

Invited lecture

Ethics and regulations of clinical research in South Africa^{*1}

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Abstract

This is the record of lecture of Professor Ames Dhai, at the seminar titled “Japanese new law on clinical research and human research ethics in South Africa: Development and ethical partnership toward global health”, organized by “Clinical Research Risk Management Study Group”, co-organized by “Clinical Evaluation (Rinsho Hyoka Kankokai Inc.)”, supported by “Japan Pharmaceutical Industry Legal Affairs Association (JPILA)” and “Japanese Association of Pharmaceutical Medicine (JAPhMed)”. The seminar was held on September 29, 2016, at Venue: Mitsui Sumitomo Insurance, Tokyo, Japan.

She introduced her contribution to set up the Centre with the name of Steve Biko, a prominent human rights activist, who was killed at 31 years of age, in the apartheid regime, as he struggled for “black consciousness” and establishment of equality and freedom of black people.

After the abolishment of apartheid in 1994, South African Constitution was established. It defines the “Bill of Rights” which clarifies that everyone has the right to bodily and psychological integrity, including the right not to be subjected to medical or scientific experiments without their informed consent. This is based on the United Nation’s International Covenant on Civil and Political Rights as agreed in 1966.

She also introduced South Africa’s regulatory framework of research ethics to protect human and animal research subjects, including ICH-compatible GCP regulations for clinical trials. Her lecture provided much of insights and wisdom for the Japanese to learn true meaning of ethics, human rights and research regulations in the international context.

Key words

bioethics, human rights, South Africa, apartheid, clinical trial

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^{*1} The record of the lecture on September 29, 2016, at Venue: Mitsui Sumitomo Insurance, Tokyo, Japan.



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Director of the Steve Biko Centre for Bioethics at the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, the Republic of South Africa.

She established the Centre in 2007. The Centre, which runs Masters and PhD programs in Bioethics and Health Law, has local and international recognition as a leading Centre in these disciplines and in 2013 was awarded the World Medical Association Co-operating Centre and the South African Unit of the UNESCO International Network in Bioethics status. Professor Dhai serves on several policy making bodies in the country and is a Past President of the South African Medical Association. She also serves regularly as a consultant / expert advisor for the World Health Organisation, and is on the WHO's African Advisory Committee for Health Research and Development. She served on the World

Medical Association's (WMA) Working Group on Health Databases and Biobanks where she was involved in developing international policy. She participated in the WMA's Working Group on amendments to the Declaration of Helsinki and in activities of the Institutes of Medicine (USA), and the National Academies of Sciences (USA). Professor Dhai is an ethicist of international standing who can be credited with entrenching bioethics as an integral aspect of health sciences in South Africa. She started off her career as a medical doctor, specialised in Obstetrics and Gynaecology, and then went on to graduate with a Masters in Law and Ethics.

Source: <https://www.wits.ac.za/staff/academic-a-z-listing/d/amesdhaiwitsacza/>

The photograph is at the time of lecture in Tokyo, September 29, 2016

1. Origin and overview of Steve Biko Centre for Bioethics

I will talk about research ethics and why it is important to think about ethics when we are doing clinical research. I will talk about some tragedies and scandals, both international and locally relevant in South Africa. I will look at some international ethics and regulatory instruments together with our South African regulatory instruments. I will highlight some of the gaps that we have in South Africa with regards to participant protection, what are some of our most relevant in terms of our governments' instruments. Currently, there is a reawakening of discussion of what should the standards of care be in clinical trials and what should the post-trial access be – I will say a few

words on this as well.

Steven Bantu Biko was the father of the black consciousness movement (Fig. 1). He was born in 1946, but had a very short life. At 31 years of age, he was killed by the apartheid regime, because he was trying to conscientize us into believing in ourselves as black people who were equal to anyone else in the country. I met Steven in my first year of medical school at university. At that stage, Steven was already banned by the South African government and had been placed under house arrest in a province a distance away from us. Despite the house arrest and banning, he managed to come across to the university to get us to believe in ourselves that as black people we were equal to anyone else in the world. He influenced our lives and our thinking greatly. When I was asked to set up a centre for bioethics, I was really happy that the uni-

Fig. 1 Steven Bantu Biko**Steven Bantu Biko**

18 December 1946 - 12 September 1977

versity was supportive of the name of the centre, which is the Steve Biko Centre for Bioethics.

Why did I think about the Steve Biko Centre for Bioethics? Steven Biko's name serves as a constant reminder to us as medical people as to how low we can stoop when it comes to recognizing our patients and doing whatever is in the best interest of our patients (Table 1). Biko was detained in a jail where he was subjected to harsh brutal treatment by the South African police during his interrogation. South African doctors were called in to assess his medical condition. The police would torture and damage Steve to a point whereby he would not be able to respond, and then the doctors would come in

and resuscitate him and get him to a point where they could start the interrogation again. During his last incarceration, he had terrible head injuries as a result of the brutality of the South African regime. When the doctors were called in to look at him, he already had concussions, but they failed to take his condition seriously. They did not even do a proper medical examination. They failed to institute care in his best interests. They wrote false medical certificates which conveyed false information. They allowed Steve to be examined in the presence of the security police. How does that align with respecting the privacy and confidentiality of your patient?

Basically, they subordinated the welfare of their patient to the interest of the security policy, and yet when we take our Hippocratic Oath, we pledge that the welfare of our patients and the best interest of our patients should be our first consideration. In the apartheid era, doctors took this oath, but they didn't apply them. The interest of the apartheid state was the doctor's first consideration. They transported him under very sick condition from one prison to a central security prison about 12,000 kilometers away. He received inadequate medical care in that prison as well. So, it is not surprising that he succumbed and he was pronounced dead after a day at the prison. At that

Table 1 Biko – improper care

- Doctors failed to regard Biko's condition seriously
- Inadequate medical examination
- Failure to provide nursing care
- Failure to observe Biko closely
- Wrote a false medical certificate and also conveyed incorrect information
- Allowed Biko to be examined in the presence of the security police
- ***Subordinated the welfare of their patient to the interest of the security police***
- Transported a very sick patient under extremely unsatisfactory conditions without a medical attendant
- Transferred a patient without a referral note
- Received inadequate care in Pretoria prison

stage, we had very little bioethics teaching in the country. Bioethics was specifically not allowed in the medical school that I went to. It was the only black medical school. It was University of Natal-Black Section. If black students were taught bioethics, it could “start us thinking” and we would start demanding a realization of our human rights. It was the apartheid government’s decision never to allow us to have any involvement in bioethics. However, on the evening that Biko died, as students at the University of Natal we put together the very first faculty bioethics lecture, and it was planned for 6 o’clock that evening. After all was done in getting the speakers together and getting the lecture off the ground, at 5:30pm the lecture was banned by the South African government.

However, we have risen above that. Post-1994, we have got a centre for bioethics in Steve’s name, and it is one of the leading centres in the country.

We have a strong staff component, both Council funded, that is, university funded, and grant funded, and we have got a set of honorary lecturers as well. Some of the activities that we are involved in is teaching, research in bioethics and health law. We do a considerable amount of academic advocacy. When we are not happy with what’s happening with regard to the ethical treatment of patients in the country, through the position of academia, we put into motion our agency as advocates for our patients. We also do consultations, both clinical and non-clinical, for university staff and the greater South African community should there be any concerns that they may have in bioethics.

The teaching that we do includes undergraduate and postgraduate teaching. We have the regulator for clinicians in the country, the Health Professions Council of South Africa (HPCSA). The Centre was active in contributing to the development of a core



When Steve Biko Centre for Bioethics was established in 1994 at the University of the Witwatersrand, Professor Dhai was designated as the director of the centre.

The photo panel of an educational TV series in 2002 titled “Tobias’s Body” guided by Professor Phillip Vallentine Tobias, at the entrance of Steve Biko Centre for Bioethics, with the words of Professor Tobias: “The so-called race of mankind are simply a variety of different sorts of surface anatomy. What is on the surface is just a frill of variation.”

Photo: Chieko Kurihara, May 11, 2016.

The entrance to Steve Biko Centre for Bioethics in the “Health Science Building” with the name of Professor Phillip Vallentine Tobias.

Photo: Chieko Kurihara, May 11, 2016.





curriculum in bioethics, human rights and health law by the HPCSA. The HPCSA has mandated every faculty of health sciences in the country to ensure that at least 10% of the core curriculum in health sciences training is a combination of bioethics, human rights, and health law. This has to be taught vertically through the study years, and it must be examinable as well. That is where we are with our undergraduates. To incentivize our students, the Centre managed to get some funding, and we have a bioethics prize now that is awarded to the health science student with the highest academic marks in bioethics every year across all the disciplines. In terms of the postgraduate programs, we have short courses of competency in bioethics, human rights, and health law. We have also established a Masters program in this discipline. More recently, we developed a PhD program, which started in 2010, and we have graduated three so far and we hope to graduate about two a year. Of course, we do a lot of Continuing Professional Development (CPD) to graduates for bioethics.

2. Research ethics: objectives, components, and challenges

By way of introduction to research ethics, I would like to quote Leon Kass, a very renowned ethicist. In one of his publications, he said, “The benefits of biomedical progress are obvious, clear and powerful. But the hazards are much less well appreciated.” That is the reason we need to have regulatory controls and ethical controls, because the hazards are not really appreciated when it comes to biomedical progress. What are the objectives of ethics? We talk about ethics all the time, but what does ethics really mean? It is how we ought to be acting in a given situation. Ethics provides us with strong reasons for acting in a particular way. It involves a critical reflection of morality. The intention of ethics is to safeguard human dignity, to promote justice, equality, truth, and trust. This is so pertinent in our South African context, especially considering the situation that we had in apartheid and the situation that continues



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The Human Research Ethics Committee (Medical) at one of its monthly meetings

at the moment in our country. In terms of ethics, regulations, and laws, it is very important for ethics to inform laws and regulations rather than laws and regulations to inform ethical guidelines. Whenever I do a talk, I am asked, “But you are talking about ethics? Yes, we should be considering this, but what does the law say?” It’s not what does the law say, but how has ethics informed the law - that should be the question.

What is ethics in research? It is simply about how we can ensure that people that are vulnerable are protected from exploitation and other forms of harms. What we see in ethics in research, is that there is an evolving language where we move from a passive subject to an active participant. We look at person-centered ethics in research as well, just like we have patient-centered ethics in the health-care context. This is especially pertinent in the

context of South African vulnerability and our apartheid legacy.

In terms of ethics, we focus on principle-based ethics in research. We look at *autonomy*, which basically boils down to *informed consent*. When participants are involved in research, they need to make a full informed consent, and their *confidentiality* has to be protected. When it comes to *benefits and risks*, that is, *beneficence/non-maleficence*, it translates in research ethics to the benefits of research outweighing any perceived harms. It is important to realize that there is a dissymmetry in this when you look at risks. The risks are now immediate within the research context for future benefits, and it’s important that the participant understands this. When it comes to *justice* in research, it is important to discuss what the *standards of care* will be especially if it’s international

collaborative research. Would one have the same standards within your research site as compared to the sponsor company's site? Or would you have a lower standard? If you demand the same standard, how would that pan out, especially when you consider that that standard may not be the standard of care within the country, because if one insists on an outside standard, if that standard is proven, then the research is proven to be beneficial. What if your country cannot afford to give that as the standard of care thereafter in line with the Declaration of Helsinki in terms of *post-trial access* and standard of care. There are no clear-cut answers. While we do have guidelines, we try to look at each situation on an ad-hoc basis and say to ourselves what would the best situation be for participants and communities in terms of this particular dilemma for us in South Africa. There are also issues in terms of justice when it comes to *compensation for research-related injury*. Prior to 1994, that was totally ignored. If you were involved in research as a black participant, if you got injured as a result of being in the research, there was not much in terms of compensation and you got into the healthcare sector, which was a very skeletal healthcare centre with very little to offer black South Africans and then you became a victim of that situation.

I have already said that ethics is not a law. It's a distinct entity. Ethics unfortunately is constrained by the law, but I would always say to the lawyers and they get very unhappy with me is that the law is the minimum standard, and ethics must rise above the law should the law demand you to do anything unethical. Lawyers are not happy to hear this, but it is very important that lawyers must be bound by ethics as well. Very important is if ethics informs the law, then ethics is imbedded in the law. Any regulations or guideline documents that come out of the law, because the law will state that you need guidelines and regulations in A, B, and C, those

documents will have quasi-legal status. Oftentimes, researchers will come to us and say that this is a guidance document; it does not have a clout of the law. We would say, no, it's got quasi-legal standing, because it's a response to our Constitution and our National Health Act. Therefore, you are legally bound to the ethics within the documents.

Basically, when it comes to research ethics, there are two components: regulatory and ethical. But, when we look at health research, there are many challenges to health research, but all these challenges hinge around one question and that single question is whether the demands and goals of science and biomedical research can be pursued with full protection of the rights and dignity of the research participant and communities. This is a real dilemma. The dilemma is intensified when we think about the goals of medical research. The goals of medical research is to promote well-being for humankind. How do you arrive at this balance?

3. Tragedies and scandals

Let me describe this with some of the realities that we see. An Italian Researcher Giuseppe Sanerilli. Around 1893, he thought that he had discovered the organism that caused Yellow Fever. He injected a whole lot of subjects with this organism, and needless to say, several died and others became very sick. There was huge mortality and morbidity. At that time, there was no telephone or internet, but there were sailors going from shore to shore. Very soon in the 1890s, the world woke up in shock because researchers were using human beings as guinea pigs. That's where the guinea pig terminology started. Next example is about gypsy twins. This was an atrocity committed during the WWII. We have read a lot about the atrocities committed by Hitler amongst the Jews, but Hitler also wanted to get rid of gypsies that were living in Germany

because he wanted a pure Aryan race. His idea of pure Aryan race was fair skin, blue eyes, blond hair. These gypsy twins had been captured during the WWII. His chief scientist, Dr. Mengele, anesthetized them, then injected potassium chloride into their hearts killing them off, and removed their eyes and shipped them off to Berlin for study, because he wanted to know how one could study the natural processes, and tamper them towards what they wanted in terms of an Aryan race.

The story about an ex-professor Werner Bezwoda is also well known. He was a professor of oncology at University of the Witwatersrand. In 1999, he went to the European Oncology Society where he presented some very good oncology research results on breast cancer. Then, in 2000, he presented in America to the International Society of Oncologists. It was chemotherapy coupled with stem cell rescue. His results were so good that oncologists that attended his conferences went back to their practices and tried the regimes that he had showed, only to find that their patients were doing worse or they were dying.

The International Oncology Society asked him for his data, because it could be that we had some specific nuances in Africa whereby our patients were surviving but patients in the west were not, and he did not give them data. Because the data was not forthcoming, a group from International Oncology Society came through to South Africa and engaged with the dean of the medical school and then got into Prof. Bezwoda's site only to find that he had fabricated his results. He did not even have a proper protocol. This research did not undergo research ethics review, although they had a strong research ethics committee in the institution already at that stage. When he presented his

results, he showed that 75% of his participants were white women and 25% were black African women, but when they went through his documents, it was reverse – 75% were African women with no informed consent and 25% were white. When they looked at follow-up, they couldn't trace these women, so many of them were probably dead.

There was a disciplinary hearing. He lost his job and was stripped off his professorship. He was blacklisted. He cannot do research in the country at all. He was reported to our Health Professions Council, which is our regulatory board, and they suspended him from practice for a few years. He is now back in private practice, but it hurt the reputation of South Africa and our institution. Because of this, we made sure that we tightened our regulations on health research.

This is a picture of demonstrators at an international HIV/AIDS conference. It was at the time of pre-exposure prophylaxis trials. There were three countries involved, two in Africa and one in the East. The reason for the demonstrations was there wasn't adequate informed consent, or proper standard of care. In terms of access for the communities, there wasn't anything brought in. Governments were not aware of the exact ethical implications, and based on these demonstrations, the three governments stepped in and shut down the trials prematurely.

We have had many international problems, African together with South African problems. I am sure you will agree with me when I say ethics in research was "born in scandal," and it is now reared and nurtured in protectionism^{*2}.

^{*2} Levine C. Has AIDS changed the ethics of human subjects research? *Law, Medicine and Health Care*. 1988; 16(3-4): 167-73.

4. International ethics and regulatory instruments

We have some pertinent international instruments and guidelines starting from Nuremberg Code 1947 moving into the International Covenant on Civil and Political Rights 1966, where specifically informed consent is mentioned^{*3}. Then there is the Declaration of Helsinki 1964. It's been updated seven times, and the latest version is in 2013. One may ask, if the principles of ethics don't change, why do you have to be updating something all the time? That is because with the rapid advancement of science and technology, scientific processes change. Therefore, while the principles remain the same, the application of the principles may differ. Then there is the CIOMS guidelines, the ICH-GCP which has been mentioned already, and of course, Singapore Statement on Research Integrity (2010). This is specifically to safeguard against scientific misconduct. Japan was quite a catalyst when it came to the Singapore Statement, because my very first trip to Japan was around 2008-2009 where the Ministry of Science and Technology hosted the OECD countries. The huge concern at that stage was the fabrication, falsification, and plagiarism that we were seeing in science. At that meeting, I represented the South African Department of Science & Technology. That meeting was the catalyst for the very first international symposium on research integrity which took place in 2009 in Portugal. From then, the Statement was born. Between 2009 and 2010, the Statement was being worked on, finalized, and launched in the Second World Conference on Research Integrity in 2010 in Singapore. So, Japan has played quite a big role in

the Singapore Statement, and this is important history that should not be forgotten.

5. South African ethics and regulatory instruments

What about South African Instruments and Guidelines? Because of our history together with the fact that lots of clinical research is done in South Africa, we have a tier-sort of ethical regulatory legal protections. We are protected by the Bill of Rights of the Constitution of South Africa. Then, we have our National Health Act, which is an act of parliament. In terms of Chapter 9 of our National Health Act, it's specific to the formation of a National Health Research Ethics Council that has to put together guidelines for good practice. So the GCP guidelines together with the Ethics in Health Research Guidelines are a result of the work done by the National Health Research Ethics Council. I was deputy chair of that Council for 2 years and was also involved in the interim council that worked to put in together these guidelines. We also have our Health Professions Council of South Africa Guidelines that has three booklets on Ethics in Research; one is general research. Should there be any infringement of the ethics, then the researcher gets reported to the Health Professions Council and is either fined or goes up for a full inquiry and may be suspended or lose his or her registration with the Council.

Here are some pictures of the reality of South Africa that we live in. We have very, very high levels of poverty. In Africa, most of our populations are vulnerable. We have little or no health-care for our patients. There are failing or failed health systems. There are low levels of literacy. You

^{*3} International Covenant on Civil and Political Rights. 1966: "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation".

can see a classroom there filled with many students. How does one learn in a classroom like that? Very little clean drinking water. The shacks are the types of dwellings that we have. In the far right, there is a child sitting in an open toilet. Where is human dignity? These are the conditions in Africa that we as advocates for our patients have to fight against. We have had transition and we have had change, but there has not been adequate change for those that do not have. Here, we have huge contrast, vast disparities, no equality. At the same Cape Town, we have got Khayelitsha, so two different states of living a few kilometers away from each other. Again, one type of classroom for learning, another type of school for learning. You can see the disparities that we have. That is why it is so important for us that are involved in protectionism to ensure that our participants who come from these communities are protected in research.

6. South African ethics and regulatory instruments: Bill of Rights (Table 2)

In terms of Bill of Rights of our constitution, when we look at Section 12, “Everyone has the right to bodily and psychological integrity, which includes the right ... not to be subjected to medical or scientific experiments without their informed consent.” This is very similar wording to the International Covenant on Civil and Political Rights in the country. In terms of South Africa, we have gone a long way. The South African government has done a lot in that many of us do have civil and political rights at the moment. I would not have been at the University of the Witwatersrand Medical School if we had not had the transition. There has been a lot done for us, but there hasn’t been much done for socioeconomic rights and that is a huge problem. What are some other applicable rights when it

comes to research? It’s the right to equality, so no vulnerable group should be subjected to research for the value of beneficial few, those who can manage to afford the interventions proven useful by the research. There should be equitable distribution of the risks and benefits of research throughout our communities. Our research participants need to be treated in a dignified way. They have a right to life. They cannot be subjected to experimentation where they could die. We had the example of Professor Werner Bezwoda at my own medical school where the right to life was possibly infringed. There is also the right to privacy and the right of freedom of belief and opinion. In other words, freedom of religion, if a research participant has a particular viewpoint. For example, if they are going to do this research on sterilization or abortion, and it is against their religious beliefs to be involved in something like this, it’s important to respect that and not to force them to be part of the research project. Also access to information, the participants need to know what the participation entails and what has happened to the data that they have given you on the research side. What are the results of the research? How are the results going to benefit them at all?

7. South African ethics and regulatory instruments: National Health Act and National Health Research Ethics Council

In terms of our National Health Act, we have a definition of health research. Any health research that falls under this definition must be reviewed and approved by a research ethics committee, which is both registered and accredited by the National Health Research Ethics Council. Health research is defined as any research which contributes to the

Table 2 South African instruments and guidelines for health research

- Bill of Rights of the Constitution of South Africa
 - 12(2)
 - Everyone has the right to bodily and psychological integrity, which includes the right ...
 - (c) not to be subjected to medical or scientific experiments without their informed consent.
 - Some other applicable rights:
 - 9 - Equality;
 - 10 - Human dignity;
 - 11 - Life;
 - 14 - Privacy;
 - 15 - Freedom of religion, belief and opinion;
 - 32 - Access to information
- National Health Act (No.61 of 2003)
 - “health research” includes any research which contributes to the knowledge of:
 - the biological, clinical, psychological, social processes
 - improved methods for provision of health services
 - human pathology
 - the causes of disease
 - the effects of environment on human body
 - the development of new applications of pharmaceuticals, medicines, related substances
 - the development of new applications of health technology
- National Health Research Ethics Council (NHA - sec 72(2))
 - determine guidelines for the functioning of health research
 - ethics committees,
 - register and audit health research ethics committees,
 - set norms and standards for conducting research on humans and animals, including norms and standards for conducting clinical trials,
 - adjudicate complaints about the functioning of the health research ethics committees,
 - refer to the relevant health professional councils any violations
 - institute disciplinary actions,
 - advise the national department and provincial departments on any ethical issues concerning research.
- Clinical Trials (NHA - sec 71)
 - “... a systematic study involving human subjects that aims to answer specific questions about the safety or efficacy of a medicine or method of treatment.”
- Health Research Ethics Committees (NHA)
 - 73(1) Institutions at which health research is conducted, to establish / have access to health research ethics committee, registered with the NHREC.
 - 73(2) A health research ethics committee must -
 - (a) review research proposals to ensure that research will promote health, contribute to the prevention of communicable or non-communicable diseases and or disability or result in cures
 - (b) grant approval for research where proposals meet the ethical standards
- Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa - 2006 (2ed)
- Ethics in Health Research: Principles, Processes and Structures - 2004; 2015 (2ed)
- Ethical and Legal Guidelines for Biotechnology Research in South Africa (DST) - 2006
- Health Professions Council of South Africa Ethical Guidelines

knowledge of biological, clinical, psychological, and social processes; improved methods for provision of health services; human pathology; causes of disease; effects of environment on human body; development of new applications of pharmaceuticals, medicines, related substances; and development of new applications of health technology. You can see it is very broad. It is not only drug development, but it is a wide range. It includes social sciences type of research which has an implication on health as well.

In terms of our National Health Act, there is a need for a National Health Research Ethics Council. It is mandated by the Act. The National Health Research Ethics Council has already been established. There was an interim council followed by the appointment of a full council. The council has just completed its third term. I served on two terms as deputy chair, the first and second term, together with being a member in the interim Research Ethics Council. I took a break in the third term. While I am sitting in Japan, I got a call from our Director General of Health asking whether I would chair the new Council that is about to be established. I am still thinking about it because it's a lot of work, and it will be quite a challenge. But the job of a National Health Research Ethics Council as per the Act is to determine guidelines for the functioning of health research ethics committees, to register and audit health research ethics committees - and they have done so already, and currently, we have about 38 research ethics committees that have been registered in the country and already audited - to set norms and standards for conducting research on humans and animals, including norms and standards for conducting clinical trials and that is why we do the GCP guidelines as well. Why animals? There is lot of phase I research that is informed by animal trials. We need some protection for the animals as well, so this is why we have this. Should there be

any violations that are reported to the National Health Research Ethics Council, these can also be referred to the relevant health professional councils. For example, if someone is registered with the Health Professionals Council, they can be referred for disciplinary action. The National Health Research Ethics Council is also mandated to advise our national department of health and provincial departments on any ethical issues concerning research. It has got quite a heavy mandate.

8. South African ethics and regulatory instruments: clinical trials and Health Research Ethics Committee

In terms of our National Health Act, a clinical trial is defined as “a systematic study involving human subjects that aims to answer specific questions about the safety or efficacy of a medicine or method of treatment.” You can see, it is not restricted to drug development, but any method of treatment, because you have quite a bit in terms of psychology trials where they try to check what the best method of treatment would be. In terms of the Act, 73(1) states that institutions where research is conducted must either establish or have access to health research ethics committee, which are registered with the NHREC. That is clear-cut, black and white, and we have been functioning in that way since 2004. In terms of what a research ethics committee must do, it's built into an act of parliament. This is what I meant when I said law can be influenced by ethics. A research ethics committee must review research proposals to ensure that research will promote health, contribute to the prevention of communicable or non-communicable diseases and or disability or result in cures. It tells you the type of research as well that you are expected to look at, and the research ethics committee grants approval

for research where proposals meet the ethical standards. I have not gone into the detail, but Chapter 9 of the Act stipulates how informed consent is to be obtained from the research participants. It divides the informed consent to adults and minors. There are a number of stipulations which I haven't gone into in the interest of time.

Here is my university. It has the oldest research ethics committee in Africa established in 1966 very soon after the first Declaration of Helsinki in 1964 and also as a response to the very first article by Beecher in early 1966 which exposed a whole lot of ethics violations in research^{*4}. Beecher reviewed a number of trials that had been published in high-ranking peer-reviewed scientific journals. He looked at 54, but the journal article only considered 22 trials because of space limitations as well. Soon after that, the University of the Witwatersrand established its research ethics committee and here we are. As a research ethics committee, we meet once a month and review our research ethics trials very much in line with our country level guidelines and where our country level guidelines are deficient, we use the Declaration of Helsinki to rise above the country level guidelines.

In terms of Research Ethics Oversight, we have gone beyond just the research, but also we look at biobanks. Our research ethics guidelines were revised in 2015 to include biobanks. In terms of the guidelines any new repositories or biobanks must have prior research ethics committee approval. Before that stipulation in 2013, the research ethics committee at my university took OECD guidelines^{*5} and started working on guidelines for biobank approval. We established a Biobanks Ethics Committee, and I chair that ethics committee. When the stipulation came through in our

revised guidelines, we were already ready. So, we review and approve biobanks. This is a highly specialized committee that looks at genomics and genetics research and reviews and approves any research that involves a biobank.

9. South African ethics and regulatory instruments: other oversight committees

We have other oversight bodies. A very important oversight body is the Medicines Control Council. It's a regulatory body and a government body that you would have. It applies standards as laid down by an act of parliament, which is the Medicines and Related Substances Act, which governs the manufacture, distribution, sale and marketing of medicine. The Medicines Control Council has got an arm called the Clinical Trials Committee. When you have a clinical trial for drug development, the actual applications that the sponsor will send in parallel, one would be to the Medicines Control Council who will look at the scientific aspects of the research, although they are now looking at ethics as well, which is very good, and the other body would be the research ethics committee. This is to avoid delays. When we look at the trials, if we do approve, we give conditional approvals. The Research Ethics Committee will say, approved conditional to Medicines Control Council approval, or Medicines Control Council will say approved conditional to Research Ethics Committee approval. As soon as the two approvals come through, they will get a final unconditional approval.

^{*4} Beecher HK. Ethics and clinical research. *N Engl J Med*. 1966; 274(24): 1354-60.

^{*5} OECD guidelines on human biobanks and genetic research databases. 2009.

10. South African regulatory gaps and current standards of care discussion

What are some of our gaps or problems in terms of regulations and ethics in terms of our latest 2015 edition of our Department of Health Guidelines from the National Health Research Ethics Council, “Principles, Processes and Structures (PPS)”^{*6} (Table 3). I will say I wasn’t part of that development. It was when I stepped down. There are huge problems with the latest guidelines. I will just talk on three or four. It says right at its preamble that it will not deal with clinical trials (CTs) and yet it makes reference to CTs throughout the document. It does not take into account the National Health Act definition of CTs. When it comes to science type of research, these researchers are now confused what guidance documents to follow. It does not mention anything about post-trial provisions or about standards of care. All it says is for these aspects look at GCP guidelines, and our old GCP guidelines is of 2006^{*7}. Because of issues of HIV, standards of care and post-trial provisions are specific to HIV in that GCP document, but research has moved in the interim, and this has not been updated to take into consideration other aspects of research, which are not HIV specific. What our research ethics committees do is we look now at the Declaration of Helsinki. Our guideline documents are silent on post-trial provisions and standard of care, and we say what does the Helsinki stipulates.

We go to the higher standard that is the Helsinki, which makes it a responsibility of sponsors, researchers, and host country governments to provide post-trial access of medications. The Helsinki Declaration states that this information has to be disclosed during the informed consent process.

In terms of the Standard of Care, the Helsinki states that testing is to be done against those of best proven interventions except where none exists or where there is compelling scientific/methodological reason, one would employ a placebo in the control arm. Our research ethics guidelines at the moment looks at reimbursements for participation in trials and says that we need to pay our research participants. This can be calculated against the current hourly rate for unskilled labor in marketplace of \$1.5 per hour. We have concerns with that. How do they work this out? They view labour law to work it out, but what they have done in the process is commoditized and commercialized the researcher-participant relationship. We feel that it is important that research participants do not bear the costs of being involved in research. They need to be reimbursed for transport, meal, and out-of-pocket expenses. This needs to be calculated on an ad-hoc basis with some guidance, but not stipulation of this.

Currently work-in-progress, our Medicines Control Council is also very worried about post-trial access, especially with the problems we have in our guidelines. It has put together a document that is undergoing consultation at the moment. What this document says is very clearly the first

^{*6} Department of Health, Republic of South Africa. Ethics in Health Research: Principles, Processes and Structures, second edition. 2015. Available from: <http://www.sun.ac.za/english/faculty/healthsciences/rdsd/Documents/Ethics/DoH%202015%20Ethics%20in%20Health%20Research%20-%20Principles,%20Processes%20and%20Structures%202nd%20Ed.pdf>

^{*7} Department of Health, 2006. Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa. Department of Health: Pretoria, South Africa. 2006. Available from: [http://www.sun.ac.za/english/faculty/healthsciences/rdsd/Documents/Ethics/DoH%20\(2006\)%20Guidelines%20for%20Good%20Practice%20in%20Conduct%20of%20CTs.pdf](http://www.sun.ac.za/english/faculty/healthsciences/rdsd/Documents/Ethics/DoH%20(2006)%20Guidelines%20for%20Good%20Practice%20in%20Conduct%20of%20CTs.pdf)

Table 3 Regulatory gaps in PPS and MCC Document (guidelines)

<p>Principles, Processes and Structures (PPS)</p> <p>1.1.14 “This document does not deal with clinical trials which form the subject matter of the Department of Health’s Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, 2nd edition (2006) or its successor. However, this document includes guidance on insurance against research-related bodily injury, including in clinical trials.”</p> <p>→ PPS does not deal with clinical trials, yet reference to CTs throughout document.</p> <p>3.1.7 “Reimbursements and inducements for participants</p> <p>Participants should not have to incur expenses to take part in research. Consequently, researchers should budget to reimburse expenses incurred by participants for travel, refreshments and also for inconvenience, depending on the circumstances. If no travel or other expenses are incurred, reimbursement is not required unless an inconvenience reimbursement is justifiable.</p> <p>A fair rate of reimbursement should be calculated using the Time, Inconvenience and Expenses (TIE) method to determine the cost to participants for time expended, inconvenience and refreshments associated with research participation. This method costs expenses at the current hourly rate for unskilled labour in the market place *, regardless of whether the participant is employed. See NHREC (2012) Payment of trial participants in South Africa: ethical consideration for Research Ethics Committees.”</p> <p>* There is a footnote to indicate current hourly rate for unskilled labour in market place of R15-R25/ hour</p> <p>→ commodification & commercialising researcher-participant relationship.</p>
<p>MCC Document (Not finalized yet)</p> <ul style="list-style-type: none"> • 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 a beneficial in the trial. • This information must also be disclosed to participants during the informed consent process. • The issue of post-trial access has become very important as many patients on clinical trials who benefit from study treatment cannot access their treatment independently once the trial is completed. • This is particularly important in patients with serious illnesses requiring lifesaving therapy or treatments providing significant symptom relief which is not available from other therapies. • As participants in clinical trials have contributed significantly to the study sponsors in many ways, there is an obligation on the part of the sponsor to continue to provide study medication at no cost to all participants who are still benefiting. <p>MCC Document - Guidelines (Not finalized yet)</p> <ul style="list-style-type: none"> • All patients, private and public on medication on clinical trials must be provided with post trial access of their medication without any cost to them as long as they benefit from the medication and where withdrawal is likely to lead to deterioration of the individual health status as assessed by the investigator. • Upfront submission of a roll-over trial protocol to provide post trial access is recommended. • Care must be taken to prevent gaps in patient treatment between the original and roll-over protocols. • Details of post-trial access should be included in the clinical trial form 1, and informed consent document/patient information leaflet. • Public sector patients cannot obtain many registered medicines due to cost and essential medicines list constraints making it essential for such patients to receive therapy post-trial until the medication is available to public sector patients and not just until it is commercially available.

two bullet points are in line with the Helsinki which allows for the provisions for post-trial access and disclosure during informed consent. It goes on further to say that the issue of post-trial access is

very important in our country, because many patients on clinical trials who benefit from study treatment are not able to access their treatment independently once the trial is over. This is par-

ticularly important in patients with serious illnesses requiring life-saving therapy or treatments providing significant symptom relief, which is not available from the therapies. As participants in clinical trials have contributed significantly to the study sponsors in many ways, there is an ethical obligation on the part of the sponsor to continue to provide study medication at no cost to all participants who are still benefiting. This is the real stringent route that we have gone in the country, but it's still under discussion waiting to be finalized.

The guidelines go further to state all patients, whether private or public on medication, and the situation in South Africa is we don't have any national health insurance or universal healthcare as yet. We are very much like the United States where the rich can afford healthcare and poor go to state health facilities. All patients must be provided with post trial access of their medication without any cost to them. As long as they are benefiting from the medication, they must be provided, because if we are going to withdraw the treatment, this could lead to deterioration in their health. If the sponsor feels that rather than providing post-trial access, have a phase IV post-marketing trial, (the roll-over trial), then there is an expectation that there must be an upfront submission at the time of submitting the phase III, submit the phase IV of the roll-over trial. It is very important they also said that care must be taken to prevent gaps in

patient treatment between the original trial and the roll-over trials. There has got to be continuity of getting that intervention. They also say all these details must be included in all the documents including the informed consent document. Then, another stipulation it makes is that public sector patients cannot obtain many registered medicines. It can have a drug and it gets registered, but it does not become part of the standard of care, and this is because of cost, it's too expensive, and we have an essential medicines list, which will have certain number of medications only. It is constrained in that the intervention that has been proven to be effective may not be part of that essential medicines list at that stage, and therefore, it is essential for such patients in the public sector to receive the therapy post-trial until the medication is available in the public sector, not only until it is commercially available. Because these are some of the things that the pharmaceutical industry has been trying to do and saying, we will provide post-trial access until it becomes commercially available, but transactional cost won't make it possible for those that cannot afford and so this would take care of all that.

I must tell you that IPASA (Innovative Pharmaceutical Association of South Africa) is not happy with this guideline, and so they are in the process of preparing a very strong response against this.

Thank you very much for your attention.



< Q&A >

Organizer (Chieko Kurihara) Thank you very much Professor Dhai, we learned so much from South Africa, where people's history and social background is much different from ours, and people have developed basic structure of research ethics and regulations, as well as principles and practice. In Japan, the issues of drug promotion-oriented clinical researches conducted by companies led to proposal of the Clinical Research Act. Companies and researchers should rethink about their target of research and development, learning from the society where people who need drug cannot access to their essential drugs and where people have developed such robust research ethics framework. This is my motivation of proposal and planning of today's seminar.

Organizer (Yuzo Nabeoka) Earth's atmosphere is becoming hot and communicative disease is increasing. Some pharmaceutical companies provide free license to research for this kind of disease. It will be good opportunity for the African people to develop evidence for this kind of disease, not only for African people but also for the world.

Dhai The whole issue of climate change and



Yuzo Nabeoka, one of the organizers of this seminar, a member of Clinical Research Risk Management Study Group.

environmental impact it has together with the impact on health has become a bioethical issue as well. It is very important for us in our institutions in Africa and throughout the globe to develop these public-private partnerships and work together because after all it's one common goal.



Chieko Kurihara, at the time of introductory presentation before Professor Dhai's lecture, as a member of Clinical Research Risk Management Study Group.



Professor Dhai, during the lecture.

Q Is Medicines Control Council only involved in new drug review?

Dhai The Medicines Control Council in terms of the Medicines and Related Substances Control Act will be involved in new drug review, or new applications for a drug that is already registered but not for that particular application. It's just involved in that. The National Health Research Ethics Council is involved in all types of health-related research as per the definition of the National Health Act.

Q How many ethics committee do you have in your university?

Dhai In my university in terms of research, we have three research ethics committees. It's a very large university, 35,000 students, 5,000 staff members. We have one called Human Research Ethics Committee – Medical. This is the Committee that I serve on that has been established since 1966. Later on in time in the early 2000s, there was the establishment of the Human Research Ethics

Committee – Humanities/Non-Medical. They would look at all research that does not fall under the definition of health research as per the National Health Act. Oftentimes, from the humanities disciplines, you will find that research is sent to us at the medical school, because of the impact on health. We see a lot of social sciences and lot of psychology research. If there is maybe an engineering type of research, the Humanities Committee may look at that to ensure that the science is good and there is going to be no adverse effect on humanity as well. Then, we have got one Animal Research Ethics Committee.

Q How often do the Ethics Committee for Clinical Research meet?

Dhai We meet once a month. We have two arms of that ethics committee. We have the industry related research and the investigator-driven research. We have about 10 clinical trials a month from the industry related research and we have between 80 and 90 research projects a month, which

are new protocols, investigator-driven, and this could be highly complex research funded by international research organizations to simple retrospective studies done by students. That's the entire 80 or 90, sometimes going to a 100 just before an exam period. What happens is we have two separate administrative bodies. One administrative body that looks at the clinical trials, because you need much more there. You need the serious adverse events committee. You need to monitor the data safety monitoring board reports and the monitor reports etcetera. So, the admin is quite heavy there. The medical school formed a Section 21 company that's not a non-profit organization company, and it works on those clinical trials independently of our research office. They charge for review of trials and that is why it can put so much into administration. There is a payment for amendments as well. If you send in a trial that is very badly written and, that requires lots of amendments, and we say to you, you have got to rewrite and resubmit, you pay again as if you are submitting a brand new trial. It's a high amount. They may pay over a 10,000ZAR, which is 10,000ZAR, divided by seven, and you will be able to account for Yen.

But for our investigator trials, there is no payment at all, because this is covered by amongst others, fees and indirect costs from grants. We did not have top-heavy support for our admin for our investigator-driven trials and the range. With a lot of advocacy to the university there has been quite a change, and you will find that the Centre has extended to include research ethics administration and from one admin person we are now into three.

Q How long does it take to review such numbers of clinical trials?

Dhai The process is the chairs, we have one chair and four co-chairs, and we divide the trials amongst us so there is an in depth review of each

trial by each chair, but the trial is also sent out to the entire research ethics committee together with two in depth reviewers from the committee. It takes a long time. We are in the process of going electronic, so we are expected to review on a laptop. But I will say, no, you send me a paper copy, because I take it home and I wake up at 3 o'clock in the morning to do my reviews. You don't get paid extra, because you are balancing your faculty commitments between the reviews and some of us are passionate about what we do. We have been activists during the apartheid regime, and we continue being activists, and this is my time of activism and contribution to the needs of our country. It takes me sometimes 2 or 3 hours to review one thick investigator brochure and then read it alongside our research ethics application, but then I am given two or three a month to look at, and then I am given about six investigator-driven trials to look at. What we also do is we have a process of expedited review. All retrospective studies will be reviewed by our overall chair, Professor Cleaton-Jones, together with one other. Usually the students' studies get done through an expedited route, so it does not come to us, and co-chairs will chair all the overall ones, but again in our investigator-driven trials depending on the expertise and the background of the individual, each investigator-driven research is also reviewed by two in-depth reviewers. In terms of our guidelines, research ethics committee members and researchers now have to have research ethics training on a 3-year basis. It's when you are looking at it, not only do you ask in terms of the science, but you also ask about the ethics, it's got to be from an informed perspective. When the audit happens, then the National Health Research Ethics Council looks at the research ethics committee membership and looks to see whether all of us do have research ethics training and when was the last training. There is also a need for all of us to have



The left is Hiroshi Watanabe, Hamamatsu University School of Medicine/National Center for Global Health and Medicine, an invited chairperson for Professor Dhai's lecture.

GCP training which is different as well.

Q Why did it take such a long time, 17 years, after Nuremberg Code was published until 1964 when Helsinki Declaration occurred?

Dhai I wish I could put up my other set of slides and take you through post-Nuremberg to Helsinki. The attitude from the west was that the Nuremberg Code was for a particular type of research. It was for a barbaric, autocratically run country, which was Germany. It was not for people from the west. There were attitudes against the Nuremberg Code right from the outset. The other thing is researchers in the past were self-regulating, so they didn't feel the need to have someone to actually pressurize them into thinking ethics. They felt they were managing well without this. However, what happened was between the Nuremberg Code and the Helsinki, there were many atrocities in the west that started surfacing. If you look at it, there is the Willowbrook Trials, hepatitis transmission experimentation, where those that were mentally challenged were institutionalized and were made the subject of research. In fact, there were about 54 atrocities within the United States itself that

Beecher exposed in his article in 1966. It was because of this, but together with , the history of the World Medical Association, which first started off as a doctor grouping looking at clinical care, in the late 1940s. Soon after the Nuremberg, early 50s, they got together in Paris and felt that it was doctors that were involved in the Nazi war atrocities as well, and therefore, something had to be done for research. It was an international declaration. It took many years to get consensus between the different national medical associations. It's very, very interesting, if you are going to the World Medical Association to look at how challenging this whole process was, but they eventually got there in 1964.

Chairman (Hiroshi Watanabe) Today in the first part of this seminar we discussed various issues of clinical research in Japan, and then in the second part we learned from Professor Dhai about research ethics from international perspective. We appreciate that she appraised the contribution of Japan in the process of development of "Singapore Statement on Research Integrity" initiated by OECD. We learned much about the situation in

South Africa, where people have struggled with various social issues. We also learned that such experience of the people has led the development of robust thinking of research ethics and regulations.

We wish to continue partnership with Professor Dhai and the people who are engaged in medicine and medical ethics. Thank you very much.

Program of the seminar

Japanese new law on clinical research and human research ethics in South Africa Development and ethical partnership toward global health

Sept 29, 2016, Thursday, 15:00-18:00

Venue: Mitsui Sumitomo Insurance, 14F 1402-03

Agenda:

Japanese new law on clinical research is going to be issued to regulate clinical research to find safety or efficacy of medicinal product. Especially the research of unauthorized products or research funded by a company is to be strictly regulated by this law, with additional requirement of prior submission to regulatory authority. The law will also install legal framework of ethics committee. Furthermore, the law requires information of company's research funding to be disclosed to public. Such regulatory framework was proposed responding to recent affairs of scientific misconducts and retractions of papers from high-impact factor journals, as the results of some of inappropriate relationship among academic researchers and companies. The new law is expected to restore confidence of Japanese research and to contribute to healthcare improvement.

On the other hand, in South Africa, as the consequence of abolishment of apartheid and as the conquest of liberty of people, they established in 1996 the Constitution to assure human dignity and to prohibit human experimentation without informed consent. Their GCP regulation under pharmaceutical law covers clinical trial not limited to such trial aiming at product approval.

In recent world trend to promote international collaborative clinical development toward global health, we should find desirable and ethical path of drug development for people most in need, and how funding should be designed. We would like to provoke discussion as the first step toward ideal and ethical international partnership toward global health.

Lectures:

Dr. Yuso Tomohira, Japan Pharmaceutical Industry Legal Affairs Association (JPILA)

“Japanese new law on clinical research and future perspective” (in Japanese)

Prof. Ames Dhai, Steve Biko Centre for Bioethics, University of the Witwatersrand

“Research regulation and bioethics in South Africa” (in English)

Chairpersons:

Prof. Hiroshi Watanabe, Department of Clinical Pharmacology and Therapeutics,
Hamamatsu University School of Medicine/National Center for Global Health and Medicine

Dr. Takayoshi Tokuyasu, Japan Pharmaceutical Industry Legal Affairs Association (JPILA)

(English-Japanese explanation (not direct interpretation): Chieko Kurihara)

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