter case, seeing the ethics committee as a justification body, you probably will say, well, we need lay people in there.

For us, it is in the first place a matter of sharing responsibility towards patients. We believe the justification and permission for experimentation is a matter, which usually has to be decided by laws and regulations, and proper regulation has to be in place with that. In this regulation, there has to be a mandate by society and also by patient groups in order to look for justification or not. A function usually fulfilled by state authorities. But

again, that is a somewhat different process compared to the ethical responsibility taking that we have been promoting since 1975.

Greco I agree with the problems with ethics committee. Evaluating phase 3 trial, many times with a total of 200+ pages of documents, may signify that not even the researcher has read it all. When us, researchers, participate in some phase 3 trial we are many times just helping the industry to get something done, as we cannot change anything in the protocol. But one thing I always say and I am going to use the Brazilian example is to have one central national research ethics commission. By their mandate, each place where you have research must have at least one research ethics committee. Today, there are 865 research ethics committees spread throughout the country. Of course, some of them are very good; others, are not. And qualification of participants is certainly one important problem.

And of course, the research ethics committees have many important duties. One example that happened a few years back in Brazil when after the end of phase 3 trial funded by an international company, the needed drug was immediately discontinued and the young participant was transferred to the National Health System. Their parents, with the help of the REC and based on the obligation of post-trial access as stated in the informed consent, went to the judiciary system. The sentence obliged the company to resume payment and to repay the national health system for all costs incurred.

But many times, the Informed consent seems like nothing. No one knows if it really was understood. In a Harvard study to evaluate cancer patients just 3 or 4 weeks after the signature of the informed consent sheet, many participants did not remember to have signed it. My point is that both of them, ethics committee and informed consent are necessary, but they must be considered as a process and not just a paper to be signed by the participant. What the National research ethics commission in Brazil have been trying to mend this situation is regularly (every year) to convene regionally the research ethics committees to discuss difficulties and possible solutions, which includes committee members qualification.

Kloiber The ideas enshrined in the DoH, CIOMS ethics guidelines and others, are, redundant. The first demand is the caring of the physician or the researcher for the subjects and it should already be all-encompassing. If that always works perfectly, you wouldn't need ethics committees, informed consent, and anything else. Informed consent for the research purpose was added first time in 1900 by a law in Germany and then in '31 again; and in the DoH first time in an international canon of general ethical principles. Then in 1975, there was the introduction of an obligatory review by an ethics committee.

And we have now added publication and data sharing issues- e.g. not only publishing positive results, but all results have to be published. Another big problem is the strong commercial orientation of many scientific journals. The DoH requires redundant safeguards. They all have to be followed in order to close the holes so that nothing can go through.

7. Paternalism

Yamamoto I would like to add one thing about paternalism. Paternalism is usually denied from the viewpoint of ethics, not always, but usually clinical practice is based on the good relationship between patients and medical doctors, and also clinical research is also based on this kind of good relationships. For example, when I explain the ICF (informed consent form) to the patients even using the same documents, I

can lead the patients to say, yes or no. So, I want to say that it depends on the doctor. Paternalism is sometimes quite important, and also I experienced that patients rely on me, but I have to do explain the ICF respecting patient's autonomy.

Greco If I am a good doctor, the patient may say, whatever you want to do, let me just sign the consent form. That's not paternalistic, that's authoritarian. They see you as an authority and rely on you and they believe on you. The question is that maybe the informed consent process should not be given by the researcher himself. In many projects, they are asking to have community associated boards to be part of that. There is a conflict of interest every time a researcher asks someone to participate in research.

Kloiber I don't share the sentiments of anti-paternalism which we have seen over the past two decades. There are different aspects of safeguards. The first one, your obligation towards caring for the patient is a paternalistic argument and it is a good one. The problem is the asymmetry. A data protection officer once told us, patients come to a doctor not because they want to be autonomous. They see a doctor because they are sick and need help.

In an ideal situation you can help or empower a patient in his or her emancipation during the process. That is a process of development. In healthcare, there are also many situations where you can't do that, e.g., emergency situations, but the ideal process nowadays with chronic situations is that you bring your patient into a situation where the patient really masters his or her disease. It has to be combined with the idea of emancipation of your patient, but also keeping in mind that this is an option of the patient not an obligation.

Greco Just a small disagreement again, when you talk about the relationship between doctor and a patient. This is different from the relationship between the researcher and the subject. If I consider the doctor and patient relationship, what I want as a doctor is to have my point of view respected and discussed and to have patients emancipated in many ways so they can give a truly informed consent if they agree with the procedures planned. And there are international movements to change this uneven relationship between physician and patient. It seems that the best approach is to be sure that all adequate information is provided to the participant, all eventual questions be clarified and his or her final decision will be taken together with the attending physician or researcher.

Kloiber I agree with you, but the difference is paternalism. The difference in what is ethical and what is not ethical is just the portion of paternalism that helps patients to takes decisions. Having this role whether you call it paternalism or parenting or coaching, in any case it is a very positive role. It is a very enriching role. It is a role of fostering emancipation.

One of the problems which we had with the DoH in 1964, which we have now with the Declaration of Taipei, in case using only databanks or biobanks, is that we have a number of our colleagues, professors of medicine, who say "why should I ask the patients? I know better for them", But this is not paternalism. It is patronizing patients. This is something which clearly is contravening the ideas of the DoH.

Greco The difficulty is that in the end the decision should not be exclusively by the physician. It should be by the patient. That's the difference when I use paternalism. One is that when I, a physician, say I know what to do, you should trust me so we have to do that. That's a paternalistic way, and what I mean by the other way is that when I say that to them, they have the possibility of asking questions and be adequately informed to take a decision.

Kloiber We agree that you don't get trust by saying "you have to trust me". That doesn't work.



8. Secondary use and broad consent

Kurihara It is very important that the DoH states that physician has a responsibility even if the patient consents. There is also patient right, which is stated in another document of the WMA. The patient's right to know and not to know, all of these are very important. Now I would like to ask a question about the broad consent, related to the Declaration of Taipei. Broad consent is not enough. Even if there is a broad consent, it is necessary to get another ethical approval for the future secondary use, and sometimes re-consent or opt-out would be necessary.

When a researcher asks a candidate subject for informed consent to this clinical trial or this research, this researcher may have a clear plan of future secondary use of the data obtained in this trial or research, or otherwise a bit ambiguous possibility of future secondary use. In both cases, these researchers should tell this candidate subject that there is a possibility of secondary use. In such case, this researcher should include this kind of description in the informed consent form. Study subject has a right to be informed about the secondary use whether already planned or possibility in the future. How do you think about this point?

Kloiber Informed consent is only valid when it is extremely specific and clear to the point of what you do, what are the risks, what are the potential benefits are so that a subject can understand what the implications of a very specific situation are. The Informed Consent is one of the biggest achievements in patient and research subject protection of the last century. We are strictly against giving this up.

If you give a broad consent to a secondary use, the informed consent is basically useless. If a broad consent is given for a secondary use, a malicious researcher can hide any bad experiment behind a nice one. Broad consent is contradictory to informed consent, thus contradictory to patient protection.

On the other hand, we think it is useful to collect data, to collect specimen. We don't know the character-



istic of future research, the questions, the risks, and the benefits. It may be one experiment or one question. It may be thousands of them. The informed consent as we give it right now is most likely an impractical one for databases and biobanks. The question is, do we give up all this research on data and specimen, or do we find another way, which provides a similar protection like the classical informed consent. Our answer is clearly we believe the research can be extremely helpful in the future if we can use the data, so we need a substitute for the informed consent.

The idea is that when you give an initial consent to a collection of data or specimens, in return protection should be provided. So those who collect data or specimens must give you a clear declaration of the governance of the database or biobank. How is the data being used? Who may have access, or under which conditions somebody may have had access to the data? What will happen with the data in the databank, for instance, if the databank is being sold or is being closed? Will it be destroyed? Will it be handed over to somebody else? Which questions can be asked – only research questions, or can there be marketing questions being asked, or can there be political questions asked?

There must be a very clear process, and there has to be an ethics committee or access committee, which will get the question or the research projects to be agreed. This committee then has to look whether there is any chance of damage or repercussion to the person who has given the data or the specimen. Based on the protocol they can advise the researcher either that initial consent is enough, because not damage is possible or in case there may be an effect, that there have to be safeguards, for instance anonymization or aggregation. Or, it may be that the study would reveal information that may harm or affect a person directly and then the project sponsor would still have to get informed consent.

Greco I agree completely. I don't think we should ever use the term broad consent for anything that we are asking from anyone. The only thing I may be a little bit more conservative or more protective is that in most situations a new informed consent has to be sought.

Kloiber In some system like France or Japan everybody has health insurance regardless of a pre-existing condition. In other systems knowledge about, pre-existing condition may make a difference for your protection. Let's say, stigmatization or a preexisting condition would be harming your insurance rights, then certainly people have to be asked before such findings could occur. Sometimes this may be solved by aggregating the data, so that you cannot conclude to a specific individual.

Kurihara The one thing we are worrying is that it is difficult for ordinary researcher to make a link between the DoH and the Declaration of Taipei. One is for the research and another is for the health databases and bio-banks. Now I had one idea which may be an easy way for us, research ethics experts, to explain to a researcher. When a researcher is starting a research and preparing informed consent form and this researcher has an idea of future use and banking of sample or data, in this case, there would be very simple way of saying, we have a plan of banking of data or samples. So, we will follow the Declaration of Taipei. It will be very simple.

Kloiber That's a very good idea. Maybe we should add this to the DoH.

Kurihara Another point we are worrying is that there is no description of the incidental finding in the DoH. There is a paragraph that study subject should take an option to be informed of the research result, but there is no description of the incidental finding. But in the Declaration of Taipei, there is.

Kloiber It may be something which we indeed have to add to the DoH in the future. The high importance of incidental findings was clearly something which we learned in the process of drafting the Declaration of Taipei. It was not an item that was frequently mentioned with the discussion of the DoH in general, but it may be changed.

Imamura In my opinion, rare disease or genetic disease patient may benefit from the future research. From the point of this benefit, the patient access to the future research, or the way to access future research will be manageable and it will be influenced to the DoH or Declaration of Taipei. Is this kind of human rights accepted by future research ethics?

Kloiber This is already very difficult with a classical clinical trial setting, because you do not know what the outcome of the experiment is, and in half of the cases, the new drug is better. In the other half, it's not better, or maybe worse. What are societies willing to pay for? Unfortunately, this is messy in this world. It's not like in Japan where you have top coverage and every licensed drug that is on the market then is also prescriptible under the social insurance system.

With the database and biobanks, this gets even more complicated, because the data of a person that is being used may not have relevance for that person anymore, because the person is already through an episode. In the worst case, the person is already dead, and the data is still in the database, and it can be used for comparisons and for other questions.

There are nowadays all kinds of research. Some research is more marketing driven then really to generate scientific knowledge in a healthcare system. Some studies may be politically motivated. You can call all of this research, because in most of our systems, research is protected very highly and the freedom of research is adamant. That is good, but on the other hand, it makes it very difficult to delineate what is what. Therefore, we said the Declaration of Taipei is valid for every use of a database or biobank. Whatever you do with this data, which is not individual treatment, has to respect this Declaration.

We think that the benefit must be shared. That is part of our general deontology, enshrined in the Declaration

of Geneva.

Let me give you practical examples. For instance, we have a state-run bio-bank in Germany, which has run for over many decades years and which has taken human samples, tissue samples, blood samples, serum samples for long time and has stored them. One of the questions may read: From what time on do we see endocrine disruptors enriching in tissues. That is an important question for the general public and for the society. We should all know about this and learn from this when these things occur, but it doesn't have a direct relationship anymore to those people who gave samples 50 years ago, they will not benefit from this. But the associated benefit and scientific benefit may still be obvious. It gets very blurry the more you go into big data and bio-samples and along a time-line. Yet, we can clearly conclude there will be benefit for all of us.

9. Patient and Public Involvement (PPI)

Kurihara I have another question. Recently, many researches have patient or public involvement (PPI) plan. There are some guidelines that PPI should be described in the research protocol and reviewed by the ethics committee. This would be in the case this PPI plan is specific to one research protocol. Sometimes this kind of involved patient has to be protected and sometimes the public representative involved in the development project has to have some kind of responsibility. The DoH says it's all responsibility of the doctor or the professional, but sometimes the public or the patient has to have a responsibility.

Kloiber We are very careful with that. Number one, the DoH is addressed towards doctors and not to anybody else. The deontology can only be towards physicians, but nevertheless, you can recommend to bring in patient groups for instance. That is happening in this world already so that patient groups are very strong sometimes even to an extent that it may interfere with the scientific validity of a study. There may be biased, there may be a Hawthorne effect, there may be other effects.

Nevertheless, the patient influence is growing, and what we have to do in the future is we have to try to harvest the benefits of patient involvement by making studies more relevant to patients and patient needs. Nowadays, we are more driven by the product development of a company, which is usually looking for what they can sell.

The inclusion of patient groups, for instance, in ethics committees is a bit difficult because they have a conflict of interest. The inclusion of society or population is again also being seen from an idealistic view. People groups or communities may have different interest from patient groups. The other problem is that we don't have ideal societies or states on this planet. Look to the members of the United Nations: Two years ago was the first year in history that more than half of the governments have been elected in this world, which means still half of the governments have not been elected. We don't have ideal societies and ideal populations. We are very careful, and we know a lot of bad experiments have been justified with population or society interest. The WMA in post-war time just started from that point.

Kurihara Very important point. So I have another question. Recently patient groups come to conduct study on themselves. One example is PatientsLikeMe, which you discussed in your lecture, gathered their own data and published some research results in high impact factor journal. Another example is, in radiation disaster situation like Fukushima accident, residents started to measure their exposure dose. Then community

self-help actions arise, they come to share information among the community. Sometimes medical doctors support such activities. Some of the citizens groups come to make presentation at some academic meeting, and then in scientific journal. So I think it is necessary to think about boundary between this kind of “practice” and “research” just as Belmont Report defined the boundary between practice and research. “Research” needs ethical approval, according to the DoH.

My question is, how is WMA’s position on research on themselves; how do you think such kind of citizen’s activity gathering scientific data and make presentations sometimes without ethics committee approval.

Kloiber As for research on themselves, Nuremberg Code states that “No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.”

The DoH has not commented on physicians’ researching on themselves. But I would conclude WMA’s idea is that if a physician conducts experiment on himself/herself, without inclusion of any other person, it is outside the scope of the DoH. If there is interaction with others, it is in the scope, even if study subjects are physicians only, or even with only one person. If a study is conducted by citizens without physicians, it is out of the scope of the DoH, because our documents are addressed to physicians.

10. Conflict of interest

Saio I am also very much interested in the issue of conflict of interest between patient group and industry. Also wrong interest of the society should be scrutinized.



I have one thing to ask for your opinion. We are writing a paper in Japanese on the effectiveness of conflict of interest disclosure (*Clin Eval.* 2020; 47(3): 501-18.). There are some psychological, clinical experimentation whether or not conflict of interest disclosure is effective. The answer is “No”.

Negative effect of conflict of interest disclosure was demonstrated. COI is a process of forming the structure of collision between parties. Negative effect of disclosure would be: strategic exaggeration; moral licensing; and insinuation anxiety. This means that those who disclose the conflict of interest might do more harm because there might be some excuse.

Kurihara I am a co-author with him and wish to add something. The conflict of interest disclosure would be the psychological impact of excuse. That would be what these experimental groups said. Researchers disclose their COI in the slides with many companies' names, then some of the audience come to regard that he is a great researcher, many collaboration with pharmaceutical companies. Furthermore, sometimes, there would be promotion or even commercial advertisement of the company names. Sometimes only disclosure may be the excuse that everything is allowed by the public. So we regard management is more important, not only disclosure, and sometimes restriction of acts, e.g., declining from voting in the board decision of clinical practice guidelines.

Kloiber There is now a common understanding that just disclosing COI is not enough. You have to have system of managing conflict. You may have to exclude somebody for certain part of the exercise. There may on the other side be an upswing effect with the disclosure of interest. When the supervising board of the stock exchange in New York was concerned about very high compensations of CEOs and board members, their idea was limit this by disclosure. The opposite effect was the case. A spiraling up-race started getting more crazy than ever. That is certainly a problem with the conflict of interest disclosure as well, but the answer lies



in how to manage them.

Greco There are two different aspects. In a recent WHO/UNAIDS meeting we were requested to fill up a COI form, and in the first 2 days even those with conflict could stay there, but in the last day, where more sensitive issues and possible voting would occur, those who had conflicts of interest were not allowed to participate. That is one way of dealing with COI.

The other related thing happened in the United States with the issuing of a law in 2013 called the Physician's Sunshine Act, which was established to increase transparency around the financial relationships between physicians, teaching hospitals and manufacturers of drugs, medical devices and biologics. If you show things clearly, you may have some return. This law obliges physicians to disclose his or her relations and financial gains from the health-related companies and other funders and this certainly facilitated the decision on putting a limit to these. As of 2014, any gain above USD 10 must be posted on a publicly accessible website. Disclosure is the beginning of the process for curbing conflicts of interest. It is a long and difficult process. The Canadian Medical Association, for instance, recommends that physicians should not accept personal gifts of any significant monetary or other value from industry.

Kloiber Undue influence cannot only result from industry interests or interference. You also may have distortions by interest from payers, which don't want to pay for new drugs. This needs a balance to be found.

For that, it is important that everybody tells where he is involved and says what interest he or she has and their organizations have.

11. Best proven intervention and placebo

Kurihara At the last occasion of this session, I wish to confirm about the condition of placebo control when there is a "best proven intervention". This "best proven" means "best proven in the world" or "best proven here"?

Kloiber "Best proven in the world".

Greco Yes, it is "best proven in the world".

Kurihara "The best-proven" in the DoH is higher standard than "established effective intervention" in CIOMS?

Greco No, it's written higher, but it has the same meaning. There was a big discussion at CIOMS at the time, because people would ask what's the best proven.

Kurihara The previous Secretary General of the CIOMS, the late Dr. Juhana E. Idänpään-Heikkilä wrote that even placebo can be "established effective intervention". It is interesting and it would be true that placebo can be proven to be effective for some specific symptoms.

Also, I well understand that the idea of "best available" is rejected. But how do you think about "ethnic difference"?

Kloiber I do not think it is necessary to consider ethnic difference when we discuss about this principle of physician's obligation to provide best proven care for patients in the context of clinical trial.

Greco I agree with Dr. Kloiber.

Watanabe I would like to mention about one study of our research group to find absence of ethnic dif-

ference in pharmacokinetics of three drugs among three East Asian populations, Japanese, Chinese and Koreans; and Caucasians as a control (Hasunuma T, et al. Absence of ethnic differences in the pharmacokinetics of moxifloxacin, simvastatin, and meloxicam among three East Asian populations and Caucasians. *Br J Clin Pharmacol*. 2016 Jun;81(6):1078-90. doi: 10.1111/bcp.12884. Epub 2016 Mar 14.). This is open-label single dose PK study. The three drugs were selected because of differences in PK parameters shown by the previous studies.

Kurihara I also well understand it because there is a long history of the US FDA to accept data generated from clinical trials conducted over the world. But I wish to mention the message from the late Prof. Stephan W. Lagakos, biostatistician at Harvard, engaged in data safety monitoring board of the HIV perinatal transmission prevention study conducted without placebo, in Thailand. He mentioned some kind of difference between the US and Thailand, e.g. subtype of virus, perinatal care, optimal dose, etc., specific to some population, thus best proven intervention may not be the best for some population because of various scientific factors. Dr. Robert Temple, US Food and Drug Administration, also said that, expressing complete agreement with 2008 and 2013 versions of the DoH, there would be ethically justifiable cases, not only the cases like allergic rhinitis, even in serious or life-threatening diseases to use placebo for specific population of non-responders to the proven intervention. I think these cases can be justifiable on the ground of “scientific compelling reason” or “no best proven intervention in the world for this specific population”. This would be case by case but we should be careful so that such excuse should not be abused.

So what is the acceptable limit of placebo control when there is a best proven intervention in the world? Many people agreed with the 2008 or 2013 versions, because “or” in the 2002 note of clarification was changed to “and”, and this statement was incorporated into the main text. I learned well that Prof. Greco and some of South American countries still disagree and support 2000 version. I don’t want to ask you to debate here which version is better, because I know well about both side arguments. What I wish to ask you is, because CIOMS changed this limitation from the description in 2002 almost the same as the DoH to the new idea in 2016 “minor increase above minimal risk”. How is your opinion on the difference between these two wordings.

Kloiber The current wording comprises a realistic solution we reached after long debate. I don’t think there is much difference between these two wordings of DoH and CIOMS. If all the paragraphs of the DoH are adhered to, the acceptable risk of harm would be the same.

Greco It should be the same, but while I was at Working Group at CIOMS I defended the idea of keeping the restriction for placebo use of the 2000 DoH and the Brazilian guidelines, without any exception. It wasn’t me who proposed this wording, but this idea came from the discussion among the team and an agreement was reached in the end. We met 8 or 9 times and also had many written discussions and eventually there were pressures to make the guideline less stringent or more pragmatic, if you will.

Do you remember the last phrase in the placebo item in the DoH? Extreme caution must be taken to avoid abuse of this option. I am pretty sure that you cannot have any exception in projects involving infectious disease or cancer, but you may be able to do it, exceptionally for a new pain killer or migraine. In psychiatry, there may be other exceptions, but it may not be really an exceptional if the real effectiveness of the specific psychiatric drug has not ever been proven to be effective or it is still unclear. We should be very stringent about not opening exceptions. People have the right to access to the best proven intervention and placebo



should be used only when there is no best proven, or otherwise included as an add-on.

Kurihara I respect you and Brazil and some other South American countries to keep higher standard than DoH. My question is, in most cases of investigator-initiated studies without company's sponsorship in developing countries it is almost impossible to pay for best-proven intervention. Even in Japan, there would be many academic research like that. In such case clinical trial of a new candidate drug should not be conducted?

Greco If you allow for lowering ethical standard, many of the pharmaceutical companies which can afford to provide the best proven drug will not provide this drug. Even if you are an academic researcher, you should use the best proven. That's ethical. If you go to a country where you don't have the drug, what's the reason for not using there in a research environment? It is just economical. We cannot discuss that as if it were an ethical principle.

The question that some people brought up is that by offering the best proven it may be "undue influence" because you are going to give things that people usually do not have. But that may be similar in several situations, because even in Japan, or Brazil, if one is enrolled in a research project, everything goes faster and smoother. They have the name and phone number of the doctor. You may reach him or her anytime. They have a dedicated nurse. Could this be considered a sort of undue influence? But CIOMS concluded that there is a right to access to best proven drugs or procedure, and this should not be regarded as undue influence. And I completely agree.

Maybe there are some places where you should not do research, if the prevailing situation is so bad and the risk for exploitation high. The 2007 UNAIDS Guidance for Research in Biomedical Prevention Trials has a list of reasons for not doing research in some countries. I discussed this subject many times with colleagues

from Africa. They said that by considering these circumstances which would preclude the performance of a trial, would affect negatively people who are paid in research and would discourage research. Maybe that's the price to be ethical. We must say that research should be done in countries where the risk of exploitation is small or can be circumvented.

The point is that if the local is so vulnerable, before starting research, you should first strengthen many things, adequately inform people, ensure access during and post-trial to adequate care, establish and/or qualify members of research ethics committees. And the other point is that why should we go to very vulnerable places to do research. I defend that the proposed research should be done in less vulnerable places and make sure that the results could be applied to those vulnerable communities. The only plausible reason for an exception is in the case of evaluating whether the proposed intervention is going to be useful for that specific population in a vulnerable situation.

12. Closing remarks

Watanabe Thank you so much for all of valuable discussion. Now we have to close this session, so wish both of the guests to give us final message at this session.

Kloiber I would like to close with thanking the organizers and hosts for this discussion. Some of you I have met before like Dr. Kurihara and Dr. Greco and we are bound by a long cooperation on the research ethics issues. However, I very much appreciated this wider circle of high-ranking experts providing inside in the reception of the Declaration and in research developments and demands we have to consider in the future. To me it also demonstrates the engagement of this community to serve our patients and to engage for an



ethical progress of medicine.

Greco I want to express my gratitude to the Japanese Society of Clinical Pharmacology and Therapeutics (JSPC) and to the organizers for inviting me to participate in its 40th Annual Scientific Meeting. I thank you also for the opportunity to get to know and learn from such a competent and gentle group of colleagues from Japan and also from my colleague Dr. Otmar Kloiber, WMA. I do hope we can stay in touch.

Watanabe We appreciate so much your participation in two days discussion. Very important points have been discussed to think about future research ethics. There have been long debate on placebo trial and post-trial access of the DoH, and now we face challenging issues considering data-driven science as well as highly advanced, and highly costly medical technologies. Nonetheless, universal healthcare access would be our goal for that we should make all efforts. We appreciate to be able to learn so much the background discussion and essence of the DoH and CIOMS and other international documents and hope our discussion to contribute to future development of research ethics.

Part 2 Post-trial access and post-trial care^{* 2}

1. Question: Post-trial access and phase 1 study

Saio Thank you for this opportunity of one more additional discussion. I would like to ask a question how we can interpret the “post-trial provision” in the DoH, concerning one extremely serious event which happened in Japan. It happened in June of this year (2019) and the report of regulatory authority was released just last week:

https://www.mhlw.go.jp/stf/newpage_08131.html

The report of English version:

<https://www.mhlw.go.jp/content/11123000/000585517.pdf>

It was one of the first in human trials of an investigational drug, E2082, involving healthy male adults. I am writing a paper on it (published on December 23, 2019):

<http://cont.o.oo7.jp/48sup37/w1-w18.pdf>

One volunteer committed suicide after completion of dosing study drug. He might be suffered with acute perceptual alteration by the withdrawal of the candidate drug which possibly had some psychotropic property extrapolated from the result of the animal studies and adverse effects of a drug of the same pharmacological mechanism. After the completion of study he discharged from the phase 1 clinic. But he returned to the clinic suggestive of acute psychotic features. The clinical investigator advised that he should visit a mental clinic as soon as possible, without providing care, because there is no psychiatrist in the phase 1 clinic. However, the patient refused to visit a mental clinic, and committed suicide next morning.

Those possible psychotic features could be disappeared by re-administering the candidate drug after the completion of the study for those symptoms could be raised as the withdrawal symptoms of psychoactive substances including the candidate drug. I think this could be rationale to strengthen the post-trial access clause of the DoH. Even if it is not a “intervention identified as beneficial in the trial”, it is sometimes necessary to continue the study intervention to the subjects because of the supposedly withdrawal symptoms. It is indispensable to consider the psychoactive property of the candidate drugs in advance of the clinical trial because the psychoactive substances often have withdrawal symptoms which occur after the completion of the dosing. In addition, it should be also strengthened that post-trial access to the study drug of a participant who need it must be assured, even though it is not the one “identified as beneficial in the trial”. To prevent the withdrawal syndrome, sometimes continuing medication using the same substance would be necessary.

This is a principal question concerning the post-trial provision, not asking you for your evaluation about this case.

Kloiber To be very clearly understood, I don’t make any judgments or comments on that specific case. I just speak as theoretical of Phase 1 trials and post-trial provision in the DoH, not having heard any of the

^{* 2} This Part 2 is additional discussion with the guest lecturers at the separated occasion especially focusing the topics of “post-trial access” and “post-trial care”. Only Takeo Saio and Chieko Kurihara among the discussants of the session in Part 1 and interviewed with the two guests.

involved parties. What kind of care is necessary for subjects is different from case to case, from study to study.

I spoke before on the DoH, the paternalistic argument is there right up front and it says “you have to care”. That means you have to care before, during, and after for your subjects in a study, whether those are patients or healthy volunteers which are taking part there. That is number one, and this is probably the overarching guidance here.

But then there are three different types of paragraphs in the DoH, which come to the point when something goes wrong after the initial phase of phase 1 study. The first one which is in paragraph 22 says that “the protocol must also describe appropriate arrangements for post-trial provisions”. This is not bound to any phase, so that is for all the phases. That is something which we have to be mindful already with a protocol. Protocol design has to look into the question, is there anything that can happen afterwards? There may be, for instance, be a withdrawal symptom, or another late reaction, which is not within the acute phase of the application of the drug.

Number two is, there is a provision in the DoH that speaks of access to care after the trial. Now, this one has been brought in very specifically in view of phase 3 trials, which is a very clear protection against exploitation. People should not be used as guinea pigs and then be dropped. That means, when you start an experiment, you have to make sure that there is care afterwards and that people have access to care which are in the study. There are some different views, how that is being done but it is very clear, that there has to be effective care. You can argue that may not benefit the phase 1 trial or apply to it. In the first phase 1 trial, you have the idea of “healthy in” and “healthy out”, and ideally there should be no care necessary for the subject, if everything went properly, but nevertheless the demand for aftercare has to be observed.

The third one is a new provision which came in with a 2013 version and that is material protection. That means whenever there is an incidence and a damage produced by a trial, there has to be a system of protection. Such can be very different. This can be, for instance, a compensation fund, if you have a national health system. This can be government money, or if you have a private system there should be an insurance which covers potential damages. A cover of those damages is obligatory, and when we speak about the damages, we mean all damages that occur, so it’s not just to have a quick fix. It may also be consequential damages that occur.

These are the four different aspects: general care, proper protocol, access to care afterwards, and material protection in case something happens during the course of the clinical trial or the experiment in general.

Kurihara Thank you so much for your very clear explanation about the construction of the DoH. Just one thing I wish to confirm. The paragraph 34 states that “post-trial access for all participants who still need an intervention identified as beneficial in the trial”. “Identified as beneficial in the trial” seems to mean that “intervention proven to be effective in the trial”.

Kloiber Don’t misunderstand this. The term “found beneficial” can mean that an already existing treatment is the better one and then this has to be provided. And “Found beneficial” does not necessarily mean that only a new winner has to be provided.

Kurihara If some of the ethics committee member found that there is no such kind of description about the care of the withdrawal syndrome in phase 1 trial, is it possible for the ethics committee member to say, according to post-trial requirement of the DoH, you should include something in your protocol? This can be

any kind of care found beneficial for each participant? It may be the tested candidate substance in some case and in another case it may be another kind of care.

Kloiber That would be what an ethics committee should consider before. A group of researchers should clarify this already when submitting a protocol. If the protocol doesn't foresee this, then the ethics committee should say, "wait a minute, is it not necessary to have there also a provision for the aftercare" ?

2. Need for continuing care and relevant strategy

Greco In hindsight, you can see that something went wrong because if you had a drug that affects the central nervous system, it's very hard to affirm that this possible effect is going to stop when you stop the drug. They should have thought about that beforehand. I agree that people may think that this case does not apply to post-trial access rules because in post-trial access, we say about good things that should be given to patients. So people may wrongly think that in case of normal subject, usually when you finish, you don't have to receive the drug.

My opinion is that it is much harder for a research ethics committee to tackle that because they are used to have phase 1 trial, where normal people receive the drug during a time and then they are okay. But the researchers, especially if they are from a psychiatry background, they must have thought of something that could have happened after you take it out, especially if it's a drug that people expect to be very active. That is one of the reasons for a phase 1 trial.

The participant must be protected all the time since before the beginning and after the completion. The expectation of something happening could occur in the last day of the trial. In this specific case the adverse event had already happened because the participant told the doctors that he was not feeling well in the end. That should have raised a flag that he needed help. You should not refer the participant. You have to follow him or her. It's part of the trial to take care during and after that. Maybe DoH, as a living document, could add a clarification in this respect.

Kloiber It may be something that needs more detailed description in the CIOMS guidance. We will be in synchronicity with CIOMS. We have a very close collaboration because we want to keep the DoH as a set of principle statements.

It is true that this idea came from phase 3 trial and people discussed much about post-trial access to the drug proven to be effective in this trial. The problem is the reality we are living in. We have the rich world and the poor world. In the poor world a healthcare system may not provide a specific treatment or any treatment at all. The requirement that the treatment that is most beneficial should be provided maybe not fulfilled because the treatment is not provided there at all. Permissions for compassionate use or trial extensions maybe a solution.

In some cases, it's even unacceptable to continue with an old treatment. Let me give you an example: Therapies for hepatitis C. When several years ago, new treatments came out, they were extremely expensive in the western world. About €70,000 per case in France or Germany. The healthcare system were hesitant because it was too expensive. To me, treating somebody with the old medication comes close to a physical assault because the old trial was much worse, with often severe side effects, and a chance of healing which was far lower than with the new drug. Government tried to negotiate with this company to get the price down,

but letting patients suffer for that is not acceptable.

Kurihara I well understand that post-trial access to tested drug proven to be effective in this study is difficult many times. A sponsor should make all efforts to provide this drug to participants who need it. In Japan there is a guidance to facilitate it and there would be other countries to recommend extension trial or otherwise compassionate use. This can be done also by means of company policy. This would be the good result of extensive discussion on post-trial access in the DoH. In addition, it is good to hear that if a participant need tested drug not proven effective or other kind of intervention, it should be provided according to the post-trial and other requirements of the DoH. Keeping this in mind, we have to think about extremely expensive new interventions.

Thank you very much for this additional discussion on this specific topic.

(Published May 7, 2020)

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