



**Presidential Commission
*for the Study of Bioethical Issues***

**TRANSCRIPT
Transnational Standards**

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DR. GUTMANN:

Thank you all very much. As you know, the subject of our present investigation is human subjects research, and specifically, the protection of human subjects, both national and international, with the particular focus on the international dimension. And this panel is brought together to discuss transnational standards of human subjects research and we're going to begin with John Williams.

John Williams is an Adjunct Professor in the Department of Medicine at the University of Ottawa, and an Adjunct Research Professor in the Department of Philosophy at Carleton University, Ottawa. From 2003 to 2006, he was Director of Ethics for the World Medical Association, and during 2007 to 2008, he coordinated the revision of the WMA's Declaration of Helsinki. He previously served for 12 years as the Director of Ethics for the Canadian Medical Association. He is Chair of the Canadian Institutes of Health Research Stem Cell Oversight Committee; and a member of UNESCO Advisory Expert Committee for the Teaching of Ethics; and the Advisory Board of the Training and Resources in Research Ethics Evaluation for Africa Project, welcome John.

DR. WILLIAMS:

Thank you very much for the invitation to speak here. I'm going to move very quickly because we have 10 minutes, I see the clock is ticking down now, and there's a lot of material to cover, as I'm sure you're aware. I'm going to pick up on a number of the issues that were dealt with yesterday, and hopefully add a little bit to some of the discussion.

I think it's customary—can you hear me? – It's customary for presentations such as this to declare any potential conflicts of interest, and so I must say that I was Director, I'll be speaking about the World Medical Association, and I was an employee of there, and I have been a consultant for the WMA since then.

The presentation that I am going to give, I'm going to try to cover all this material, but if I don't in the 10 minutes then hopefully we will have a chance in the discussion afterwards to get through to some of this. So, I have to say something about the World Medical Association, for those of you who aren't familiar with it, to talk more particularly about the Declaration of Helsinki. I want to talk about an issue that came up a lot yesterday, that is the relationship of ethics guidelines versus compliance regulations; and in particular with reference to ethics and GCP, and a little bit

about the relationship of the Declaration of Helsinki, GCP, and the FDA, and then my conclusions.

The WMA is the International Federation of National Medical Associations, it was established after World War II, mainly in reaction to atrocities involving physicians especially, but not exclusively, in Nazi Germany. It is the global representative body for Physicians. Its membership includes 97 national medical associations. Now, WHO, of course, has about 200 members, and some of the other health professional associations have larger membership, but not all national—not all nations have functioning national medical associations, and there is a big gap with Muslim countries who, up till now, have not shown much interest in joining with their associates in other countries. They work very closely with other health professional associations at the international level, and does a lot of work—they do a lot of work together, especially with the WHO in advancing common causes, and things like patient safety, and other patient advocacy types of activities.

The legitimacy of the WMA comes up especially around the relationship of the Declaration of Helsinki and the FDA regulations, and it doesn't have any legal authority, it's a non-governmental association—and international non-governmental association; and so, it's authority is moral, which is a good thing for this gathering, I think. So, what are the sources of the moral association? Well, history, for one; pioneering guidelines development, it's only been around for 60 years but in that time it has established a number of policies that are quite significant on the international level, like the Declaration of Helsinki, like Declaration of Tokyo regarding torture and a number others, quite a large number of others. It does call upon the experience of its members from all over the world on health issues, and so it's a very good forum for developing international policies. It has extensive consultation and consensus building experience, and I think there's some contrast to an organization like ICH on that particular point. And then, the quality of its policies and activities, which of course can only be judged by others.

Okay, the Declaration of Helsinki, I think most know that it was first developed by the WMA in 1964, after a very long gestation period. Really, work started in 1949, there was a temporary set of guidelines developed in the mid 1950s, but it took until 1964 for the first definitive version to be adopted. There were significant additions in 1975, especially the requirement that research protocols be approved by a research ethics committee. Minor

amendments in '83, '89 and '96 and major revision and reorganization in the year 2000. I was involved in that.

There were a couple of outstanding issues at that time and they were attempted to be dealt with by notes of clarification, that was not entirely successful, so the latest revision was begun in 2007 and you have the current version now in 2008.

To talk a little bit about the influence, the some of this has been referred to yesterday. The ICH-GCP, require adherence to principles that have their origin in DoH. Very strange wording there because those principles, as many people pointed out, really didn't originate in the Declaration of Helsinki; they were stated there, but clearly they come from earlier sources.

And other documents have followed the DoH. The FDA of course has recently eliminated reference to Declaration of Helsinki. We'll talk about that later. In terms of its influence, there have been a couple of studies done in Africa as to what documents are used by research ethics committees there and Declaration of Helsinki, is named first by a long shot in these particular surveys. And the Standing Committee of European Doctors issued a resolution calling upon calling for compliance with the Declaration of Helsinki, and there are many other documents that could be cited and examples that could be cited about the influence. So it really is often referred to as the grandfather or the premiere document in research ethics.

Now you have to remember it is a short document, you know, 3 pages, compared to CIOMS, which is close to 100 pages and close to-- compared to our Canadian new version of the tri council statement, which is 200 pages. So it clearly is a summary of research ethics.

Regulation first as guidelines. Well, very simply the way I see it, is regulations and laws--what must be done under pain of penalty. Ethics--what should be done, even if it is not required. I did speak to a International Association of Compliance Professionals--these are mainly employees of pharmaceutical companies and also employees or people who work for controlling companies like KPMG, this is a large business of helping the companies — sponsors of research — really to comply with the multitude of requirements and regulations and laws, all over the world as clinical trials really expand in a global manner, as we heard yesterday.

And I think they are quite aware that it's not enough just to do

the minimum. That there are advantages to doing more than the minimum; to be ethical rather than just compliant. Values, of course, are important, but reputation; and the reputation of many of these companies have suffered a great deal because of breaches of not only ethics, but laws, as well.

Okay. So, some of the international ethics guidelines... the WHO Operational Guidelines for Ethics Committees, that's currently under review and there should be a new edition out fairly soon. CIOMS you will hear about and Declaration of Helsinki. The principle did I miss something? The compliance guidelines, ICH. Now, it is called guideline, but really it's incorporated into the national laws and regulations, so it really becomes much more than guideline; it becomes a regulation – a set of regulations. And in Europe, too, there are international – and I'm talking about international documents here.

Now let me just move on to relationship of ethics--ethics and clinical practice and I want to in particular in the time that is left, which isn't very much, to compare and contrast the DoH and ICH-GCP, and there are a lot of similarities and that is very good. But the difference is that there are important omissions in the GCP. One reason for that, it's very old. It goes back to 1996, [??] and some of the things that we find in documents such as the Declaration of Helsinki, which are not in GCP, are: research on human tissues and data, including important matters of privacy and confidentiality there; consideration for the environment; access to benefits, and that's a big, big issue that you'll want to address, I think; role of families and communities; clinical trial registration, which is dealt with in other documents; who should seek and obtain consent; the ascent of incompetent research subjects; publication of results, especially negative results; enrolling patients as research subjects, the possible conflict of interest there, of health professionals; and therapeutic innovations and how that relates to research. So, there is a lot of things that—reliance on ICH-GCP really doesn't get far enough in this day and age.

We can talk more about the FDA and about placebos, about access to benefits; and so, just to move to the conclusion, I think it's important to note that the congruence of some issues in compliance and research ethics doesn't--shouldn't mask the different interests that are at play. And clearly there are very different interests between industry and health—or protection of research subjects, and that should be acknowledged and be up front.

I could save this for later, the one take home point, but I'll say it now. Interest of research subjects, whether individual or a community, should prevail over those of researchers, research institutions, commercial enterprises, sponsors and funders; and I think all stakeholders should aim for the highest ethical standards. Thank you. DR GUTMANN: Excellent. Thank you very much and you are welcome to repeat it and elaborate on it later. So thank you, Dr. Williams. Our next speaker is Dr. Johannes van Delden, who is the President of the Council for International Organizations of Medical Sciences. We've heard a lot about CIOMS. He--and we will hear more now from somebody who has been leading this very important effort. He is also full professor of medical ethics at the Utrecht University Medical Center where he and colleagues focus on research ethics, moral problems at the end of life, and moral problems in the care for the elderly.

Until recently he has also worked as a nursing home physician in the Netherlands. Dr. van Delden was one of the principal researchers for the Ramalink--have I got that right?--Committee, which completed a major study of medical decisions at the end of life, and also served as the Secretary of the International Association of Bioethics. Welcome, we're delighted to have you here.

DR. VAN DELDEN:

Thank you. Okay. Of course I would like to thank you for the invitation to CIOMS and to be able to say a few words here in 10 minutes. And for a non-native speaker, that is a challenge.

Yes, well I'm basically doing, of course, something of the same nature as the previous speaker. Explaining--how do I go forward. Yeah. Explaining what CIOMS is and then address the issue of, which I thought was the key issue here, whether international guidelines adequately guard the health and well-being of participants in scientific studies. I'll say a bit about the case in Guatemala, of course I know it's not my job to go into that case here extensively.

So what is CIOMS? CIOMS is an organization of organizations. So it's an NGO, an international nongovernmental non-profit organization, it's a forum to consider and prepare advice on contentious issues, such as in research ethics and the safety of pharmaceuticals, and does so for WHO; public health authorities; academia; pharmaceutical industries and others. It was established in 1949, the same year, by WHO and UNESCO,

together. But since the offices are located in Geneva, actually in the building of the WHO now, one is tempted to say that the bond with WHO is somewhat stronger than with UNESCO, although of course Dafna and I meet quite often all over the globe.

Who is CIOMS? At present we have 48 international member organizations and again these are – I mean, you can see the number 48 and think that is not too much, but in reality of course there are thousands of people who are members of these organizations so it's – there is wide diversity of groups and quite a number of people who in one way are related to CIOMS. Our member organizations represent biomedical disciplines; you might for instance see the World Organization of Epidemiology or the Global Organization for Internal Medicine.

We also have national members and they mainly represent National Academy of Sciences and maybe also medical research councils. There's an executive committee consisting of 10 member organizations, a representative of those and I'm its President at this moment.

The main fields of interest are drug safety and drug development, I will not address that here, and bioethics. I was told-- that is, I was too young to notice it back then myself-- but it was said that ethics was a subject too sensitive at that time for WHO in the '70s. And that that was the reason to ask CIOMS to indicate how the Helsinki Declaration, which indeed had a major revision in 1975, could be applied particularly to developing countries. And I would like to stress here and later on that, of course, the CIOMS declaration or the CIOMS guidelines were never meant as substitute for the WMA Helsinki Declaration, but as an elaboration of that. So, there is no rivalry between those guidelines.

This process started in the '70s and ended in 1982 when the guidelines on biomedical research were published and indeed, they now contain something like 100 pages, so it's quite great. The guidelines were revised in '93 and 2002, and actually last November we decided that a new revision was necessary and this year saw the start of that process. It may take a while, it may take another three year maybe, but we intend to have the fourth version of these guidelines in the near future.

The purpose of these guidelines is to indicate how fundamental ethical principles and the Declaration of Helsinki, can be applied effectively in medical research worldwide, in different cultures,

traditions, socioeconomic circumstances, and of course, with a special attention for developing countries.

The content is different as you will have noted because of the 100 pages. It's not just guidelines, but it's guidelines plus commentaries; and what I hear is that indeed these the commentaries serve as a very valuable addition because they explain how terms are meant and what-- at least what the scope of what is being said is meant to be.

As far as we can see, these CIOMS guidelines indeed have been widely used, as well, mainly in developing countries. Now again, I should be humble here and not suggest that I am the one to judge what went wrong in Guatemala so please don't take me wrong here; but I thought by looking at that case I could also try to see whether the CIOMS guidelines would have made a difference if they would have existed.

DR. GUTMANN:

I should say, no apologies necessary, everyone should judge it.

DR. VAN DELDEN:

Okay. Well, Okay. And I use the Belmont principles as a way of structuring this. As far as I can see, and this is not meant to be an illuminative list, what went wrong, amongst other things, is that: participants were merely used as a means to further science, that no informed consent was sought, obviously that deception was there, that participants were deliberately harmed, there was no trial to have fair subject selection, I mean participants were well known available and contained and of course there was no fair share of benefit, at least not on the individual level. It is notable that some benefits were there for the institutions and for the country, but not for the individuals.

So supposing, and this is of course a mind game and not reality, but supposing the CIOMS guidelines would have been there, what would they have said? Well, they would have pointed to guidelines 4 to 7 and say, well, you need to show respect for autonomy and there are a number of pages on informed consent so that would have covered that. And of course, there are also guidelines on how to include non-autonomous persons in scientific research. So, that may have addressed those participants in Guatemala.

There is a lot of talk on the balancing of risks and benefits, which actually is a very difficult issue, but the most important contribution I think would be on justice and the CIOMS

guidelines would point to things like responsiveness to health needs; you cannot do research in a place that is not responsive to the health need of that population. There should be a reasonable availability of the drug, if it's a drug, if it's proven effective. Of course, the choice of control would have been addressed, and the equitable distribution of burdens and benefits over groups would have been a matter for discussion within this non-existing ethics research guideline--committee, if it would have existed.

So in one way, we can think, well, that's okay, if the CIOMS guidelines would have existed, they would have covered at least some of the issues and maybe pointed to what went wrong and maybe prevented that. But I'm a little bit more pessimistic than that. Because the truth is, and that is going to be my conclusion, sorry, I'll have to move two slides here. That actually was what's going on and I'm sure that the distinguished Commissioners will be very much aware of that; that indeed research ethics is a field in which discussion continues. It's not settled.

If I again use the Belmont principles, I can say that there is still a lot of discussion going on on how to improve informed consent. There is evidence, the evidence is not very widely used, I should say. There is a continuing discussion on the level of risk that is acceptable in non-therapeutic research with non-autonomous participants, children, for example; and is it just minimal, or a minor increase over minimal, or just something else.

It continues, risk benefit assessment is a difficult issue. Even the risk benefit analysis is already difficult let alone the assessment of that, and when it comes to justice, it's my impression, that a lot of these guidelines are there, but we do not really exactly know what we mean by them. For instance, I just said that the study needs to be responsive and everyone sort of felt "yes, why not?" But the truth is what exactly do we mean by that? When is something responsive? What is the condition in the group, which group by the way, that determines that now the issue is responsive to the health needs of that population? And which population is it just respondents or some wider group? We don't know.

Fair share of benefit, great, but what exactly would count as such? Can it be substituted? Does it have to be the product that was proven positive or can it be substituted by something else? By the way, that was exactly what was done in Guatemala. Some of the benefits that were provided never benefited the participants, but other groups did benefit. So there is a continuing discussion on all these issues and probably, I mean, the CIOMS guidelines would have addressed some of these issues and they

would have marked at least some questions could be raised, but I'm not sure everything would have been prevented by using these international guidelines.

Critical, right? So can we rest reassured? I don't think so. There are no absolute safeguards, there are a lot of open-ended terms with different interpretations in the guidelines, which to a certain extent is good because, of course, you need to address a wide variety of research projects. What I find, and that is an interesting point that was your major point and it's my major point, as well, actually—that there may be a tendency to emphasize interests of the community more, and to maybe question supremacy of the individual interests, I was struck by the way that you framed that, but we should discuss that maybe. The good point maybe is existence of research ethics committee in themselves. Because I really believe in reasoned deliberation and I think that is our best choice to have a mechanism here. But, we have to acknowledge, and I cite Zeke Emmanuel here, that by placing some people at risk of harm for the good of others, clinical research has the potential of exploitation, and that will remain. Thank you.

DR. GUTMANN:

Thank you very much. Excellent, Thank you. We are now moving to Dafna Feinholz. Dafna Feinholz is the Chief of the Bioethics section of the Division of Ethics of Science and Technology of the Sector for Social and Human Services at the United Nations Educational, Scientific and Cultural Organizations. That title is maybe the longest one, but before joining UNESCO she was Executive Director of the National Commission of Bioethics in Mexico, and is a member of Mexico's national research system. She was also tutor for post graduate programs of bioethics at the National University of Mexico and has wide experience as member of ethics research committees in Mexico and abroad. In 2005 Dr. Feinholz was Mexico's representative to UNESCO to the expert intergovernmental meetings to finish the universal declaration of bioethics and human rights. Welcome, Dr. Feinholz.

DR. FEINHOLZ:

Thank you. Well, thank you so much. I am joining the previous speakers in thanking you for the invitation and also for the possibility of sharing with you, which I think, as you said, I was representative of Mexico when the declaration was drafted and now I'm here in order to-- for me is a real opportunity too, because when we asked member states were discuss this instrument it was in light of possible real situations such as the one we are facing now. So it's for me, now as an official staff of

UNESCO, really a nice opportunity to be here. And so of course I decided to use this opportunity of my presentation in these 10 minutes, I'm not going to say what UNESCO is about, but more that what are the challenges that we are facing and what this document could be useful; and I chose only one of the articles, which I thought was more relevant for the discussion that we're having today.

So, I think what Guatemala is an example, but it's not the only case, not the only thing we have to think about because there are many challenges now that we have to face, which is basically how we can – how can bring the same level of protection for human research participants across borders and international close border research? And how can we do it universally? And there are many realities we have to take into account when we are trying to do this, which is – it's a fact that there is diversity of legal and ethical review system in each country. Whether by law, whether by capacity in the members who are the people who are conducting these activities, the diversity of health systems, which is also very important and linked also with resources available for research because that is also a way of how governments, many times, see research in international corporation if this is an investment, or if this is something that is important, or if this is only mean to get things into countries and why that's why possible potential conflict of interest come or potential problems of exploitation, or defining benefits when an agreement is set by different governments that are going into the enterprise.

And of course involving different levels of empowerment of participants, and in fact, we have different societies which are I mean the possibility of citizens to use their rights, it's very different, both in the health sector and in others. Of course the differences in culture and in system values, which is also very important in how people are understanding the rights and the participation in on the different ethical values involved in safeguarding the participants in research. There is also an ambiguity regarding existing loss of regulations because every state has different regulations and different right traditions, and it's also not always clear who is the relevant authority in each country to be acknowledged, to have some action in when decision has to be made regarding research. And I think transport or flow of tissue collection and genetic data or sample is one of the good examples that we can see where this ambiguity is causing problems, and definitely by a medical research in poor countries, which really need and call for greater vigilance to avoid exploitation.

I guess something that is very clear is that against all these, or in the background of all these, is one ethical principle there all the time, which is that violation to human rights, no matter who is committing that violation is of relevance for the entire community. It's not something that can be blamed or put only on the one who is doing it. So the globalization is leading to spreading the scientific and technological advances, but also creates a particular bioethical dilemma and spreads the bioethical dilemmas that are already in place because of the advancement of science and technology. Of course these global characters of contemporary science and the increasing number of research coming from different countries, it's calling for global approach of bioethics. It's really the time that regulations and perspective do not reflect only the interest or approaches of any particular region but of the global community. And that is why UNESCO was founded, to enable debate and it's really one of the unique global imperialistic forums to discuss all these complex issues.

And I think one of the best, really the most important achievement, has been the universal declaration of bioethics and human rights. That was adopted in 2005, and it is important to say that it was adopted by acclamation, which is not very common thing to do. And if we think this is about bioethics, which is such a sensitive issue, it's also I guess very important to brief comments on the process. There is a committee of independent experts who draft the first—who prepare the first drafting after a very wide concentration of at least two years with many various stakeholders and then this documents go to the intergovernmental committee experts, who are really representatives of governments who look at documents from different perspective, which is, “what does it mean in terms of political commitments?” And they endorsed it and then it goes to the general conference who endorsed it by acclamation. So I think this is important because who is who were the ones who committed themselves to this document? They were 191 governments and, of course, the U.S. Government was one of the most active in the drafting of this declaration in the intergovernmental committee.

So the countries that have submitted—that have agreed to declaration—are committed themselves to pass national legislations on bioethics, and to promote systems of review at the national level, and promote and enhance education and encourage public debate, and basically through different organizations such as national committee as you are.

The document is important to read as a whole. It's not it's very difficult as any other to use only one of the principles, and there are – but I'm not going to talk about all of them, but as you can see amongst the many principles identified many aspects related to research and other issues are already there as: consent, confidentiality, benefits, solidarity, protection of environment.

But I'm going to concentrate on article 21, which is devoted only to transnational practices. And the article, the first part reads well, in short the key message of the article is that, it calls for states to ensure compliance with the principle of the declaration regardless of the difference of geographical context and ambiguity of authority-which is of course, a challenge because that is exactly what needs to be done, but at least this is the context. And then, it says when research is undertaken or otherwise pursued in one or more states, the whole state or states funded by source in another state, should research be the object of an appropriate level of ethical review, both in the host state and in the states where the funder is located.

I think this is real important because this is pointing to the need of multiple review of research, and the idea basically is to avoid to have different ethical standards and, of course, to avoid the exploitation of poor, and ignorant, and dis-empowered populations. And there is a claim that sometimes, you know, the issue -- the fact that there are health needs that are very urgent that need to have been solved, that they could be an excuse for researchers in developed countries to look different on the ethical principles because, as if the time was more important to justify, right?

The importance of the multiple review is also related to other part of the article, which is already, has already been mentioned, that is their research needs to be responsive to the local health needs. And how is this going to be defined? It is true it's not easy but it can only be done if the local researchers and the local ethics committees and local authorities are involved in the discussion with the funded agency or country. And also promotes this harmonization of discord and policies, because it's only in this dialogue that you can do; and also to define and ensure the benefits, both for the population participants and for the country. It's only in this dialogue that it can be achieved.

So—and also it's important because the fourth part of the article is encouraging a basis or to foster equal participation in negotiation in terms of collaboration. Also in defining those benefits and something that I think is very important is to foster

more horizontal collaboration between the host and the funding countries, and to foster capacity building. The only way of doing that—I mean, and everything is self helping, because if you promote more capacity building, then you are in better terms to really enter negotiations in better, in more equal circumstances. Which is part of the reason why it is not possible now, even if we have it as ideal, but if you don't have sources or capacity, how will you? So, I think it is important to build confidence between countries.

The last one I just wanted to say is that there are other things-- and also I just want to say this is important also because in the declaration when we speak about benefit sharing, because there is another article which I would have developed more if I had 20 minutes, but we will do during the discussion, would have benefit sharing and in declaration it states that there shouldn't be coercion, not only for individuals, but also for states when defining benefits. That is why I think it is important. So just a final thought about the importance of the role of industry and how the market is being developed in such a way that market is developed, but not of the same, not at the same pace, to cover the needs of the more needed one. Thank you.

DR. GUTMANN:

Thank you, Dr. Feinholz. Our next speaker is Francis Crawley, and he is the Executive Director of the Good Clinical Practice Alliance, Europe in Brussels, Belgium. He is also chairman of the ethical review committee of the International Network for Cancer Treatment and Research, INCTR. He's a member of the ethics committee of the European organization for research and treatment of cancer, consultant to the Peking University institutional review board and a member of the steering committee of the Chinese ethics committee of registering clinical trials. He is also co founder and a steering committee member of the strategic initiative for developing capacity and ethical review. Mr. Crawley's research focuses on ethical, legal, and regulatory issues in health research. Welcome.

FRANCIS CRAWLEY:

Thank you, Madam Chair and thank you to the members of the Commission. It's really an honor and privilege to be here and I was asked to speak today about transnational research as were my colleagues here, but in particular to focus on good clinical practice.

It was really a great privilege yesterday to be able to listen to you and hear what your reflections were. And I think Dr. Grady, and

in subsequent discussion and discussion so far this morning, has given a very good and clear understanding of good clinical practice, both with regard to, more or less let's say, how it's situated with regard to research today, but also with regard to some of the questions that arise with it, as well.

For myself, I do appreciate good clinical practice. I think John will tell you my real love is Declaration of Helsinki. That's what I really, really do appreciate very much, as well as having worked on UNESCO, CIOMS, WHO and other, UNA and so forth guidelines. I really do appreciate this field here today.

I just want to jump to the end of my presentation, if I could, probably the end of today from what I understood yesterday and the single word I will use is "transparency." I very much want to really express my appreciation to Dr. Reverby and in particular, but also to the CDC, and also to you folks here as well as your staff and the work that they're doing with regard to the Guatemalan studies. I think this work which Dr. Reverby as done in an exemplary way as historian, as an ethicist, as a human being, to really show what is important here. And one of the things Dr. Reverby has done and now together with others in collaboration, including people in Guatemala, is to bring something out of darkness. This is really very, very important for us. And this is what I would like to stress during my presentation here.

First thing I would say, and really this is from my perspective good clinical practice transnational framework, if you want, science is a public good. The pursuit and results of science belong to the public. And that means not the public of this place or that place, these people or that people, it's really to humanity, as is well stressed, I believe, also in UNESCO's guidelines.

The pursuit of knowledge is an obligation and a responsibility. Now, this sounds very naive, but for me, I have a very strong question in my mind always: "Why do we permit people to experiment on human beings?" This is a very serious question. The answer is anything, to me, but obvious.

What happened during World War II, what happened during the Cold War, what happened in Guatemala, in particular, what happened in South Africa, what probably is happening right now as we speak in North Korea. So these are very serious issues and I think we have to give an appropriate response. I also think we need to consider very carefully what we do as ethicists, and bioethicists. That is, are we protecting human subjects? Is that what we're about? Are we justifying research on human subjects?

Is that what we're about here? Are we advancing health and how are we advancing health? What is it, what are our roles? And I think all these are involved here. What are our roles and what should be our principle objective here?

I think really the principle objective has to be health. And I want to stress something as well, and I think Dr. Feinholz has done that very well, research is embedded. Research is not a stand alone activity, it involves so many aspects of our society. So this diversion that we receive with regard to our discussion, how to protect human subjects, how to do research, this can only really be understood when we understand that, say here in the U.S., how other things function. How healthcare functions, how insurance functions, how medical education takes place, how hospitals function, that's the same issues we have in Belgium, as well. This is why for example in Belgium our GCP is quite different than compatriots in Netherlands or France. We have really, in a certain sense, to understand the context in which we are doing this.

I want to state really clearly from my perspective here, and I think it is perspective of GCP, research on human subjects is never right. Now, we can talk about a lot of rights, we can talk about a lot of human rights and even say the pursuit of knowledge is a right, and we've had a large discussion within bioethics particularly during the 1990s in Europe with regard to the relationship between the right to pursue science and the need or the rights of those individuals on whom science is being experimented.

We need, I think, to compliment a right based ethics with an ethics of responsibility. In other words, we have to say, "if you want to engage in human subjects research, you have responsibilities and these responsibilities need to be clearly articulated and clearly engaged."

I think it's obvious, there is a trust deficit with regard to scientific health research, bioethics research, clinical trials, whatever we call it. There is deficit with regard to the trust. This deficit is understandable and we can explain it really very well here. I think the response that we have been giving, so I'm not saying anything new here really, the response we have seen over the last 10 years, in particular the last five years really, from the international community from the U.S. Government with leadership, clinicaltrials.gov, from the WHO, from Europe, with also many of its actions since the implementation of GCP, has been a move toward transparency and the move is building very fast.

I want to submit to you, though, that secret science is never acceptable and I mean I don't want to go into other kinds of science, but science, health science, or any science with experiment on human subjects done secretly-this is not acceptable. Now, whatever regulations, whatever guidelines we have, whatever kinds of regulatory systems we build, as long as science is secret, we risk the kinds of experiments that happened in Guatemala.

Let us take for granted, as in many cases in these experiments, people did follow regulations. Let's assume they followed regulations. Whether they follow regulations or not that is probably not what is most important here. What is most important here, is this was not done in broad daylight. It needs to be done in broad daylight.

Now, to say something about GCP, this is a short history of GCP. It's an enormously complex history. Just European GCP is already really difficult, let alone WHO-GCP or ICH-GCP or FDA-GCP. This is really a complex and difficult thing. The relationship between GCP, and other international guidance, regulations, laws, is also very complex. I don't think that we can achieve, or that we need to, or should insist on having one rule, one way of doing it. I don't think anybody at the table would insist on that either. We have different situations, we have different kinds of concerns, and we have different aspects of our discussion that we need to be able to clarify and bring out strongly.

ICH-GCP is certainly, the gold standard. I highly recommend you all read it. It is the clearest GCP that's ever been written. The WHO-GCP from 1995 is excellent, as well. There is a reason, there are good reasons, why the U.S. Government moved towards a GCP framework. It is not only to do with a rejection of the Declaration of Helsinki, rejection is not the right word here. There are also good reasons why people doubt good clinical practice. We saw this particularly in the discussion that led to the 2001 European directive on GCP. People doubted GCP, legitimately, because ICH had six partners; three from governments from the U.S., the European Union, and Japan, the leading countries at that time in doing clinical research, and three from industry from the same regions and there was a lack in the discussion and that remains. We have also, within European GCP, I think what has been important and valuable for us in Europe with regard to GCP has not been the directive itself, it has been the 10 years of discussion it took to achieve the directive and the 10 years of discussion that were still involved with the implementation of the directive, and now perhaps revising that

directive. That discussion is very valuable. That discussion has strengthened our ethics, that discussion has strengthened our ethical review committee, our IRBs, that discussion has enormously strengthened patient subject participation in research.

One last slide, I apologize for going overtime. I propose for the commission that you seriously consider the Common Rule, to revise the Common Rule, that's what has to be done, I believe. There is a lot of commonness in U.S. federal regulation that is scattered over many different places within the regulations. That commonness can be brought together and the exceptions or the differences, they can also be more rationally put together, as well. I think those differences are there for a good reason. We saw that yesterday, as well. What is common there, what's common particularly between the Common Rule and the FDA rule, that is common.

That can be explained much more exclusively. Also, is common internationally, that can be done, as well. There is a lot, a great deal that is common while also allowing for diversity there. We need to find, really, an appropriate platform, an inclusive platform internationally to do this, and I think that we should begin to consider how to do this more generally.

At the end of the day what we want to insist on really is that research, we want to achieve culture of research, not just regulation of research, culture of research that says: research is done in broad daylight.

That is our best protection for human subjects. Thank you all.

DR GUTMANN: Thank you very much. I just want before we go into the question period to thank Dafna, Johannes, John, and Francis for four excellent presentations. Thank you very, very much. (Applause)

DR. GUTMANN:

Let me kickoff with a question and then ask the Commission members for questions. Each of you represents in your own careers and work, a dedication to upholding the highest standards, and I emphasize highest standards, in human subjects research. We were called together as a Commission, as all of you recognize, because of experiments done in Guatemala between '46 and '48, 1946 and '48, we're in a new century now, which were, to put it crudely, but not inaccurately, quite the opposite of highest standards. So one of the things that President Obama has asked us is to look at present standards, which you all have spoken to, and give him an answer to the question, "are the present

standards such that what happened in Guatemala couldn't happen today or would be very unlikely to happen today?" That isn't our only mission, we also are asked to advise on what would be the best standards for protecting human subjects. But let's talk about, just to begin with, I just want to ask each of you to tell me what your answer to the question is: given the standards and practices now of government funded research, because that's the specific question, "could Guatemala happen today?"

DR. FEINHOLZ:

Many things of what happened there, no. Because informed consent and many of the things are there already and that could have been protection of vulnerable populations is considered, so it wouldn't be possible to use those research groups.

I would say that the room for improvement would be probably, how to enter in negotiations about the projects, the research projects. About how relevant and about why it is conducted there. Because let's say the kind of question is a relevant question, but why did it have to be done there? I think that's still a relevant question today.

So I would say even despite other regulations in place, which I think at the moment will not allow many of the biggest problems that happened in Guatemala to happen again, no. But even if you follow some of the rules, as we said, there is a lot of room for ambiguity. And basically I would say, I would go back to why do you conduct research, fund research in another country? For whom is it relevant, and when you discuss also the terms of the collaboration, I still think there is room for improvement.

DR. GUTMANN:

Good. That's very helpful and that's why I'm asking that questions, because I think it will be helpful to focus on what are the most open, most important ethical questions here. Yes, Hans, you began to answer that question, but I would like to focus on that.

DR. VAN DELDEN:

I think I took your question a structuring question for my presentation, indeed. So I answered it a little bit already and I will be hesitant to claim that such a thing would never be possible now. Some elements would probably be impossible, but we would have discussion on other elements just as the one that Dafna just mentioned.

I'd actually like to quote what Francis Crawley just said,

“transparency.” I think transparency is the main issue, although Guatemala was not completely in the dark. I mean, there were discussions, it was known what was happening. It was not him on his own. But anyway, I think an independent committee nowadays at least, would address several of the issues and probably have a hard time with other issues such as responsiveness, and sharing of benefits, and equitable distribution, and fair subject selection. So there would still be a lot of questions to address for committee if they would see a case like this now.

DR. GUTMANN:

But fair subject selection, would a committee allow

DR. VAN DELDEN:

Probably not, probably not.

DR. GUTMANN:

Right, so let's just—

DR. VAN DELDEN:

But the thing is, and I already stressed that, a lot of these terms—I mean if look at them—if you look at the Guatemala case and look at these guidelines, you'll say, “well that's clearly a breach of the guidelines,” but of course the more subtle cases would still need a lot of talk because it's not so clear.

DR. GUTMANN:

Right, well I'm asking which guidelines. I want us to focus because there are a lot of guidelines here, which are the guidelines that it would clearly violate and which guidelines still are—

DR. VAN DELDEN:

Okay, I would say Guideline 10, of our book which is—

DR. GUTMANN:

Not numbers, names.

DR. VAN DELDEN:

Okay. Responsiveness to health needs in connection to benefit shares.

DR. GUTMANN:

Right.

DR. VAN DELDEN:

Guideline 10.

DR. WILLIAMS:

Could I go back to your opening expression, namely highest standards, and I think it is important for you to decide what you mean by standards and then what we're talking about the highest standards. So standards can either be compliance standards or ethical standards. Clearly, as I think everybody has discussed, they're different. When we talk about the highest standards, I think we have to get back to the old adage, "perfect is the enemy of the good." The higher the requirements are, the more difficult it is, the greater, to use Christine Grady's expression, the burden is on researchers and on everybody in the whole research enterprise, and of course you have all seen the criticisms of the current process. So, I think you are going to have to deal with this in terms of what is the acceptable minimum that is required for research on humans, and I think by any standard nowadays, minimum or whatever, the Guatemalan one would be regarded as unacceptable.

But how far do you go beyond that? This was a big question in the debate over the revision of the Declaration of Helsinki. What sort of document is it? It is bottom line set of standards that everybody has to accept? Or is it an aspirational document? I think it's little bit of combination of both.

DR. GUTMANN:

John, you have gotten exactly why I asked this question, which is it's not compliance versus ethics, but it's is there a distinction between necessary and desirable that is absolutely necessary standards which if not met are egregious violations? Versus desirable standards--and let me just give you an example, because I think this is part, very micro example. So, it comes from the edited volume on exploitation, which you probably read. So I'm driving late at night along a road and the tire on my car blows and I'm stuck there and someone comes along and offers to help change it and charges me, says, "I'll do it for \$100." I know that in normal times if this weren't a deserted road I could get it changed for \$50; I'm being exploited by this guy. Yet, he's helping me, I'm not going to die, if I say "no," somebody will probably come along. It would be desirable for him to do it for, I'm just stipulating, for \$50 not \$100.

So, what you just said, are there standards that would be really good in these documents but are not absolutely necessary to enforce? Versus standards that when we look at Guatemala, and

I'm not saying just Guatemala, but there are also things go on today that if they're not done, they are truly egregious violations of basic ethical, as well as compliant, standards. I think that's what you are getting at in your

DR. WILLIAMS:

My quick answer would be yes.

DR. GUTMANN:

Okay. We have to keep that in mind because all of the documents that you have put forward have standards that are necessary and desirable--I mean in them. Okay. Francis?

FRANCIS CRAWLEY:

Yes. Yes, the experiments that were carried out in Guatemala could happen again today and do happen. To give you a very clear example, a few years ago I was in Nepal to help the government write their National Bioethics guideline. And at the end of the meeting the next day I had one day for myself, so I rented a motorcycle and I drove from Kat Man Du up to the border of Tibet. I really wanted to get to Tibet, I got about 10 kilometers from the border of Tibet on a very rocky road on this motorcycle that was falling apart and I got a flat tire. It was 5:00 at night and I had a plane the next day, and I had a motorcycle I didn't want anymore. Some guys came by in a truck. They picked me up and they charged me really more than double what they should have charged me, so it does happen today. (Laughter)

DR. GUTMANN:

But that wouldn't have become a national and international scandal, correct?

FRANCIS CRAWLEY:

No, no, I'm sorry. What I want to say is this. There are two things that were said yesterday that I wanted to bring in here. First is what Dr. Fins said, I believe it was Dr. Fins, he said "tinkering won't work." We can't tinker, it won't work. The second thing is, what our colleague from Lanset said, Mia. She asked, "who is responsible or who has responsibility for asking the research question?" Actually that question is, "who?" because according to Chinese GCP, the one who asked the question is the one who is responsible, The one who initiates the research. The question really is: who is responsible for research? And again, the only answer can be transparency.

DR. GUTMANN:

Can I just ask you to be a little bit more refined

FRANCIS CRAWLEY:

What happened

DR. GUTMANN:

Wait--let me ask the question first. You said, "scientific research on human subjects has to be done in broad daylight," I believe that is a quote. Now, you don't mean presumably that people who take imagine your best human subjects research experiment, you don't mean that those people have to be in broad public view? I'm just asking you to be clearer about what you mean by done in broad public daylight.

FRANCIS CRAWLEY:

My apologies I haven't been so clear.

DR. GUTMANN:

It's just helpful for us, that is why I'm asking.

FRANCIS CRAWLEY:

What I wanted to say at the beginning of my presentation, is science is a public good. The science needs to be in broad daylight. I'll add something else from my experience, but not with motorcycles here. That is I am also was a member of the scientific committee with the WHO for their clinical trial registry platform. We spent two years talking about 20 items, 20 items to be put out in the public. At the beginning of that discussion people were saying, "we can't put that in the public, we have confidentiality, we won't have competition, we won't get things done." By the time we agreed on those 20 items, the whole community was way past that, Pharma was past that, Pharma was saying, "we will put more out than you are saying." That's one thing I want to say.

The second thing-- in other words, we overemphasize this need for confidentiality. We overemphasize the need for competition and so forth. And this is incorrect, vis-à-vis, the responsibilities we have when we engage human subject research. The second thing I want to say is with regard to tinkering, more particularly with regard to U.S. regulations, which has been mentioned yesterday, as well, was we should be regulating research, or science or the scientific engagement of human persons in experimentation. That is what we should be regulating. We should not regulating money, we should not be regulating NIH, we should not be regulating products. We should be regulating that engagement itself.

DR. GUTMANN:
Nelson

DR. MICHAEL:
So this is a question for all or some of you. And it reflects maybe some of the confusion about how one takes the input of so many excellent normative bodies that you all represent and to knit them together into something that is cogent to look at a way forward. So, an example would be, if you have vibrant research relationships that are essentially bilateral, let's say as an example between a funder like the United States and the Republic of South Africa or like the EC, Germany, and Tanzania, those relationships are vibrant and there are lots of lessons learned. How do you take those kinds of examples and spread them across the rest of the regions that are surrounding those countries, so that you as normative bodies can help develop south south relationships, there is more transparency. How can you use your pulpit to help bring other countries where the research relationship is less vibrant, and I would posit more susceptible to the kinds of concerns that are raised by Guatemala, how can your agencies be part of that solution?

DR. VAN DELDEN:
Well, yeah, the truth is of course I would never call CIOMS an agency. I mean, if you look at the Secretary to CIOMS, there is only just a few people working there. So, I don't think we have the power to really spread the message in another way, but through involving people from all kinds of regions, south south, southern parts of this hemisphere, and make sure their points of view are well taken into, for instance, this revision process.

But it would not be possible for CIOMS to, sort of, do capacity building in itself. That would be impossible for us.

DR. GUTMANN:
Doctor.

DR. VAN DELDEN:
UNESCO though...

DR. FEINHOLZ:
Yes, what we do in fact, after the approval of the declaration, since one of the articles of the declaration is the commitment of governments to establish bodies at different level in the states, to as I said, pass national legislation, education and so forth, and to review research and to deal with ethical dilemmas. We develop

two important activities. One, John, is very much involved which is education in ethics, but the other one, it's a main program that we have, is the ABC project which consists we help member states to establish national committees of bioethics.

One of the tasks of these committees is to set all the bioethical infrastructure for public policy and include of course, the review of research from the ethics point of view. And one very important thing that we do is we foster collaboration, south south and north south collaboration, because one of the things we do is first of all the training, which is conducted in newly established committee, is done by experts. International expert teams that speaks to three languages, English, Spanish, and French and the idea is to bring them to share experiences of everything, of how to define this the mandate of the new committee for example.

And then, the second part is that after three years that we do training, UNESCO conducts the training with these experts, we also foster a collaboration between those newly established committees and those who are already established, so they continue their relationship when UNESCO is there. It's out. So, this is the way we foster these exchange.

DR. GUTMANN:
Christine.

DR. GRADY:
First I want to thank you all, a very interesting panel. I have about 20 questions, but I'm going to limit it to the top two, I think, and I'm going to ask two. But the first one is sort of trying to understand-- I agree that the Declaration of Helsinki, is a sort of document that many people around the world hold. So the question is: From your angle, do you think that CIOMS is the same in many respects as the Declaration of Helsinki, with respect to fundamental principles? Because it's often interpreted as not being the same, and yet I heard you say and I know the history, it was an effort to elaborate the principles for a specific kind of, so-- and GCP also refers to Helsinki, but it is also perceived to be different. That is one question.

The second question is maybe a little harder to answer, but I think it's important. Several of you said especially the first two speakers, that it's critical to remember that the interests of the individual always trump the interests of everybody else. And I think that I don't think anyone in this room would disagree with that, but I think that statement has been subject to great misinterpretation, especially in the context of what research is.

Because research is by design, to answer, to gather knowledge, it's not to benefit the people that are in it per se. So how do you explain that statement? What do you think that really means, in terms of, what interests are we talking about of the individual?

DR. GUTMANN:

Could you begin answering the first--second question and then go back to the other?

DR. WILLIAMS:

Okay. As far as the other 18 questions are concerned, I think this is only the beginning of dialogue. So we'll certainly, speaking for myself, I'd be happy to continue in some other way of dealing with these questions.

There has been an evolution, as you well know in ethics, bioethics in general and research ethics in particular over the years. The Declaration of Helsinki, because it comes from the World Medical Association, at a time when almost all clinical research was done by physicians, so it was a natural body to formulate this back in the 1960s, was based on the Hippocratic oath as reformulated in Declaration of Geneva, where the responsibility of physicians was really first and foremost to the health of the individual patient. And that's been a very strong part of professional ethics, both for physicians and for other health professions forever, including up until now.

But at the same time there has been evolution, so when the international court of medical ethics for World Medical Association was revised in 1966, it was explicitly stated that the statement considered first the interest of the patient, did not mean consider only the interest of the patient. It meant that there are other considerations, too, and some were enumerated, basically responsibilities to society. In which cases the patient's interests may have to be subordinated to interest of others and you find that in requirements to report child abuse, for instance, and to declare that some people are incapable of continuing to hold a driver's license and there is a number of other particular issues and instances of that. So, basically it's to say that the injunction in research ethics to consider basically first the interests of the individual patient does not mean something exclusive, it means that really is extremely important and perhaps the most important part of it especially for vulnerable or patients of one tort or another, but that other interest enter in, too. So that is where ethics comes in, it's really a matter of considering all the considerations, all the important things in any particular instance,

and to come up with balanced judgment about what is most important in that situation.

DR. GUTMANN:

Isn't it more specific in human subjects trials on the notion of principle of equipoise? That-- in other words, you don't experiment on human subjects unless they stand to benefit from the experiment and if you find in the middle of the experiment that the no?

DR. MICHAEL:

Not phase one.

DR. GUTMANN:

Not phase one. Okay. Go ahead.

DR. WILLIAMS:

It also raises another big issue in research ethics and that is relationship of protection, basically, the responsibility to protect potential research subjects against the autonomy, encouragement and facilitation of autonomy. It comes down to, should people be allowed to participate in research that is clearly dangerous to them, and under what conditions? And so the research ethics committee has to make a decision that people should not be allowed to participate in research even if they want to, and of course there is many instances of that. The Liberation treatment from multiple sclerosis is sort of a contemporary one now.

And some, the emphasis traditionally has been on protection and for good reasons. But increasingly I think there is emphasis on facilitating autonomy and to get that balance right is difficult, and again that is ethical exercise.

DR. GUTMANN:

Could I ask--Christine, do you mind answering your question about putting human subjects first and if you would enlighten us on where equipoise comes in?

DR. GRADY:

Well, the reason I asked the question is, and I'm sure many people in this room know, sometimes I think that statement, the interest of the subjects should always take precedence over everything else, confuses people about what research really is about. And if research is the activity of developing new knowledge that might be helpful for other people, then sometimes the interests, the immediate interests, especially the medical interests of the individual at hand, are not the primary focus of what is going on. I think as Dr. Williams just said, the sort of struggle that has

occupied many people for many years is what level of risk do we allow people to take if they are able to make autonomous decisions in the interest of science, in the interest of developing new knowledge that will help other people. That is really a very tough question. One of you, I forget which one, I apologize, had on a slide that the very important extension of that question, what level of risk do we allow people who can't make their autonomous decisions to take, as well? That is another one that baffles the community.

Just with respect to equipoise, that is a huge discussion we could have, but I think it is a very misunderstood concept. I also think it is a concept that primarily makes sense in a very limited context of clinical trials and clinical research is—you know, there's so many types, there are so many different examples and it just can't make sense in every case.

DR. GUTMANN:

Good. Thank you. That is helpful, because I want to get out some of the many issues here. Hans.

DR. VAN DELDEN:

I agree with the position on equipoise, we just wrote an article in the Journal of Clinical Trials in response to Frank Miller's piece in the New England Journal.

DR. GUTMANN:

We will read it.

DR. VAN DELDEN:

Please. There's limited space for that only. When it comes to the interest of individual, it's noteworthy that in the Declaration of Helsinki in 2002 and 2008, it was indeed the individual that trumped everything else, right? In the way you just formulated it, it was the individual and the community that would take precedence over the other things. So already the community is now on the other side. Which in a way I think is probably the better way of putting this, because as you said, indeed, clinical research cannot be beneficial for the participant in most cases. I mean, of course we can make up a case in which it is, but usually there will be procedures—I mean the drawing of blood, of course, or other procedures that are harmful or certainly not beneficial, or discomforts, so indeed it cannot be always if we really took seriously what was the Declaration of Helsinki '05, and now '06, I think we would not have research.

DR. GUTMANN:

That's a

DR. GRADY:

That's why I asked the question.

DR. GUTMANN:

Anita.

DR. ALLEN:

I have two questions. One for Dr. Crowley, and one for Dr. Feinholz. I was very intrigued by your emphasis on transparency. It is often said that African Americans are distrustful of clinical medicine and also of healthcare research. Some African Americans seem to believe that if a group is low enough in social status or in power, that unethical conduct and unjust conduct can happen in broad daylight. So for example, slavery happened in broad daylight, the holocaust happened in broad daylight. So, my question to you is transparency the key or is something like equal respect for human rights the key? Little bit vaguer notion right? Broader notion, but maybe it really is the key. I talked to Dr. Reverby yesterday and she told me Guatemala was not a secret, you made that point. And I think Dr. Reverby also told me the document concerning Guatemala were in a available archive in a publicly affiliated university in Pennsylvania, so no secrecy there, it was all in broad daylight. So is human rights and equality really the key? My question for Dr. Feinholz is, you that mentioned in some cases urgency of medical need undercuts the mandate for careful ethical review and I wonder if you had a particular example in mind when you said that? Thank you.

DR. GUTMANN:

Good. Thank you. Francis, equal rights, respect for rights is the overarching value here and sometimes transparency is not? Therefore?

FRANCIS CRAWLEY:

Thank you for the question. I agree with you entirely and I want to come back to what Dr. Reverby said with her two statements yesterday morning: trust is really the key issue here. It's very important that we maintain trust in research. This discussion on equipoise, paragraph six of the Declaration of Helsinki, I agree entirely with you even more so.

Science is never in the interest of the individual, it is impossible to conceive of science of being in the interest of the individual. That's what I learned in high school: science is generalizable

knowledge, that's what it sees. People go into clinical trials, I would say generally, for access to something, treatment, access to something, but the science comparing A to B, that is something else. And I think this kind of confusion, with regard to our understanding and this is why really in bioethics we need to be very clear, this kind of confusion does lead to distrust.

With regard to what you say, I agree with you entirely, transparency is in and of itself insufficient and it will never be sufficient. Doing things in broad daylight is not sufficient. It's a necessary condition, I say, and I will insist it is a necessary condition, but it's not sufficient. We will have to do other things, we will have to do other things in order to build a community of respect and that is where we will gain our trust. Thank you.

DR. FEINHOLZ:

I would like to make just another comment of the other things that have been discussed and I will answer the question. First the question is that for example all the research about HIV in Africa, the transmission from mother to children, which was one of the most famous examples and trigger on the discussion about this, but there are many others of vaccines that are going to be tried, for example, proposed to be proven or trial in developing countries while there is epidemia. So, if they need to be tested in order to have some approval for market then it goes there because it will help these people that are in desperate need. So instead of doing that trial in other country they go to those countries. This is like two very clear examples.

I just wanted to-- and I think it is important and in that sense, probably Guatemala could happen again in that regard, that's why I was going back to what is the question, "why should be research there?" And it is probably related to this thing of, if research is going to benefit an individual or a community. Yeah, but it is true that it is sometimes the individual cannot be benefit and that is not the reason not to conduct research in general. But it is true also that it is not an excuse to, and as you said, we get to this very difficult question of what is the degree of risk we can put them? Or, what kind of any benefit or is there really nothing we can do? It should also not be an excuse to just go ahead, because otherwise, others will not benefit in the future and I think that is exactly that.

And probably that is why also communities are taken into account not only the individuals in instruments like the Declaration, because it is true, I mean both can be harmed and benefited, not only individuals. I think that's really the ethical

question about why do we conduct research for, and why, and who and how? and not research as such a good thing, which it is. I'm not questioning that.

DR. GUTMANN:

Thank you, Nita.

DR. ALLEN:

First I want to thank Christine for that question, because it was that in particular I wanted to focus on. But I want to clarify perhaps and make sure that I understand what you mean by the individual rights versus the individual good. So the way I took it, we have to respect individuals with respect to rights, but not expect the benefit for individuals. So individual rights need to be respected such they aren't exploited for the community, and that informed consent is assured. But once we can be assured there is informed consent of the individual, it's the shared benefit to the community that we're interested. Which could mean that an individual who is well informed could accept unbalanced risk, recognizing that they're taking on greater burden than they expect to benefit, in order to benefit science or in order to benefit society generally. So is the right way to think about it, individual rights rather than individual benefits; respecting the autonomy of the individual, but not benefits to the individual?

DR. GUTMANN:

John.

DR. WILLIAMS:

Yes to about 90% of what you are saying. But there is still the question of how far should people be allowed to, should be allowed, and this is the judgment of the ethics committee, to undertake risks that are clearly, to an objective sense, detrimental to their best interests? And that, as Dr. Beatty says, is an open question, is a very debatable question. But for the rest of what you said, yes, I think that is good way of putting it.

DR. GUTMANN:

Dafna.

DR. FEINHOLZ:

I just wanted also to go back to link again with these cases, which is, why would people agree to those risks? And when you are speaking about the research being conducted, for example in less developed countries, there it becomes very unclear if it's really for the benefit of science and others, or because probably just even if it is not conceived as a benefit, what they are going to have access

to the research is already benefit in itself for themselves. So probably that would be a reason to go into that research even if it is not really for the benefit of others.

I just wanted to make a comment on transparency because I think it is very important, and human rights. I don't think we should choose between any of them, I think both are needed because we were also discussing what is needed and what is desirable. I think both are needed and transparency is needed and I agree totally that it is not enough, but it is needed and should not be one or the other, I think.

DR. GUTMANN:

Hans.

DR. VAN DELDEN:

Just in response to what you raised, in cogent terms what we want to prevent using people merely as a means. It's my belief that end sharing would prevent that. That puts big emphasis on informed consent, which was actually one of the questions I raised, how to improve informed consent? It is not just writing up everything that you are doing, but improving understanding of what is happening. Because through that mechanism, you could reach that stage in which participant shares with the end of researcher, of the research being done. That might also be on the scientific end pursued, and that in itself might also prevent the person being used merely as a means. There is a connection there.

DR. GUTMANN:

I'm going to ask, I saw a hand up. Francis, you had your hand up earlier, do you come up, someone will give you a microphone. Because otherwise

FRANCIS:

It just struck me that a distinction philosophers sometimes use between one's goals of action and the constraints on action, would help in this discussion between Christine Grady and the others. Because when Christine Grady said, research is not about, you know, the individual who is being tested, but for the good of the community and finding out-- but it may not be about that person, but that doesn't mean that there isn't a side constraint on the use of that person. I think that came out here in discussion.

DR. GUTMANN:

Right.

FRANCES:

One way of distinguishing this is to distinguish within one's ethical theory between the goals of action, what one is trying to achieve, and the side constraints, how one does achieve that, you know. And that's a common distinction in moral philosophy that triggered me, it would clarify issues right away the goals versus the side constraints. When Professor Delmar, is it? Hans you refer to him as? If I may, I don't know, your name. Talked about the balancing between individuals and the community, what worried me was he was at that point introducing the idea of balancing individuals in community at this constraint level of discussion, rather than the goals and that is a different issue. I mean, when you think of rights as individuals, as constraints on the pursuit of the good, that's one thing. But when you think of balancing the rights of individuals versus the community at the very time you are talking about the constraints, which is the question about how much risk can you impose on a person, then you have entered a different realm. You are now talking about whether there is a side constraint.

It's very important to keep clear in your mind whether you are talking about the goal of the research or the side constraint, and whether you are talking about the side constraint as really a constraint or whether you are willing to talk about balancing risks versus benefits to that individual. I'm just trying to clarify the terms of the debate. Sorry, I hope you could hear me, I wasn't always talking. Thank you.

DR. GUTMAN:

Christine, do you want to respond?

DR. GRADY:

That's helpful, Frances, I just want to make one thing clear in terms of my question. The side constraints-- we need to be clear about what the side constraints are. And rights, I think everybody agree, are a part of it. But part of what's been a source of confusion I think, in terms of ethical discussion about research, is the statement in Helsinki that says, "the interest of the subject." And so interest is a broad category and it's hard to decipher, it's hard to pull out what interests are we talking about. So that is why I asked the question.

DR. GUTMANN:

Yes, and Nita's question, all this is, I think, very clarifying. That if you are clear that the side constraints are rights, you have real side constraints. If you expand the notion of interest of the individual you are in a different realm as Professor Kantz said.

It's very any response if you want. Let me just say before we end, everything that you have added and said is enormously useful in exactly the right realm of our deliberations, so thank you.

DR. ARRAS:

A final word of thanks for really stimulating panel. I appreciate all of your comments. I have two questions, both of them derived from the fact there are four of you sitting there instead of just one, okay. So my first question really is a repeat of Christine's first question, which has to do with diversity within these four sets of norms. In your opinion, you know, how much diversity is there between Helsinki, CIOMS, Good Clinical Practice, human rights, right? And to what extent do you think this is a problem? And to I'm sneaking in more questions obviously. And what sorts of solutions to that sort of cacophony do you think would be helpful? Okay. That is question number one.

DR. GUTMANN:

John, we just don't have the time.

DR. ARRAS:

That's okay. That's okay. That's all right. Maybe over coffee.

DR. GUTMANN:

Over coffee. Thank you.

SPEAKER:

What's number two?

DR. ARRAS:

You want number two? I've been forbidden to talk about number two.

DR. GUTMANN:

It's just, we have to have a break and stay on time. So... let's go. John.

DR. WILLIAMS:

Do you want an answer?

DR. GUTMANN:

Yeah.

DR. WILLIAMS:

Oh okay, there's many ways to answer the series of questions. But in terms of harmonization or consolidation of the different

policies and of course there are others represented more yesterday than today, I think in terms of your mandate, one thing to deal with, one way of focusing the question is what should be the mandate of the IRB? And I think it's interesting where we come from, we use different expression, it's research ethics committees or ethics board, there is ethics in there whereas IRB there is no ethics in the term. And from what I've heard yesterday I think that really reflects reality that IRBs are basically institutional committees that lean more toward regulations, than towards ethics. If that's the way it's going to be, that should be accepted.

If on the other hand there should be more ethics in IRBs, and maybe it would be a good idea to change the name, but that would give a different flavor to the whole exercise and perhaps give more emphasis on the documents that we have been talking about, rather than on what the FDA wants and some of the other regulations and the whole compliance approach to things.

So I think that's something for you to consider: Should the entire approach of research review by IRBs continue, as it seems to be the focus more on compliance, with regulation or should be it opened up to ethical considerations that are front and center of the documents that we've been talking about?

DR. VAN DELDEN:

As Professor of Medical Ethics, the diversity between the documents is the that way I earn my living. Because it's by studying diversity and subtle differences that I can write articles. I don't think it is cacophony actually, there is a lot of consistency between them. And I tend to look at those documents as provisional fixed points as Norm Daniels called them. And in a way that's the way it goes. So we can now say there needs to be one global document that ends all discussion, but that would be the wrong move because we don't want to end all discussion.

In a way this is a sensible approach, one, and there is a little bit difference, our formulation on the choice of the controls is little different than the Declaration of Helsinki, and probably in the next version, a little different again because there is growing insight.

So we shouldn't try to stop that and make sure there is just one document because the next moment you will find another proposal somewhere else.

DR. FEINHOLZ:

I also wanted to say that there are some differences, but I would say there are a lot of common issues which prevalent and which are, I would say, captured in a way in a more ethical or human

rights approach, which they are. There many things they are toward the cooperation, the dialogue, which I think it is the real point about these documents. I agree that--you have a document that true, it will never be definite because it should be the result of these discussions and to prove what is a reality, and reality is being complex. So I think there will never be one that will have all the answers.

But I think in this document, there are many principles, as we were asked at the very beginning if some, they are both aspirational and necessary, that are common that I think could be the basis for the very specifics that can never be found in any document, any document could give that.

DR. GUTMANN:

I want to thank all of you once again for wonderful presentations and especially for the response to the questions. Thank you.
(Applause) –

(Whereupon the above matter concluded at 10:40AM).