

Interview

Discussion toward the 50th anniversary of the Declaration of Helsinki

— Interview with Dr. Otmar Kloiber,
Secretary General, World Medical Association *1 —

Otmar Kloiber

Secretary General of the World Medical Association

Interview and translation :

Chieko Kurihara¹⁾ **Takeo Saio**²⁾

1) Molecular Imaging Center, National Institute of Radiological Sciences

2) Fuji Toranomom Health Promotion Center

(March 2, 2013, Imperial Hotel Tokyo, Tokyo, Japan)

Abstract

This article is the record of our interview with Dr. Otmar Kloiber, Secretary General of the World Medical Association (WMA) during his visit to Tokyo for the World Medical Association's "Expert Conference on the Revision of the Declaration of Helsinki" held on February 28 and March 1, 2013, and hosted by the Japan Medical Association (JMA).

We were privileged to have the opportunity to interview with Dr. Kloiber after the Conference, on the important topics related to the 2013 revision of the Declaration such as: biobank, compensation for research-related harm, research in resource-poor setting, post-study access, vulnerable populations, ethics committee. Dr. Kloiber shared with us his thoughts and opinions on these topics as well as on the issue of ethical principle for placebo-controlled clinical trial. He explained the standpoint of WMA on these topics especially on the 2002 Note of Clarification and the 2008 revision in which the revised version of this Note of Clarification to the placebo principle was moved into the main text of the Declaration.

The Declaration of Helsinki was first issued in 1964. Next year, 2014, will be its 50th anniversary. The WMA is now vigorously working on the final version of the current revision, which we hope to be adopted in October 2013, reviewing all the topics that have been intensively discussed during the past decades.

Key words

Declaration of Helsinki, research ethics, placebo-controlled clinical trial, post-study access, compensation for research-related injury

*1 Japanese translation of this interview is published in *Rinsho Hyoka (Clin Eval)*. 2013 ; 41 (2) : 351-72. Citation of this English version : Kloiber O. Interviewed and translated by Kurihara C, Saio T. Discussion toward the 50th anniversary of the Declaration of Helsinki — Interview with Dr. Otmar Kloiber, Secretary General, World Medical Association —. *Rinsho Hyoka (Clin Eval)*. 2013 ; 41 (2) e. (http://homepage3.nifty.com/cont/41_2/p351-72eng.pdf)

1. Expert Conference on the Revision of the Declaration of Helsinki

Interviewer Thank you so much for accommodating this interview right after the meeting of the World Medical Association's (WMA) "Expert Conference on the Revision of the Declaration of Helsinki," hosted by the Japan Medical Association (JMA), from February 28 to March 1, 2013 in Tokyo. As Secretary General of the WMA, we suppose you have a lot of work to do during the conference and also after the conference. So we thank you very much for this opportunity and for giving us your time. It was surprising and remarkable that such kind of discussion meeting for the revision of the Declaration was held open to the public.

Kloiber Usually we do not publicly discuss our drafts of the revision of the Declaration of Helsinki. There's nothing secret, but we do not publish drafts until the planned time, because we have experienced that many of the drafts, actually nearly all of the drafts, have received amendments. Often we find that the initial ideas are not sufficient and we want to come to a better product. And we have found that it is highly confusing when preliminary versions are out.

On the other hand, we are trying to get expert input to our drafting process. The Declaration of Helsinki has received so much public attention. And therefore we do a two-step process: We first produce a draft which the Council accepts, and only when the Council has decided to have it discussed publicly we go out with them. And it has turned out in the past that this is a very beneficial process, and therefore we most likely will repeat this with the Declaration of Helsinki.

Interviewer Is it no problem to ask you some questions concerning the draft of the Declaration

just before finalization? And also is it no problem to ask some of the delegates of some countries' Medical Associations or speakers about their opinions on the draft?

Kloiber You are absolutely free to do what you want. We are an organization that stands for the freedom of research and the freedom of publication. That means not only our freedom but your freedom as well.

Interviewer That's great. Thank you. So how is your impression of the discussion this time in Tokyo compared to the other open discussions held in the past?

Kloiber There was a lot of interest here in Tokyo. Actually, it was the biggest of the conferences which we have had so far. I think we had more participants than in Cape Town and Rotterdam. That is at least in part due to the work of the Japan Medical Association. Everyone seems to have a very strong interest in the issue of subject protection. We also have seen quite some interest on the question of research in resource-poor settings. We have heard various arguments concerning biobanks, all pointing to a stronger role for ethics committees. There is obviously a stronger demand for protection of human-derived material, and there is a demand for compensation for research-related injuries of subjects. All in all - everyone seems to be very supportive of our work. So I found these two days conference here in Tokyo very rewarding.

Interviewer It is also important and a good idea that editorial work such as creating subheadings and arranging the order of the ideas according to topics, which we also thought for long time should be done. Our journal have had discussions about the Declaration^{1~3)} several times in the past, and also published interviews with Dr. Delon Human⁴⁾, when he was the Secretary General of WMA, and with Dr. Eitaka Tsuboi⁵⁾, just after his



Dr. Otmar Kloiber, giving speech during the World Medical Association's "Expert Conference on the Revision of the Declaration of Helsinki", hosted by the Japan Medical Association, February 28 to March 1, 2013, Tokyo.

Dr. Otmar Kloiber is currently Secretary General of the World Medical Association. He has been engaged in international medical relations and spearheaded various health collaborations for more than 20 years. His expertise includes medical ethics, health policy, government affairs and management of relationships with patients, other health professionals, manufacturers and other medical stakeholders. He has been chief executive of the WMA since 2005. Between 1997 and 2005, he served as Deputy Secretary General and Secretary of the German Medical Association (GMA). During his tenure in GMA, he was appointed as Member of the Study Commission on the Law and Ethics of Modern Medicine of the German Bundestag (Parliament), 14th electoral term. Between 1991 and 2005, he was also a key liaison to the Standing Committee of European Doctors, the WMA, the Inter-

national Conference of Medical Chambers, the European Forum of the World Health Organization and individual national medical associations. Additionally, for six years, he was the foreign relations adviser to the German Medical Association, focusing on international health and social policy reforms and construction of the German Health Network.

He holds an MD (1984) and PhD (1986) from University of Cologne, was a postdoctoral fellow in the Department of Biochemistry at the University of Minnesota, and was a research assistant at the Max Planck Institute for Neurological Research. In 2006, he was awarded an honorary doctorate by the Victor Babes University for Medicine and Pharmaceutics, Timisoara, Romania. He was appointed Clinical Professor in Health Administration at the Brooks College of Health, University of North Florida from 2009 to 2013.

Quoted from the web-site of OECD: <http://www.oecd.org/health/ministerial/worldmedicalassociationotmarkloibersecretarygeneral.htm>

tenure as President of WMA. So you were appointed after Dr. Delon Human?

Kloiber Yes, I'm following Dr. Delon Human in the office.

Interviewer You have been engaged in WMA since before the time Dr. Human was secretary-general?

Kloiber Indeed. I'm engaged in the association since 1991; so actually the time before Dr. Human came. I have been part of the discussion on the Declaration from the middle of the 1990s until now.

Interviewer After the Tokyo Conference, we heard that WMA is going to have a public consulta-

tion on the proposed revision and will have a meeting in Washington D.C. in August 26-27, and then finalize this current revision during the General Assembly on October 16-19, 2013 in Brazil. So next year, 2014, is the 50th year anniversary of the Declaration. What is your plan toward this 50th year anniversary?

Kloiber Provided the WMA Council agrees, we are planning to have a public consultation during the summer. After that, the workgroup will analyze the comments and critique coming in. This may lead to a new draft to be discussed again in a conference we plan for August in Washington D.C.. In the end, our aspiration is to have a final draft



Dr. Kloiber giving a speech on March 1, 2013, at the closing of the “Expert Conference on the Revision of the Declaration of Helsinki.”

ready for the General Assembly in Brazil in October this year ^{*2}. However, let me emphasize this: Our focus is on the quality of the document, not the timeline. If we don’t finish this year, we will do it next year.

In 1964, the Declaration of Helsinki was handed over to the President of Finland. It was a documentation of self-governance and social responsibility. We have asked the President of Finland to again share this moment with us, celebrating 50 years of the Declaration, and we are proud to say the President of Finland has agreed to do that. So we will celebrate 50 years of the Declaration of Helsinki next year in Helsinki and we are sure it will get some attention.

2. Issue of placebo-controlled trial

Interviewer We supposed that in the meetings held in the past to intensively debate the placebo

issue, more people participated in the discussion.

Kloiber The placebo issue was very much expert discussions, and we invited all those people who had scientifically published on the methodology of using placebos, because we want to make sure that there is good scientific evidence for the use of placebos, even if there is already an established therapy. There are of course such situations where you never can replace a drug by a placebo because the drug treatment is essential, and it would be threatening to the patient to remove such treatment. But we learned that there are many other instances and diseases, especially when it comes to symptomatic treatment where we deem it now necessary to have the chance to do placebo studies. So currently I see a trend to use three-arm studies – to have a verum arm, to have active comparator, and where necessary also a smaller placebo arm.

Interviewer In Japan, there are many psychia-

^{*2} Postscript by Dr. Otmar Kloiber: The meeting in Washington DC was successful and there will be a final draft.

trists and persons in the field of medicine or medical ethics who protest against the use of placebo in clinical trials. But very recently such trend of psychiatrists protesting against the use of placebo is changing because of the increasing number of reviews or meta-analysis of research on psychiatric drugs for depression ^{6~8)}, and schizophrenia ⁹⁾ showing that there is no significant difference between the test drug and placebo. Yesterday, during a break in the meeting, we talked to a delegate from another medical association. He is a psychiatrist, and he told us very clearly that placebo should be used in the area of psychiatry.

Kloiber We thought at some point we can identify a “best-proven” therapy for each disease. But if you take for instance the established anti-depressants, we now know that many of those drugs turn out to be not so effective. Also, we have not yet understood for all the different diseases and therapies, how to select the right drugs for each potential subgroup of patients with one disease, because what we often see is that there are collectives of responders and non-responders. We always have to

retest whether our assumptions are really correct. The placebo can be very good instrument to do that. To ban the placebo completely, we now are sure would in turn be damaging the science, and by that it would most likely harm patients more than using the placebo correctly. But – to make that very clear – this is not about using the placebo as a cheaper alternative instead of an active drug. We are talking scientific, not economic reasons to use placebos.

Interviewer The 2008 revision seemed to be the conclusion of this kind of placebo debate. The condition on the use of placebo is that even if there is a proven therapy, placebo can be used when there is the scientific reason and it will not subject the patient to any risk of serious or irreversible harm. These are very well written descriptions. But why was there so much debate raised after this 2008 revision and discussed in São Paulo in 2012?

A delegate from the Japanese Medical Association wrote that the Brazilian Medical Association, on behalf of developing countries, expressed strong opposition to Paragraph 32 of that time ¹⁰⁾.

Box 1 Provision concerning “Use of Placebo”, in the proposed revision of the Declaration of Helsinki

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best ~~current~~-proven intervention(s), except in the following circumstances:

The use of placebo, or no ~~treatment~~intervention is acceptable in studies where no ~~current~~ proven intervention exists; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, placebo or no treatment is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo or no treatment will not be subject to ~~any~~additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Comment by WMA: Old paragraph 32.

Excerpt of the proposed revision shown in the version released for public consultation to revise the 2008 version. Paragraph 32 of the 2008 version has become Paragraph 33. A final decision on this proposed revision would be made during the General Assembly of WMA in October 16-19, 2013 in Brazil.



Dr. Kloiber, responding to a journalist during the Press Conference held on March 1, 2013, after the conclusion of the “Expert Conference on the Revision of the Declaration of Helsinki”.

Kloiber After the 2000 revision, there were many lawmakers and regulators, especially in Latin American countries, who banned the use of placebo in clinical trials if there is an established treatment. In a number of Latin-American countries placebo-controlled trials are impossible if there is an active compound to treat with. Of course we could be proud that lawmakers and regulators have followed our Declaration, but at this point it becomes clear why there is a difference between an ethical guideline and a law. After the 2000 version banning more or less the placebo use, we learnt that this was too strict and we have taken the consequence to change. But once you have a law or a government regulation, it's very difficult to change. Knowledge grows, sciences changes, new methods come in. We can revisit ethical principles and the rules we derive from them – and so we do. We have had discussions from 2005 to 2008 about the use of

placebos. We think it's necessary to make very clear to all the lawmakers that indiscriminately banning placebos is not a good idea because there is a need for placebos.

Interviewer So you mean that some scientists in Latin American countries (especially the Brazil Medical Association) want to revise the 2008 revision because of that kind of prohibition in the law?

Kloiber They say 2008 version is not acceptable to them because the law says they cannot use the placebos. We now know that this is not correct because there are good reasons to use placebos in clinical studies.

Interviewer We heard from someone that there are some religious people in Latin America who protested against the use of placebo.

Kloiber I have not heard any religious arguments concerning the use of placebos. I have heard from some of the activists groups, especially in Europe, who have said that there are placebo studies being done in resource-poor countries, and they are raising the assumption that these studies are being done because it's cheaper to test against placebos instead of a real medicine. And this is unacceptable for us as well. Placebos must never been used for economic reasons in clinical studies. However, if you look into those studies that have been criticized, you will find that the studies have been done multi-nationally with the same design not only in poor countries but also in richer countries. So the argument of exploitation does not seem to be correct. There may be studies which are being done and produced unethically. The Declaration of Helsinki is exactly about preventing those studies.

3. Note of Clarification for the principles of placebo-controlled trial

Interviewer So before the 2008 revision,

there was the 2002 Note of Clarification for Paragraph “29”. It was strange and seemed for us a little bit tricky. There was a conjunction “or” in this Note of Clarification, that is, “scientific compelling reason OR no additional risk of serious or irreversible harm for the subjects....”

Kloiber There was one discussion point that we said that there are many studies which are not about serious diseases. The idea was that an individual person can decide whether they want to take the risk of being in a placebo group.

Interviewer That is the point raised by Dr. Temple and other FDA staff wrote articles ^{11, 12)} about.

Kloiber Yes, they made a point.

Interviewer The point which seems to be tricky is that in the Note of Clarification, there is the conjunction “or”. Not “and”.

Kloiber In the 2008 version, we decided for the stricter version by introducing the conjunction “and”, which means both conditions must apply.

Interviewer Wasn’t it just a mistake or some very tricky person inserted this conjunction “or”?

Kloiber The conjunction “or” was put in there by purpose. The question whether it should be “and” or “or” had been discussed. And it was for the reason which I mentioned, that it was made an “or” at that time. Nevertheless, the WMA General Assembly in 2008 decided for the stricter version.

Interviewer If this is an “or”, then the use placebo is permitted only for scientific compelling reason, even if the study may cause serious harm to the subjects.

Kloiber At no point! It was clear that the placebo use should be only permitted if the study adheres to all other conditions in the Declaration.

Interviewer You mean that if the study adheres to all the other conditions, ethics committee and the prospective subjects can properly evaluate the risk of harm? Is that what you mean?

Kloiber Yes. That was the idea of the note of clarification. But this is history. The 2008 version is much stricter. Already in 2000, it was clear to us that we had to continue the work on the Declaration of Helsinki because there were many issues where we thought that this was not final. The Declaration of Helsinki has always been a living document. Some of us were also convinced that the solution for placebos and for the continuation of treatment after the trials was not perfect. So we made the note of clarifications in 2002 on placebo, and in 2004 on the post-trial access to care. And it was also clear that we have to bring it back into the main text of the principle, not as a note of clarification. So when I came into office in 2005, I proposed immediately that we look into producing a new revision in order to have a clean text. And that was the purpose for 2008.

Interviewer It became very clear to us now. After 2008, there were some questions remaining. Were these questions resolved during the meeting in São Paulo, because there was no discussion on that in Tokyo?

Kloiber In 2008, we saw a strong opposition by some of our colleagues, especially from Latin America against the placebo rule. The Council told me: “We take these concerns very seriously, and we want you monitor the situation and report back to us whether the new (2008) version is appropriate or not.”

Interviewer When we saw the note of clarification, it seemed strange that the Note of Clarification (i.e. placebo-controlled can be allowed if there is scientific reason, on condition that the Declaration is adhered to) upend the statement of the principles in the main text (i.e. placebo-controlled can be allowed only when there is no established method) concerning placebo use.

Kloiber It’s probably not. The Note of Clarification was made because we thought that we had

not expressed the principles clearly enough in 2000. It has never been intended as an opposition to the principles. However, we found that we had written a non-working rule. The aspirational rule simply saying “no placebos” was just not working. The principle behind that is non-exploitation or “do no harm”. We must prevent that people are being subject to exploitation by the use of placebos for economic reason. But when the use of placebo is scientifically necessary, not using placebos may do more harm.

Interviewer We understand completely what you mean. So how about the next discussion on placebo? There is no discussion in Tokyo about the placebo issue; instead the discussion has shifted to the post-access issue.

Kloiber We think the rule on placebo in 2008 is correct. We will probably develop a little more precise wording, but the rule is fine. We think it’s not only necessary to explain why you use placebo instead of the best-proven practice or treatment; we’ll also ask why do you use anything else but the best-proven treatment. Sometimes new compounds or procedures are not tested against the best-proven treatment but tested against the second-best. We want to make sure that this is only being

done for valid scientific reasons and not because second best is cheaper. This is important for all patients, not only for those in poor countries.

4. Post-study access and resource-poor setting

Interviewer Now, let’s shift the topic to post-study access and resource-poor setting. How is your impression of yesterday’s discussion on this, especially the comment of a delegate from India about exploitation of subjects in the trial? Some of the delegates from pharmaceutical companies explained something in response to that.

Kloiber First of all, it’s not only a problem in the resource-poor settings. Actually, I get these questions concerning the post-trial access to the best-proven treatment from rich countries as well. Also, patients in rich countries don’t necessarily get the newest drug or the best-proven drug. Even in the rich countries, payers or regulators tell the patients “No, you have to take a cheaper one because the best-proven, may be 5 percent better, but we don’t pay five times more money for that. We only pay for the second best.”

A mistake in the 2000 version was that we put

Box 2 Provision concerning “Post-trial Access”, in the proposed revision of the Declaration of Helsinki

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the study. This information should also be disclosed to participants during the informed consent process. All study participants should be informed about the outcome of the study.

~~At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.~~

Comment by WMA: Old paragraph 33.

Clarifies and strengthens post-trial access issue.

Excerpt of the proposed revision shown in the version released for public consultation to revise the 2008 version. Paragraph 33 of the 2008 version has become Paragraph 34. A final decision on this proposed revision would be made during the General Assembly of WMA in October 16-19, 2013 in Brazil.



Interview with Dr. Kloiber

the burden on the continuation of healthcare after the end of a study on the sponsor of the study and the researcher. But indeed, this is not their duty. It's the duty of the states to provide healthcare in one way or another. It can be a private healthcare system or public healthcare system. It can be a healthcare system by a social insurance. But we believe it is the obligation of the state to make sure that everybody gets the healthcare a person needs; to ensure this is not the obligation of a researcher or the sponsor of a study. Of course, what we see is that by doing the research and by offering treatment in a research program, people may have an undue inducement to be part of an experiment. That is unfortunately correct. That is what Dr. Kumar described as the treatment naïve people, who are strongly induced to be part of an experiment because otherwise they don't get treatment.

But this is a general problem, not only a problem in resource poor settings. In my country (Germany) ten years ago, if you had macular degeneration, the only way to get an effective treatment was to become part of a study because the healthcare system would not pay for the drug. Things have

changed. I am very happy that many companies now provide medicines for post-trial care. I think that is already a big win which the Declaration of Helsinki may have triggered.

But we also have to come back and say, "States, it's your business to make sure that there is a healthcare system; that people get appropriate healthcare when they need it and want it." Most sponsors of clinical trials – the universities, foundations – even many companies are not able to do that. They cannot replace the functions of a state.

So we have to step back, and what we say is these conditions have to be explained beforehand. People have to know what happens with them during and after a clinical trial; and what that means for their health. People can then decide whether they want to be part of that trial or not. The empowerment of patients is probably the most important aspect of this rule.

We also say there has to be a sharing of the results, and that can be that a pharmaceutical company provides drugs after the trial. It can be that information is being given to the community and that the whole community has a win from that. Very

often we find patients who are very willing to take part in a trial even though they know that they themselves will not benefit from it. Think about cancer treatments. Very often patients clearly understand that they may not be saved from a trial. But they well know that the knowledge that is being generated may help the future patients. In the end, we had to come to a more realistic wording but also a wording that puts the obligation to ensure health-care back to the states without prescribing a specific type of health care system.

Interviewer It's a very important point. Another point is that too much emphasis on the post-study access can bring some harm to the patient. There is one example – post-study access includes the problem of expanded access.

Kloiber You are absolutely correct.

Interviewer In Japan, a new molecular-targeted cancer drug gefitiniv (Iressa[®]) was approved earlier than in the U.S. or Europe. Such case was very rare in Japan at that time. But soon after approval, and also before the approval, many of the newspapers or other media released information about the drug, and many patients got the drug through the scheme called “Expanded Access Program” which is not legally well-defined system in Japan. And then so many adverse events came out and lawsuits were raised by patients groups in Japan.

Kloiber Yes, that is a problem. Unfortunately, the rule in the 2000 version of the Declaration did not take in account that a single clinical trial nearly never ever gives you a definite result. Usually, several trials in different places are needed. Second, if a new drug is being tested in a trial, and even if it's been found more beneficial than an old one, it does not mean that you have a marketing authority for that. The marketing authority may take another two years to come. So that was why we finally found that the rule in 2000 version was unrealistic.

5. Obligation of states to assure health for nations

Interviewer You said that “post-study access” is an obligation of the state. So which kind of obligation? Is it correct to say ethical obligation?

Kloiber It's a human right. Health is a human right. The states, in one way or another, have to provide a functioning healthcare system.

Interviewer It's a very important suggestion. There is also another point: post-study access is very much a monetary issue, same as compensation issue and ancillary care. Ancillary care is not included in this Helsinki Declaration, but is very much discussed in the U.S. by bioethicists.

Kloiber Ancillary care is part of the health-care that has to be provided by the health care system in general. Now, for a functioning clinical research environment you need functioning ancillary care. Because you cannot do any drug study on substances on blood pressure regulation when your people are starving or are not being taken care of, and so far, it is part of a good clinical practice. But this is also an ethical dimension that reaches into the other questions of the human right, that is, to have proper health care.

People tend to read the Declaration of Helsinki as a solitary document. It is not. It's part of our policy compendium. In our policy compendium, we also have a Charter on Patient's Rights which clearly states that persons have a right to appropriate and timely treatment. There's the International Code of Medical Ethics; the Declaration of Geneva; the Declaration of Lisbon on Patient's Rights. The Declaration of Helsinki is not in a vacuum.

6. Resource poor setting and capacity development

Interviewer We regard that a very important characteristic of the Declaration of Helsinki is research ethics, human research. So let's go back to another point of resource-poor setting. When I (Kurihara) visited the University of the Philippines, I discussed with the members of their ethics committee about the north-south issue and ethics of international clinical research (Table 1)¹³. We discussed about the comparison between the Declaration of Helsinki and the CIOMS guideline¹⁴. Comparing the Declaration and CIOMS, the wordings on placebo issue became almost the same after the 2008 revision. Healthcare needs issue and post-study access issue are also the same.

The only difference is that capacity development

issue is included in the CIOMS but not in Declaration of Helsinki. Capacity development is very important but a little bit tricky if it becomes a substitute for post-study access. It's like saying, "I am sorry we cannot give you continuing therapy but we can provide you with capacity development opportunity." If it is true that they cannot provide continuing therapy but they could contribute in capacity development, it could be welcomed.

Kloiber But we think it's not an "or". It's an "and". So both have to be achieved. But we also believe that CIOMS and WMA are not apart. We think that the participation in research is extremely important for the development of healthcare systems. Having a perspective for academic development is a strong incentive for the retention of health personnel in those countries. Currently the rich countries of this world are stealing the health professionals from the poor countries of this world.

Table 1 Obligation of the researcher in collaboration with resource-limited community

Declaration of Helsinki	CIOMS
Placebo or no treatment control 32. Placebo or no treatment control may be acceptable when it will not be subject to any risk of serious or irreversible harm.	Placebo or no treatment control 11. Placebo or no treatment control may be acceptable when it would not add any risk of serious or irreversible harm to the subjects.
Health needs 17. Research involving a disadvantaged or vulnerable community is only justified if the research is responsive to the health needs of this community.	Health needs 10. The Research in communities with limited resources should be responsive to the health needs of the community.
Post study access 14. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial. 33. At the conclusion of the study, patient participants are entitled to be informed about the outcome of the study and to share any benefits that result from it.	Post study access 10. Any intervention or product developed will be made reasonably available for the benefit of that community.
	Capacity development 20. The research projects should contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research.

Quoted from reference No. 13. Numbers of provisions of the Declaration of Helsinki are from 2008 version.

And if we want to have healthcare in the resource poor countries as well, there have to be research opportunities as well. Capacity building is extremely important. But it must not be at the expense of safety or correct ethical behavior. Both have to come together.

Interviewer In the description of CIOMS, I think their idea is the same as yours. Both should be kept together. But in the description of CIOMS, they say that even if it is very difficult to provide the new therapy after the completion of the study, it would be acceptable if the conduct of the study helps in capacity development.

Kloiber Well, if you read our document that would not be in contradiction with that because what we are saying right now is that it has to be explained what is happening after that and that the benefits have to be shared. But there is no guarantee for anything automatically.

Although we are 49 years further now, the Declaration of Helsinki in the beginning was a document that has been made to enable research in humans, to make research acceptable. And we still say, health research, clinical research is necessary and has to be done in order to advance medicine and to save people and to prevent disease and to alleviate the suffering. And we always stress that we believe that health research has to be brought to all people, all communities, and all professionals.

Interviewer So how do you think of Singapore as an example? There are many Phase 1 studies being conducted in Singapore. They very much welcome global pharmaceutical companies to come and conduct Phase 1 study, even if it is not assured that all the successful studies will proceed to later phases in Singapore. These later phases may be conducted outside Singapore, in other countries where many patients can be recruited in large hospitals in a short period of time. In these days, most of the early phase clinical trials are not so risky,

and human research volunteers are very much protected. Also sometimes this kind of early phase clinical trial on patient can show efficacy. But this kind of situation is far from the assurance of post-study access to best proven treatment.

Kloiber I think the future markets for drug development, and the future demands for drug development are coming from those big countries which right now people have no proper or do not yet have full access to the available drugs: China, India, but also Philippines, Indonesia, and many African and South American countries. As I said before, we strongly believe that those communities should be part of the scientific development as well. If it is okay to have such a study being done in Japan, it should also be okay to be done in the Philippines, provided that the technical and ethical safeguards are absolutely the same.

Again, when it comes to the post-trial access, we say the benefits have to be shared, in one way or another, it's not clear what that has to mean in each individual case. But people have to be told what happens to them afterwards, so that people can decide whether they want to be part of that. What we don't accept is that people are being paid for clinical studies. That is an undue inducement.

But then again, we are convinced that bringing research to a country, in many cases will, increase or improve the health care situation in general. That is a benefit, and it's not an incorrect benefit of having that. The rich countries have enjoyed this benefit for all the last decades.

7. Compensation for research-related harms

Interviewer So, how is your opinion on the compensation issue? It must be very important but seems very difficult to include such issue in this kind of ethical guidelines. Theoretically, "no-fault"

**Box 3 Provision concerning “compensation for research-related harms”,
in the proposed revision of the Declaration of Helsinki**

15. Adequate compensation and treatment for subjects who are harmed as a result of participating in the research must be ensured.

Comment by WMA: New paragraph. It reflects the obligation to ensure that subjects who are harmed will receive compensation and treatment.

Excerpt of the proposed revision shown in the version released for public consultation to revise the 2008 version. In the 2008 version, paragraph 14 included the statement: “The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.”

A final decision on the above proposed revision would be made during the General Assembly of WMA in October 16-19, 2013 in Brazil.

compensation needs legal bases. Because tort-law or civil law grants people the right to be compensated on the bases of negligence liability of the person who is responsible for the harm. So granting “no-fault” compensation is difficult without legal bases, even if ethical principles require it.

Kloiber It was not that difficult, we have already included this request in the 2008 revision. The question is – do we have to get a little bit stricter on that? We believe it is necessary that the research subjects are protected against any adverse effect of the study. Some countries have compensation funds for patients. Some countries use insurance systems. The nations have to find out how that should be done. What we want is certainly that any researcher, any physician, is aware that there has to be some mechanism of a proper compensation if damages occur caused by the research.

Interviewer We understand the ethical principle that a person who worked for a social benefit, taking the risk of participating in an experimentation, should be compensated for an injury that he/she sustained even if the injury resulted without the fault of the other person. This idea was written in the report in 1982 of the U.S. President’s commission¹⁵. However even now, the U.S. still does not have a system of providing “no-fault” compensation for research-related injury.

In Japan, there is a discrepancy between clinical

trial conducted by pharmaceutical companies under the pharmaceutical affairs law, and the investigator-initiated clinical research which is under the guidelines. In the cases of clinical trials conducted by pharmaceutical companies in Japan, the amount of compensation provided for research-related injuries are higher compared to trials in other countries. On the other hand, in investigator-initiated trials, the clinical research guidelines require only that experimental trial of drug or device to prepare for compensation, but for other type of research (e.g., interventional, but not using drugs or devices) it is allowed only to say that researcher has to explain to the patients whether there is or not the compensation.

Kloiber Our approach is different. We say there has to be a compensation, not you can explain whether there is or there isn’t.

Interviewer This seems to be an idea coming from Europe because some of the European countries have laws to provide no-fault compensation for research-related injuries, or not only research-related but also medical-related injuries.

Kloiber Yes.

Interviewer But in U.S. the situation is different.

Kloiber Yes, I know. It’s different because there is no legal regulation on that.

Interviewer How is the debate on this point? I

mean the debate with the U.S. delegates.

Kloiber No, I see the American Medical Association is with us. There has to be a mechanism for compensation. That is part of the Declaration of Helsinki already, and they fully subscribe to that.

8. FDA and AMA, ICH-GCP and Declaration of Helsinki

Interviewer One more interesting issue was that FDA changed their policy to include Declaration of Helsinki in their regulation for the clinical trials conducted outside U.S.. They changed to ICH-GCP. That may be the reason why they can agree very easily. This is very cynically saying.

Kloiber No, that's not cynical. The one thing is the FDA is a government authority. If they think they can go to lower ethical standards, that's their decision. The AMA has not done so. The AMA upholds high ethical standards. And that is something I would like to stress here. It is the government which has lowered the standards, not the AMA. Very important.

Interviewer So you think that even if the FDA exclude the Declaration of Helsinki, it is no problem if AMA does not do it. The Declaration says that "No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration."

Kloiber No, they have not excluded it. They have only said that they are not demanding it from the studies from outside. We still ask all physicians in this world to obey the Declaration of Helsinki. And we also expect that, for instance, publishers, editors ask for compliance with the Declaration of Helsinki before results are accepted for publication. And this would include also the question whether there has been a system for compensation

– and not just telling people you will not get compensation. It will mean there has to be a system for compensation. If there is no compensation mechanism, the study has not followed the Declaration of Helsinki and we demand from editors not to accept such studies for publication.

Interviewer So your idea is that the Declaration of Helsinki has such power.

Kloiber Well, many journals ask the researchers to show that they have followed the Declaration of Helsinki. Whether they will and can test for each and any detail, I doubt. They will have to trust the investigator to a large extent.

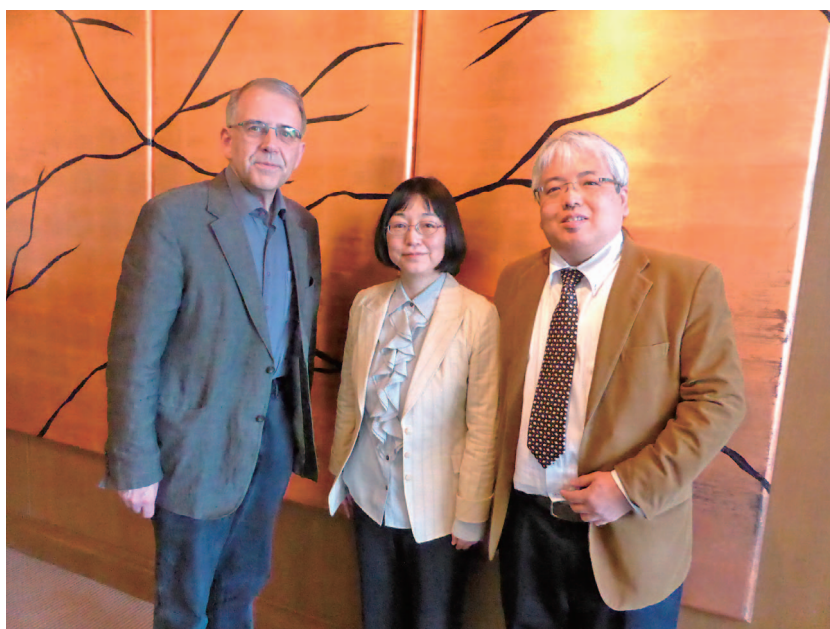
9. Biobanks and broad consent

Interviewer So another topic, in this Tokyo meeting, a new upcoming issue is biobanks.

Kloiber Well, biobanks are not really a new issue. We have been discussing this with the Government of Iceland in the end of the '90s when they started their project with DeCode Genetics. And we have discussed it with governments in Estonia and in Sweden. We have seen similar Biobanks being installed in other countries.

But concerning the rules of the Declaration of Helsinki, we also anticipate experiments being done in simulation, without any physical material or persons; just with data. Therefore, already the 2000 revision of the Declaration of Helsinki covered not only experiments in real persons but all research with identifiable samples and/or data.

The strict application of the Declaration of Helsinki in the 2000 version limited further use of specimens in biobanks because you cannot give informed consent to experiments which you do not know. One solution that is currently being discussed may be the broad consent. I'm not sure whether the World Medical Association will say this is enough. We have heard yesterday from the



After the interview, from the left - Dr. Kloiber, Kurihara, Dr. Saio.

researchers that they say broad consent may be a part of it but it will not be enough to protect people. So there must be broad consent and there must also be some governance structure in order to protect the individuals. And I think that is a very, very tricky question. Currently, we have a rule that to me is very realistic, requiring consent by an ethics committee when individual consent cannot be achieved.

Interviewer But many of the U.S. people seem to regard that if the researcher provide enough explanation about what is the broad consent, and if the subject accepts it, it is enough. We translated Robert Amdur's "IRB Handbook"¹⁶⁾, which is very much well used in the U.S.. The author described such kind of idea in a persuasive way.

Kloiber Maybe. Maybe not. I think people cannot imagine what can come out from this data or specimen experiments. The quoted suggestion seems to be a very simplistic view and in my country this probably would not be enough. A broad

consent in the end means rubber stamping everything, and this is not an informed consent. This is worth nothing. In the end, such procedure will seriously damage the image of research.

Interviewer Is there any background, some kind of ethical or legal background on that in your country?

Kloiber Well, there have been court decisions about informed consent for medical treatment. And the decisions have always stressed that an informed consent has to be very specific, it has to be direct to the point, and there cannot be any blanket informed consent. So you cannot go to a patient and say, we operate you tomorrow, and then there maybe the danger that the anesthesia doesn't work, that your heart stops and that you may die. This is not enough. They have to be very precise and they have to be clear to the point. And the same is true for research.

Interviewer This kind of explanation would be necessary for some surgery or something or medi-

cal care. But in case of providing human samples, is it the same?

Kloiber Well, if there is a potential danger falling back to the participant, yes. You may, for instance, learn about a disease you have, that cannot be treated. You may end up in a disease group that is stigmatized or you may receive knowledge that makes your future insurance more expensive or even impossible. The future research may entail ethical or commercial aspects you don't agree with. A blanket consent cannot cover the unforeseeable and therefore does not provide protection to the individual giving that consent.

Interviewer It's a very important point. I (Kurihara) once wrote an academic article with my colleagues to propose Human Research Subject Protection Act. In this proposal, we included "broad consent" with the requirement that the summary of the categories of possible future research should be described. There would be one option to explain that the researcher should declare that future research would be in the range of socially, ethically acceptable one. This kind of declaration would avoid the situation where the sample is used for unethical research or activity, such as research on human cloning. Another option, which is included in the Japanese clinical research guideline, is a statement saying that future ethics committee will discuss about each future research. This is one of

the conditions to allow broad consent.

Kloiber Currently, it is for secondary use of samples or data whether they are in single repositories or biobanks or medical data banks. The broad consent is not an issue for the Declaration of Helsinki because it has only the informed consent and it does not accept the broad consent currently. And then maybe that if we go in dealing with biobanks separately apart from the Declaration of Helsinki.

Interviewer Declaration of Helsinki doesn't allow broad consent but since the 2008 revision it already allows research without informed consent when it is not realistic or impossible to obtain such consent. You mean that if the ethics committee authorizes such research after considering minimal risk or significant importance of the research and other things, such exceptional case is acceptable, although broad consent is not acceptable?

Kloiber Yes, the difference to the broad consent is the decision by ethics committee, which will be able to weigh risks and benefits. Such a consideration is excluded by a solitary broad consent.

Interviewer Okay. In Japanese guidelines, broad consent is allowed on condition that the expected subject is explained that the future individual research is to be discussed by future ethics committee and allowed only when the committee gives authorization, so I think our guidelines are

Box 4 Provision concerning "biobank", in the proposed revision of the Declaration of Helsinki

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must normally seek consent for the-its collection, analysis, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable ~~impractical~~ to obtain for such research ~~or would pose a threat to the validity of the research~~. In such situations the research may be done only after consideration and approval of a research ethics committee.

Comment by WMA: Old paragraph 25.

Excerpt of the proposed revision shown in the version released for public consultation to revise the 2008 version. Paragraph 25 of the 2008 version has become Paragraph 32. A final decision on this proposed revision would be made during the General Assembly of WMA in October 16-19, 2013 in Brazil.

compatible with the principle of the Declaration. Then how about to say biobank is not a research project but biobank itself is project, including many kinds of research projects?

Kloiber Exactly. That may be the case. Our solution is if you cannot ask the persons themselves whether you can use their specimen for an unforeseen secondary use and an informed consent is impossible or impractical, then it should be done with the permission of an ethics committee. Listening to our conference, I think we will find a solution which maybe a combination of broad consent plus a governance structure, like ethics committees, in order to put in safeguards. But just broad consent doesn't seem to be acceptable.

10. Issues of marginal or out of the scope of the Declaration of Helsinki:

iPS cells; disease kidney/uterus transplantation; neuro-ethics; dual use

iPS cell

Interviewer You are very much experienced and also has deep insight for ethical analysis of the difficult issues so we would like to ask you several kinds of ethical questions on the issues discussed in Japan.

First of all, we want to ask you about iPS cells issue. At the press conference, some media person asked you a question about iPS cells issue, although it was not discussed at the meeting. I think it is not necessary to describe specifically about iPS cells in the Declaration of Helsinki, but some people in Japan may think that including iPS cells issue into Declaration of Helsinki is a good idea because a very peculiar situation in Japan is that there is no comprehensive law for human research, but very recently laws to regulate regenerative medicine

have been developed, especially focusing iPS cells.

Kloiber The iPS cells raise the question on whether the reprogrammed cells can be seen as embryos themselves, and if that is the case then they would have the same problem as any embryonic stem cell research. As in the start, iPS cells are somatic cells and no embryo has to be sacrificed to win them and most people will find them more acceptable than embryonic stem cells. Concerning the Declaration of Helsinki and the research on that, I don't think that there has to be a specific edition to that. They will fall under the Declaration of Helsinki like any other experiment.

Interviewer Many people may think that iPS cells can be replaced with embryonic stem cells, destroying embryo. But one very serious ethical problem of iPS cells is that if it is possible to create embryo from iPS cells, it may cause human cloning to become very easy. I think this kind of ethical debate is not in the Declaration of Helsinki but in some other documents, such as, European Council, UNESCO.

Kloiber Yes, but World Medical Association also has spoken out against reproductive cloning. But this is a specific research matter. And regardless whether you are against or for cloning, if you produce a new embryo then the question of human dignity applies to that embryo as well.

Diseased kidney transplantation

Interviewer In Japan, there is a doctor who conducted very peculiar kidney transplantation surgery: from a patient who is to undergo surgery to remove kidney because of kidney disease to another patient who wants to be a recipient of kidney transplantation. We call this "diseased kidney transplantation". This very outstanding doctor, a practitioner rather than a researcher conducted this surgery in several patients, but the academic society did not like that, so there were several

Box 5 Provision concerning “Unproven Interventions”, in the proposed revision of the Declaration of Helsinki

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

Comment by WMA: Old paragraph 35.

Intended to clarify the intent of this paragraph. Strengthens requirement to make the intervention the object of subsequent research.

Excerpt of the proposed revision shown in the version released for public consultation to revise the 2008 version. Paragraph 35 of the 2008 version has become Paragraph 37. A final decision on this proposed revision would be made during the General Assembly of WMA in October 16-19, 2013 in Brazil.

debates and the society said that it should be evaluated in the academic society, and at this time such kind of surgical procedure should be conducted as “research”, and not practice. I think the Declaration of Helsinki also say that such experimental practice can be done by a physician but it should be made subject of research program.

Kloiber Yes, that's right. As for the “disease kidney transplantation”, in the beginning it sounds odd and very difficult to accept. However, you have to ask questions. For instance, can you exclude that you transplant the cancer into the next person. Or is it a cancer that is very slowly growing so that it does not affect the lifetime of that patient. We, for instance, in my country we have a program which is called “old for old”. Usually only organs of younger people are being transplanted – under 50, under 55. And now we have a program where we transplant organs from people aged 60+ to people of age 60+. So if you can exclude any additional risk to that person, ethically that may be possible. I would have to look into that. If you endanger that patient, it comes under the rule “do no harm” and that is not acceptable.

Uterus transplantation

Interviewer It's a very interesting idea. There is also another issue. There are some people with gender identity disorder who don't want to have uterus for bearing children. On the other hand, there are some women who have some disorder in their uterus but wish to have a child. Recently, there is an emerging experimentation of uterus transplantation. There are some cases wherein the uterus is transplanted from mother to daughter. How do you think about transplantation of uterus from a person who can agree to removal of that organ to another who want to receive it, for example, a person with gender identity disorder or a mother who already has child and don't to wish to have more.

Kloiber We have not made policy on that, and I think that is something that we first would have to look into. And the question in the end may be: is this medically indicated or not. And it would be medically indicated if you consider the desire, a medical need of that person.

Interviewer The woman who want to have a child. Is it a medical issue or quality of life issue?

Kloiber Yes. Children are a natural event, and I think that is what we should deal with in medicine

as a natural event, not as an artificial and not as a “social accessoire”. It is our role to overcome medical problems, the problems of illness and disease. And as far as that is being done, I think there is a medical justification for it. There is no medical justification for doing things which go beyond that.

Interviewer One problem is that sometimes this comes to be undue influence (mother, sister, or relatives may feel pressure to donate utero). And a better way is donation from the brain-dead case. I think European people tend to think organ donation should be from dead people, not from living people.

Kloiber There is a lot of organ donation from living people as well – kidney, liver parts. I don’t think there is a very easy judgment. With a living donation, there is always a problem of exploitation behind that. People are being forced to give something. There may be family pressure, individual pressure. There may be payments, if recipient and donor know each other. But as long as there is free will behind that – including the necessary information about the risks involved, it’s ethically okay.

Neuro-ethics

Interviewer And another issue is how about neuro-ethics.

Kloiber Yes, we have discussed neural enhancement at an earlier conference in Rotterdam. In the end, we found that this is a general topic for the Declaration of Helsinki but not a specific one which we want to address. So most likely the workgroup will recommend not to address it separately.

Dual use

Interviewer So on another topic different from human research, we would like to ask your opinion about “dual use” issue. This means that medical research outcome may be used for development of weapons.

Kloiber We have clear statements on that. Not in the Declaration of Helsinki but in other declarations. Our answer is “no”. No physician should be involved in the development of weapons, and that applies also to any research physicians may be involved in. It is something different to look into research on the medical treatment for the effects of weapons. That has to be done because we have to treat patients which have been harmed by weapons. And I agree this is sometimes very tricky because, you cannot 100 percent separate the use of that information from the development of new weapons. Physicians should not get involved in the development of weapons.

11. Laws and ethical principles

Interviewer Another thing which was very much discussed in the Tokyo meeting was the relationship between law and ethics, which varies in each country. The Declaration says that each country’s legal regulation should not be broken down by the Declaration (“No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.”). In some of the European or international documents, the European Council, UNESCO, there’s a description that every country should have some law that protects human subjects.

Kloiber This is being done very differently in different countries. Let me give you an example. Austria and Germany are very similar countries culturally, but their approaches to the question are fundamentally different: In Germany, every insult to the body of another person is a criminal offense. Even an invasive medical treatment in the beginning is an offense. You will not be punished for this if the patient is informed and the patient wants it and if the practitioner is licensed to perform medicine.

Austria starts from the opposite direction, by that any medical act by the doctor is *per se* not a criminal offense. Very different approaches. Now in Germany, if you do something wrong in treating a patient in a trial because you do not give the informed consent, you do not work according to the professional rules, you are in most cases producing a criminal act automatically. So you don't need an extra rule for that. It is already in the law. But I agree, there should be laws protecting people in every country. But then it comes to the details and to the different principles. The placebo issue is a good example. If the law will go into details, the risk of mistakes increases. There's room for ethical rules that do not necessarily have to be followed up by state attorneys, and courts, and criminal punishment but by ethical supervision.

Interviewer In Japan, there are various opinions on that. Someone say that it is necessary to develop laws to protect human subjects. But on the other hand, there are scholars who says "soft law" (guidelines not without legal bases; ethical principle, professional code, etc.) is suitable to regulate research. These people say that Japanese researchers are very much obedient to guidelines so "legal" regulation is not necessary. It is correct to say that Japanese researchers are very much obedient to guidelines; however at the same time, there are several researchers who act against rules ^{*3}.

Kloiber One thing is that you can sanction ethical deviations, usually much easier than a criminal procedure. For a criminal case, you need extremely hard evidence. I think for most of the

instances, the soft law approach, the self-regulatory approach, is much more effective than the other ones. But as I said there are things where you have to say "Stop - this is criminal". But again this is very different from country to country; for different cultural, legal, and technical reasons.

12. Impression of Japan

Interviewer So through these discussions, I would like to ask you how is your impression of Japanese researchers, Japanese health professional community. Could you please advise or comment based on your experience of this time visiting Tokyo for this meeting.

Kloiber Oh, I am biased because I have been working with a lot of Japanese colleagues in the past. Japan is one of the leading research nations in this world. We all know that the Japanese medicine is the highest developed. You are playing in research in healthcare in the top league. And if you look in the outcome, what you produce for your people, and I think you have the best results. Everybody gets healthcare. You have an unsurmounted longevity. This is a fantastic result. I think you can be proud of that. And you get it for a very low price. So you just look to the numbers and the numbers speak for themselves.

Interviewer We really appreciate your saying such generous comments. However, we discussed with some of the delegates and they say that in Japan there are some problems, for example, in the psychiatric area, poly-pharmacy is a serious prob-

^{*3} During the Conference, Kurihara discussed with some participants who said that clinical trial regulations in the U.S. and Japan are the same, and corrected this idea saying that Japanese law on clinical trial covers only those aiming at new drug application (NDA) and introduced 3 prominent cases that violated the no-legally-bound guidelines: Announcement of fabricated research results on iPS cell clinical research at the academic meeting; extraction and use of human samples for research without informed consent; retractions of publications based on fabricated results of multicenter clinical trials of the antihypertensive drug, valsartan. (There are many other cases that violate the guidelines.)

lem. He knows it very well. And when we visited some psychiatrists in Taiwan, we found that they know such problem in Japan very well. Many psychiatrists in the world know very well about the Japanese poly-pharmacy. They also know well about long-term hospitalization in Japan. One of our interviewees said that this is because Japan is a rich country. This is problem of the rich.

Kloiber Sometimes we have problems because we are rich, and that's true. Sometimes we have problems because the ways how things are being financed determine the use. And there are problems in any healthcare system of the world, and I am sure in Japan as well. However, but if you see this in the international comparison, your problems are luxury problems.

Interviewer Yes. But we would like to say that it's quasi-rich, because you know that the Japanese government has many debts.

Kloiber Yes, Japan has a very high debt rate, but your debt is internally. The debt you have is money that the Japanese government has bought from the Japanese people. Now that is something different than in my country or the United States where the money has been bought from other countries. So if you look to the net balance in who Japan owns, you own your country. Our country may be owned by somebody else. So that's a big difference. Although the debt of the Japanese state is much higher, I think you can sleep better with that than the Americans or the Germans.

13. Important issues relating to WMA's activities

Interviewer So you are working as secretary-general of WMA, not only working for Declaration of Helsinki. What is the very important topic in WMA, aside from the Declaration of Helsinki?

Kloiber Well, the Declaration of Helsinki is of

course a very important one. But we are dealing with different questions right now. And one of the things we are very much working on and very much interested is the question of social determinants of health. We traditionally look for the pathophysiological causes of diseases, by that we are often not coming to the real causes which lie in the causes of the causes, the ways how we are being born, how we live, how we work and how we die.

Of course we are not social engineers as physicians but I think we have an obligation to tell society, if there are underlying mechanisms. And if you look to the big non-communicable diseases in this world, which are related to tobacco, wrong diet, working conditions, we think it's very important that we tell society, tell lawmakers that there are underlying conditions which they have to change, which we have to change, in order to make a difference.

The human resources for health are another big problem in this world because we are pulling human resources from poor countries to rich countries. And thirdly, we are very much concerned about human rights violations in healthcare. We see that there are more attacks on health personnel, direct or indirect. We think that human rights also of the health professionals and the patients they are caring for are now violated more often than we have seen in the past. These three issues are topics we are especially intensively dealing with currently.

Interviewer It is very much an important task. We appreciate very much your answering so many questions and you have explained in significant details the important mission of WMA to promote ethical conduct of research involving humans for better health in the world.

It is fascinating that you answered very clearly our questions and described fundamental principles and conflicting issues surrounding it. We believe this interview will enlighten many Japanese people

who are not so familiar with background philosophy of WMA and will support them to consider how to manage actual problems according to these excel-

lent norms created by wisdom of the world specialists.

Additional questions in August 2013

Interviewer We came across your article published in the World Medical Journal (Vol. 59, No. 1, page 1). In this article, you wrote that WMA submitted objections to the proposed revision of the EU Clinical Trial Directive. Especially, it is very important to say that there is no explicit description about ethics committee review in that proposed revision. We have thought about that proposal also, and we believe that the intention of this proposal is to have “one ethics review in one multinational clinical trial in EU”. In the proposed revision of this EU Directive, there is no explicit discussion about this kind of “joint-review” issue (one ethics review in one multi-center/multinational clinical trial). So could you please provide us with your opinion on this point?

Kloiber We were disappointed that the requirement of seeking the approval of an ethics committee before the beginning of a clinical trial was no longer in the draft of the proposed regulation. In the meantime, the parliament inserted as well a request for hearing on ethics committee as well as several references to the Declaration of Helsinki into the proposal. However, we would like to read that and ethics committee has to approve – not only read – the protocol. Furthermore, we are worried that a sponsor can shop around, looking for the country with the weakest ethical standards. We don't think that this is acceptable. Another problem is the extreme short time frames for the work the applications have to be processed. They are simply

unrealistic – and with the effect that a non-answer within the short return times equals a positive decision, this may be even dangerous.

Interviewer We also would like to ask for your comment concerning a serious issue in Japan. Recently in Japan, there have been a number of issues involving scientific misconducts resulting in retractions of academic research articles involving fabricated data. One of the most serious cases is the data fabrication scandal surrounding Novartis' antihypertensive drug valsartan.

The results of the post-marketing multi-center clinical trials (Prospective randomized open blinded end-point (PROBE) design) conducted by research groups in five different universities concluded that this drug seemed to include fabricated data, and some of the publications were retracted. This drug was developed as an antihypertensive, but the results of these studies showed effectiveness in preventing cardiovascular events. At least at this moment, six articles written by one of the research groups (Kyoto Heart Study) were retracted, while the other articles are under scrutiny. As for this Kyoto Heart Study, the university involved in the trial conducted its own investigation, and the results of their investigation suggested a strong possibility that data fabrication may have been committed.

It was also found that a statistician of Novartis was engaged in all these five multi-center clinical trials in question. It was alleged that Novartis had provided substantial monetary donation to the institutes of these five research groups, but not directly to the research, so there was no disclosure of conflict of interest in the published articles.

Novartis has generated huge financial profit by making use of these articles containing fabricated results.

We cannot ask for your comment on this specific matter but we would like to ask you, whether the prevention or prohibition of scientific misconduct is not the scope of the Declaration of Helsinki? The recent revision includes issues of publication ethics and conflict of interests, not only conventional items such as protecting human subjects. This kind of scientific misconduct is not a simple clinical research issue. However, it seems markedly unethical to generate fabricated data based on research involving human subjects. Additionally, it is also serious that the results from clinical research directly influence clinical practice. So we would like to ask your opinion on this point.

Kloiber I cannot comment on those specific cases, as I don't know them. But it is always good to have studies and results from differently financed source. Bringing the opposite interests together is probably the best safeguard to bias and single-sidedness. However, criminal fraud is always difficult to detect. But I hope those cases are the exception.

Interviewer Thank you for your comment. We also hope that these cases are the exception. Because scientific misconduct causes harm to patients, and in many cases, the conduct and publication of clinical trial is an international activity. Therefore, we hope to be able to discuss more about these issues internationally, considering how we should develop international normative document.

We greatly appreciate all your contribution, and hope that next year's 50th anniversary celebration of the Declaration of Helsinki will be successful. Also, we feel very honoured that Japan Medical Association can host the conference just before the final stage of the revision which will be such a

memorial event in 2014.

REFERENCES

- 1) Levine RJ, Tsutani K, Sakanoue M, Mitsuishi T, Kawai S, Sato K, Kakee N. Round table discussion: Ethics in clinical trial in the days of globalization of drug development. *Rinsho Hyoka (Clin Eval)*. 1999 ; 26(3) : 341-80. Japanese.
- 2) Sakanoue M. Recent movement at the World Medical Association on revision of the Helsinki Declaration. *Rinsho Hyoka (Clin Eval)*. 1999 ; 26(3) : 395-408. Japanese.
- 3) Levine RJ, Lurie P, Lagakos SW, Interviewed by Kurihara C. Interview with Robert J. Levine, Peter Lurie and Stephan W Lagakos: Discussion on the Declaration of Helsinki and its background. *Rinsho Hyoka (Clin Eval)*. 2001 ; 28(3) : 409-22. Japanese. Available form : http://homepage3.nifty.com/cont/28-3/contents_e.html
- 4) Human D. Interviewed by Kurihara C, Mitsuishi T. Interview with Delon Human, Secretary General of the World Medical Association: Discussion on the 2000 revision to the Declaration of Helsinki and onwards. *Rinsho Hyoka (Clin Eval)*. 2002 ; 29 (2·3) : 307-13. Japanese.
- 5) Tsuboi E. Interviewed by Kurihara C. The 2000 revision of the Declaration of Helsinki and its implications in medical ethics: Interview with the WMA Immediate Past President, Eitaka Tsuboi. *Rinsho Hyoka (Clin Eval)*. 2002 ; 30(1) : 99-107. Japanese.
- 6) Stolk P, et al. Meta-analysis of placebo rates in major depressive disorder trials. *Ann Pharmacother*. 2003 ; 37(12) : 1891-9.
- 7) Kirsch I, et al. Initial severity and antidepressant benefits: A meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med*. 2008 ; 5(2) : e45.
- 8) Fournier JC, et al. Antidepressant drug effects and depression severity: A patient-level meta-analysis. *JAMA*. 2010 ; 303(1) : 47-53.
- 9) Aaron, et al. What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? *Schizophrenia Bulletin*.

- 2010 ; 36 (3) : 504-9.
- 10) Kuroyanagi T, Ishii M. Declaration of Helsinki Expert Conference on the Ethics of Placebo Control in Clinical Trials — Comments on the “reasonable availability” approach. *JMAJ*. 2011 ; 54 (6) : 346-50. Available from : http://www.med.or.jp/english/journal/pdf/2011_06/346_350.pdf
 - 11) Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: Ethical and scientific issues. *Ann Intern Med*. 2000 ; 133 (6) : 455-63.
 - 12) Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 2: Practical issues and specific cases. *Ann Intern Med*. 2000 ; 133 (6) : 464-70.
 - 13) Kurihara C, Fukushima Y. North-South issue and ethics of international clinical research: Focus of the discussion with University of the Philippines -Manila Research Review Committee Members. *Radiological Sciences*. 2011 ; 54 (1) : 21-33. Available from : <http://www.nirs.go.jp/publication/rs-sci/pdf/201101.pdf>
 - 14) Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research Involving Human Subjects. 2002.
 - 15) President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Compensating for research injuries: The ethical and legal implications of programs to redress injured subjects. 1982.
 - 16) Amdur RJ, et al. *The Institutional Review Board Member Handbook The 2nd ed.* Jones & Bartlett Pub. 2006.

* * *