

Trend of research ethics and conflict of interest management in Korea and Taiwan: — Common sense in the world but uncommon in Japan ^{*1} —

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Abstract

In Korea the Bioethics and Safety Act was expanded in 2012 and in Taiwan the Human Subjects Research Act of 2011 and the Human Biobank Management Act of 2010 were established. In these countries a wide range of research involving human subjects and biobank projects have come to be regulated by legally-binding regulations, which cover research activities outside of pharmaceutical laws to regulate clinical trials aiming at new drug or new indication applications. In both countries leading research institutes are getting accreditation of AAHRPP (The Association for the Accreditation of Human Research Protection Programs, Inc.), the organization of the United States. Additionally in Korea, rebate taking of medical professionals became strictly prohibited.

These developments are prerequisite lessons for the Japanese research community where recently many cases of scientific misconduct in clinical research have been uncovered and where people are discussing about establishment of laws to regulate a wider range of clinical research.

This article introduces the actual situations of both countries based on the author's visits to Korea in 2013, Taiwan in 2012; and based on academic meetings where experts of these 2 countries provided lectures, held in Tokyo at the end of 2013.

We should avoid such a situation in which the Japanese research community is laughed at by the international research community for such lack of common sense about the regulations of clinical trials and conflict of interest management.

Key words

Bioethics and Safety Act, Human Subjects Research Act, Human Biobank Management Act, clinical trial, rebate

Rinsho Hyoka (Clinical Evaluation) 2014 ; 42 : 591-610.

^{*1} Original version of this article is in Japanese and is included in the Japanese journal *Rinsho Hyoka (Clin Eval)*. 2014; 42(2): 467-84.

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1. Introduction

Recently in Korea and in Taiwan, a wide range of laws on research involving human subjects were established and in Korea a medical law was revised to prohibit rebate taking of medical professionals. The following points are common in both countries unless specifically described otherwise:

- (1) Drug clinical trials are covered by GCP (Good Clinical Practice) regulations under the pharmaceutical law (not limited to the ones aiming at new drug application).
- (2) Other research involving human subjects is covered by other laws, aiming at human subject protection and/or bioethics.
- (3) Clinical trials using an approved drug is regulated by GCP if there is an intention of application for a new indication.
- (4) Leading research institutes are getting accreditations of AAHRPP (The Association for the Accreditation of Human Research Protection Programs, Inc.), the organization of the United States.
- (5) In Korea, rebate taking of medical professionals became strictly prohibited.

All of these points are prerequisite for the Japanese research community where recently many cases of scientific misconduct in clinical research have been uncovered and where people are discussing about establishment of laws to regulate a wider range of clinical research.

This article introduces the above mentioned situations based on the author's visit to Korea in 2013 and on academic meetings where experts of these 2 countries provided lectures, held in Tokyo at the end of 2013. Most part of this report is about the situation in Korea but the situation in Taiwan is reported in another article by the above mentioned expert in this journal issue ¹⁾.

2. Implementation of Bioethics and Safety Act and AAHRPP accreditations in Korea

2.1 The momentum of my visit to Korea

Prof. Bomoon Choi, the Catholic University of Korea informed me that on September 27, 2013, she and her colleagues are going to have a symposium concerning the rebate issue between pharmaceutical companies and medical professionals. Prof. Choi made a presentation on the issue of "vulnerable groups" ²⁾ at the Expert Conference on the Revision of the Declaration of Helsinki held in Tokyo, in the spring of 2013 (Photo) ³⁾.

She is also a translator of the "On the Take" by Kassirers ⁴⁾, who was the editor-in-chief of *New England Journal of Medicine*, previous to Marcia Angel who was also the editor-in-chief after him and wrote "The truth about the drug companies" ⁵⁾.

I visited in August and September the following 4 institutes (the month and year is of AAHRPP accreditation) in Seoul in order to attend this symposium as well as to follow the situation after expanding the Bioethics and Safety Act; and to fol-



Prof. Bomoon Choi, Department of Psychiatry, School of Medicine, The Catholic University of Korea, lecture at the Expert Conference on the Revision of the Declaration of Helsinki, held in Tokyo, March 1, 2013

low the situation of application/accreditation of AAHRPP, which I reported in the previous publications in this journal^{6,7}.

- **Seoul National University Hospital (December 2012)**
- **Severance Hospital, Yonsei University (June 2010)**
- **The Catholic University of Korea (June 2010)**
- **Asan Medical Center (December 2013)**

Other AAHRPP-accredited institutes in Korea are Samsung Medical Center (June 2006) and Kyung Hee University Hospital (September 2013)⁸.

Here I describe the findings according to the order of my visit.

2.2 Seoul National University (Photo)

On August 26, 2013, I visited Seoul National University Hospital (SNUH) and interviewed with Prof. Jun-Soo Kwon, Chairman of the Department of Psychiatry; Prof. Ock-Joo Kim, Director of the Center for Human Research Protection (CHRP), and being introduced by Prof. Kim, visited Medical Research Collaborating Center (MRCC) of SNUH.

(I) Interview with Prof. Jun-Soo Kwon

Prof. Kwon has wide experience as a global prin-

cipal investigator (PI) of multi-national clinical trials by global companies. More about his work is reported in my previous article⁹. I discussed with Prof. Kwon about the situation after the implementation of Bioethics and Safety Act and AAHRPP accreditation (Photo). Prof. Kwon told me that research management of SNUH is becoming stricter. Not only experimental clinical trial but also cohort observational study is audited by CHRP. For the AAHRPP accreditation, the staff of AAHRPP coming from the US interviewed all the PIs and they conducted other kinds of surveys. Both of



Prof. Jun-Soo Kwon, Department of Psychiatry, Seoul National University Hospital, August 2013



Seoul National University Hospital, August 2013

AAHRPP and SNUH- CHRP interviewed him and inquired about his detailed knowledge concerning human subject protection, e.g., informed consent process, GCP regulations.

It is also becoming stricter to regulate donations or other kinds of support from pharmaceutical companies, after the revision of the law to regulate the rebate issue. Several years ago, companies could give donations of buildings and other kinds of facilities to the university, but recently both the government and the university have come to restrict such activities. It is also becoming impossible for a company to support academic meetings held inside of the University. As for the company-supported clinical trials, everything is defined in detail by the contract, including the honorarium paid to the investigators and CRAs (clinical research associates).

(2) Interview with Prof. Ock-Joo Kim and visit to CHRP and MRCC

On the same day, I visited Prof. Kim at the CHRP. She previously allowed me to observe the IRB meeting in the Seoul National University and my interview with her^{6,7)}. She introduced me to the entrance of the building where a plaque is displayed with the words “Center for Human Research

Protection” (Photo). It does not mean that whole the building is occupied by the center but it shows the importance of the role of this center. Prof. Kim introduced her CHRP staff at the office and showed me the certification of AAHRPP accreditation (Photo). According to Prof. Kim, in the Korean regulatory framework, clinical trials of an approved drug in the range of authorized label can be conducted without



Entrance of the building with the plaque of “Center for Human Research Protection”, August 2013



Left: Prof. Ock-Joo Kim, right: author, August 2013



Medical Research Collaborating Center, August 2013

permission of the Korean Food and Drug Administration (KFDA) under the Pharmaceutical Affairs Law. But even in such a case, it is covered by the Bioethics and Safety Act. Therefore, the CHRP audits research according to a risk-based classification. If the research governance system of the institute is reliable, the government commissions the institute to audit their research.

Then I visited the Medical Research Collaborating Center (MRCC) (Photo). This center was established around 2004, after benchmarking Pennsylvania State University in US. The number of the starting staff was 7, but now it is about 30. Some design-

nated staff support 1 project continuously through protocol development, peer review, statistical analysis, and medical writing. They serve as a data management center with a US-FDA-validated system. They do not conduct monitoring. In the case of a company-initiated clinical trial a CRO contracted by a company will be engaged in monitoring.

2.3 Asan Medical Center (Photo)

On August 29, I visited the Asan Medical Center (AMC) and interviewed Dr. Ki-Eun Choi, Unit Manager of the Institutional Review Board Administrative Support Unit, and discussed about their



Asan Medical Center, copyright: AMC



From the right: Dr. Seung-Jun Oh, Associate professor, Department of Nuclear Medicine, author, Dr. Ki-Eun Choi, Unit Manager, Institutional Review Board Administrative Support Unit, Ms. Min Jeong Cho, research nurse specialist, Dr. Sang-Ju Lee, Department of Nuclear Medicine, Asan Medical Center, August 2013

situation of applying for AAHRPP accreditation, IRB review system, and post-marketing study, being supported by Dr. Seung-Jun Oh, the Department of Nuclear Medicine (Photo).

(1) Application for AAHRPP accreditation

AMC got recognition of FEACAP (Forum for Ethical Review Committees in the Asian and Western Pacific Region) in 2006 and next year applied for AAHRPP. Then the hospital already submitted all the related data and was waiting for final evaluation and decision by the AHRPP (actually got accreditation in December 2013). In March 2013, two people came from AAHRPP for inspection of the hospital and had meetings and interviews in which they reviewed the personnel and system. FERCAP was easier as it is only for IRB, but the AAHRPP is nearly nine times more difficult, as it concerns approval for the whole hospital: facility, researchers, medical doctors, IRB and any other system.

As for the hospital accreditation, AMC already received AGS (Asan Global Standard) which is the same system as the JCI (Joint Commission International, international version of hospital accreditation by US organization) but domestic organization.

The reason why the AMC applied for AAHRPP accreditation is that one global company Pfizer chose 10 excellent institutes in the world for early phase clinical trials of their products. The AMC was selected for one of these. This company supported the initial cost of the application as they wanted to conduct their trials at an AAHRPP-accredited hospital. As the company invests much money for development of their products, naturally they want to get correct, standardized data from all over the world.

Another reason was that the US-FDA and EMA (European Medicines Agency) audit and review all documents. If there is AAHRPP accreditation, for these regulatory authorities only additional data are required. I asked whether other global companies can use this AAHRPP accredited facility under the same conditions or is there any priority for this funding company. They answered that there are no conditions, as such a priority may cause conflict of interests. This company pays the accreditation application fee but does not pay for hospital management. So the benefit, return of the investment of this company is the fact that the company

can designate AMC as one of the 10 excellent institutes in the world for their conduct of early phase clinical trials.

(2) IRB review system

AMC has a total of 88 IRB members assigned to 6 IRB panels that have 9 board meetings per 1 month. There are 15-25 members in each panel, depending on the panel. Each panel reviews 3-5 new protocols in one meeting. Approximately 1,300 new projects are reviewed in a year at AMC. Among these, 800 protocols are approved, others are rejected. The total number of the protocols to be reviewed, including 1,300 new ones and reevaluation of others, is about 15,000. There are both IITs (investigator-initiated trials) and SITs (sponsor-initiated trials). For all the IITs, PIs and patients/participants are at their hospital. If you want to conduct an IIT study, all the patients should be in AMC. In case of a multi-center trial, they only review patients in AMC. AMC does not review as a central IRB; they do not engage in a joint review. They are only concerned about being responsible for their own hospital's patients. This is the same for both cases of IITs and SITs. AMC is concerned only about their own patients. KFDA (Korean FDA) is concerned about all patients. In the case of a multi-center trial, there are such cases in which AMC rejects the protocol although some other institutes approve it. As for evaluation of manufacturing, it is not the IRB's concern. Even for in-house manufactured radiopharmaceuticals, evaluation of quality control is KFDA's concern, not the IRB's responsibility. IRB review is for the patient protection side, while KFDA reviews everything.

(3) Post-marketing study

Compared to other hospitals, the principle of AMC is to reject PMS (post marketing study) generally. For new drugs, there is no problem of PMS of SIT, but in many cases, there are some legal problems in IITs using already approved drugs. So

mainstream of the practice of AMC is not to accept a phase 4 study. Because in a phase 4 study, the company provides their drugs and provides some other fees to the hospital or hospital staff. Sometimes this kind of money may be regarded as a rebate. If the company conducts a phase 4 for application for a new indication or data to be used for promotion, they submit to the KFDA for conduct of a clinical trial. This kind of phase 4 is a real clinical trial, with a real protocol, and there is no problem of rebate, so such a trial is acceptable. However, the clinical trials without submission to KFDA are not acceptable, even if the trials are conducted under the Bioethics and Safety Act. In the case of a phase 4 clinical trials of an already approved indication with an already approval label, this is something like a drug company person telling the doctors how to use this drug. This is one kind of rebate.

2.4 Severance Hospital, Yonsei University (Photo)

On September 26, I visited Severance Hospital, Yonsei University. Not only AAHRPP accreditation (Photo), this hospital also obtained hospital accreditation of JCI (Joint Commission International) (Photo). I briefly interviewed Prof. Sung-Young Rha, Director of Human Research Protection Center (HRPC); Vice Director of Yonsei Cancer Research Institute and discussed with three IRB analysts of HRPC (Photo).

According to Prof. Rha, the culture of research is now becoming mature and a higher level of ethics is coming to be required. If you work with a global company and conduct clinical trials, it is essential to establish the process of HRPP. The positive impact of acquiring AAHRPP accreditation is to increase the number of clinical trials carried out by global companies. AAHRPP accreditation is also beneficial as it facilitate better interaction with U.S. organization, including the case of FDA



Severance Hospital, Yonsei University, September 2013



Monument of the accreditation of JCI (Joint Commission International), Severance Hospital, Yonsei University, September 2013



The two IRB analysts of the Severance Hospital, left: Dr. Yang-Hee Noh; right Dr. Sin-Young Park; and center: author, Severance Hospital, Yonsei University, September 2013



The certification of AAHRPP accreditation, Severance Hospital, Yonsei University, September 2013

inspection. For the establishment of this system, specific governmental funding was not provided. There is no other external funding.

JCI is for ordinary medical practice and AAHRPP is for research. For both, a team of each organization in the U.S. comes for audits and conducts detailed interviews with the hospital staff.

2.5 Catholic University of Korea (Photo)

On September 27 I visited the Clinical Research Coordinating Center (CRCC) of St. Mary's Hospital

(also JCI-accredited hospital, Photo), Catholic University of Korea and met Prof. Hyeon-Woo Yim, Department of Preventive Medicine, Medical College, The Catholic University of Korea and IRB Chairman, and Dr. Ryang-Soon Lim, Manager of the Office of Human Research Protection (OHRP) (Photo). They explained about the HRPP (Human Research Protection Program), quality assurance system, and Central IRB review of the Catholic Medical Center (CMC) and the Medical College of Catholic University of Korea.

(I) Management of HRPP

The CMC has OHRP and CEB (CMC Executive Board for HRPP) to cover all the 8 affiliated hospitals and a medical campus, and HRPP for all the 9 institutes which are accredited by AAHRPP in 2010. There are 14 IRB panels in the CMC and medical campus. Five out of the 14 IRB panels are in Seoul St. Mary's hospital which is the biggest hospital in the CMC. The composition of CEB is the chairman or director of the IRB of each institute, and this CEB coordinates opinions of each

IRB or OHRP and makes decisions for renewing policies.

For successful operation of HRPP and IRB administrative office or OHRP, the key component is a good relationship with the Clinical Trial Center. OHRP provides an e-learning system which clinical researchers can access and get certification after completing e-learning. OHRP will conduct an audit once or more in a year and check the level of each institute's QA/QI (quality assurance/quality improvement) program. There are now 10



St. Mary's Hospital, Catholic University of Korea, September 2013



JCI accreditation, St. Mary's Hospital, Catholic University of Korea, September 2013



From the left: Prof. Hyeon-Woo Yim, Department of Preventive Medicine, Medical College, and IRB Chairman, and Dr. Ryang-Soon, Manager of the Office of Human Research Protection, The Catholic University of Korea, September 2013

full time staff in the IRB compared with only one half-full time equivalent staff in 2007. The expansion of the Bioethics and Safety Act does not have much impact because The Catholic University of Korea already has a wide range of regulations for human research. As for the clinical trials of a marketed drug, if a sponsor does not have an intention to add a new indication or to use the research results for promotion, KFDA approval is not necessary. This kind of clinical trial of an approved drug conducted without KFDA approval is covered by the Bioethics and Safety Act.

(2) Central IRB and primary reviewer system

Central IRB at CMC (Catholic Medical Center) is the only IRB which is operating successfully in Korea. Each IRB trust each other because they review according to the same criteria based on AAHRPP. If the research is collaborative research by more than 2 of these group hospitals, it should be reviewed by this CIRB. Even if the research is by only 2 of the group of institutes, the CIRB members are composed of all the institutes. On the other hand, this CIRB does not review for collaborate institutes outside the group, which means outside the AAHRPP-accredited HRPP. Approximately 5 or 6 new research protocols are reviewed at CIRB every month. In 2012, the number of new protocol reviews was 2,493, and the total number of reviews was 18,241, at the Catholic Medical Center.

They use the primary reviewer system for new protocols: professional knowledge for protocols as well as non-scientific view for protection of participants is necessary, so for 1 protocol, 1 primary reviewer is a scientific specialist; 1 is a non-scientist; 1 is a statistician; and 1 is a pharmacist to check feasibility of management of the product. Four of the Review board members are assigned for in depth reviewing of a research protocol. Sometimes 1 person is assigned as the primary reviewer of 2

or 3 protocols at one IRB meeting. All review board members should review according to the check lists. In particular, the chairperson has to review the details of all of the protocols.

At the full meeting, primary reviewers present their review, give their opinions and discuss with other members, and the chairman summarizes. Then the primary reviewers suggest their opinions again, and then make the final decision by voting. This process follows “Robert’s Rules of Order”, which is for parliament management. The voting is by raising hands. This voting system was introduced by 3 CMC (Catholic Medical Center) IRB members who have finished the Western IRB training program in U.S. funded by the educational program of the Ministry of Health. Approval of the research should be based on approval of majority.

(3) Momentum of application to AAHRPP

The first reason they applied to AAHRPP was that in 2007 they attended FERCAP and found differences from AAHRPP as FERCAP is only for IRB. There are many advantages of obtaining AAHRPP to increase the value of the institution. There was no funding for accreditation. By this accreditation, it becomes easy to get an investigation from the regulatory authority, not only KFDA but also US-FDA. At the beginning, it was in 2009 that leadership of the university started establishment of HRPP because there was a case in which some researcher published some research results without obtaining IRB approval. At the time of starting the program, there were many objections from researchers; there were complaints every day. But now there are no such complaints. People engaged in HRPP explained to these researchers that they are not inspectors but engaged in scientific and ethical support for researchers. There was another case in which CRC wrote the signature on the informed consent document instead of the Principal Investigator. At this time OHRP decided

to stop all the research for 6 months and the staff was put through an ethics educational program.

3. Symposium on rebate issue in Korea

On September 27, 2013, I participated in the symposium open to the public, titled “Physician Professionalism Crisis: Beyond Dual Punishment System in Korea”, held as the 4th Medical Ethics Symposium of the Medical Ethics Academy, under the auspices of the Korean Society for Medical Ethics, at the Faculty Conference Room of Yonsei University Health System Administration building (Photo). In Korea, the Medical Affairs Law was revised in 2011 and the “dual punishment system” was implemented. This means that if a pharmaceutical company provides economic benefit to medical professionals and this comes to be an inducement for buying this company’s product, not only this company is punished but also the medical professionals who receive this rebate are punished. There are several numbers of cases of accusations.

A lecturer from abroad was Dr. Matthew K.

Wynia, American Medical Association (AMA) (Photo), and I participated in the round-table discussion that involved a mixture of the languages of English and Korean. Dr. Wynia made a presentation titled “Sunshine, rebates, gifts and trips: US physicians’ relations with pharmaceutical compa-



Lecture by Dr. Matthew K. Wynia, American Medical Association, at the symposium “Physician Professionalism Crisis: Beyond Dual Punishment System in Korea”, the 4th Medical Ethics Symposium of the Medical Ethics Academy, under the auspices of the Korean Society for Medical Ethics, at the Yonsei University, on September 27, 2013



“Physician Professionalism Crisis: Beyond Dual Punishment System in Korea”, held as the 4th Medical Ethics Symposium of the Medical Ethics Academy, under the auspices of the Korean Society for Medical Ethics, at the Yonsei University, on September 27, 2013

nies” (not representing a policy of the AMA unless specifically saying otherwise). He introduced the “Sunshine Act”, legal background of “rebates” applied to physicians, and guidelines of AMA on this issue. Dr. Seong-Soo Hong, Korean physician, Trinity E.N.T Surgical Center gave the lecture “Dual punishment system issue from a primary care physician’s perspective” and advocated that this dual punishment system is unfair as there is no grace period for guidance and no safe-harbor or buffer zone such as self-regulations, in such a situation where the medical cost is strictly suppressed, which causes the crisis of the professionalism (Photo). His opinion was already published in this journal¹⁰⁾. Dr. Kyungsun-Kyle Choi, Korean Lawyer, Law Firm, KIM & CHANG, gave the lecture “Overseas anti-kickback regulation/Legal analysis” and compared laws of US, Japan and Germany and cautioned about the too strict rebate regulations. She mentioned about Japanese regulations which have a wider range free from regulations compared with other countries. She also introduced

well-known fines of pharmaceutical companies defined in the US court of justice as applications of False Claims Act (14 cases including biggest 3 billion USD in the case of GlaxoSmithKline), as well as the fact that German prosecutors have applied Criminal Act 299 to indict and prosecute 3,400 cases for pharmaceutical companies that have provided illegal rebates. Dr. Myounghoon Kim, the president of the Korean Society of Pharmaceutical Medicine (Bristol-Myers Squibb Company) gave the lecture “Dual punishment system on rebate; A pharmaceutical company’s perspective” and discussed about promotion activities, lecture meetings produced by companies, investigator or company-initiated clinical trials, and observational studies.

The panel discussion was chaired by Prof. Ock-Joo Kim. Prof. Bomoon Choi participated as a panelist. I explained about the valsartan issue and mentioned that the problem in Japan is opposite as medical professionals are not punished unless they are government employees. A Korean specialist said that GDP of Japan is higher and the back-



Question and answer session after the lecture of Dr. Seong-Soo Hong, Korean physician, Trinity E.N.T Surgical Center, at the symposium “Physician Professionalism Crisis: Beyond Dual Punishment System in Korea”, the 4th Medical Ethics Symposium of the Medical Ethics Academy, under the auspices of the Korean Society for Medical Ethics, at the Yonsei University, on September 27, 2013

ground situation is different; in Korea the situation is very severe as medical expenditure is strictly suppressed. From this discussion, I felt as if they are saying “Japan is a rich country so that if there is wasteful expenditure people do not complain so much against medical professionals and the government is not so eager to strengthen regulations on rebates. In Korea, we are in a very severe situation where medical expenditure is strictly suppressed and support from companies is restrained but called for ethical, credible practice of medicine and conduct of medical research.”

4. Discussion at academic meetings in Japan: Laws on research and AAHRPP accreditations in Korea and Taiwan

In December 2013 Rinsho Hyoka Kankokai Inc. (Clinical Evaluation, publisher of this journal) invited lecturers from national universities of Korea and Taiwan, who were the directors of AAHRPP-accredited Human Research Protection Centers and they lectured at 2 meetings (Box): at the Japanese Society of Clinical Pharmacology (JSCPT) they lectured about the AAHRPP-accredited system and at the Japanese Association of Pharmaceutical Medicine (JAPhMed) they lectured about a recently established legal framework to protect human research subjects, responding to social debate.

AAHRPP-accredited institutes in Taiwan are the National Taiwan University (December 2012) introduced here and Taipei Medical University Hospital (March 2014)⁸⁾.

4.1 Expansion of the Bioethics and Safety Act and AAHRPP-accredited HRPP in Seoul National University Hospital

Expanding the Bioethics and Safety Act and

HRPP in Seoul National University Hospital were already reported in this journal^{6,7)}, so this report summarizes additional information based on the lectures by Prof. Ock-Joo Kim and discussion before and after.

(1) Expansion of the Bioethics and Safety Act responding to the Hwang scandal¹¹⁾ (Photo)

Establishment of an embryonic stem cell derived from human-cloned embryo by Hwang Woo Suck who used to be a professor of the Seoul National University was concluded as a fabrication by the reports of the Seoul National University and Korean prosecutor office in 2006. The international community was amazed at the number of eggs, 242, that had been reportedly used for establishing only one stem cell line in 2004 paper and 185 for 11 cell lines in the 2005 paper. International societies expressed concerns over the possible exploitation of women. Soon after the investigation of the university, the Center for Disease Control and the police could conduct investigations, which was because, research using a human embryo could be a violation of the Korean Bioethics and Safety Act,



Lecture by Prof. Ock-Joo Kim on the Korean Bioethics and Safety Act, at the seminar of the Association of Pharmaceutical Medicine (JAPhMed), Tokyo, December 6, 2013

Box

主催：(財)日本製薬医学会 共催：臨床評価刊行会



一般財団法人 日本製薬医学会

アジアにおける医学研究制度 —逸脱事例の克服と包括的な被験者保護制度の立法—

2013年12月6日(金) 15:30～18:30

アストラゼネカ(株)東京支社 丸の内トラストタワー本館8階 会議室

<事前登録推奨セミナー>
詳細は裏面を
ご参照ください。

1. 韓国と台湾における被験者保護

栗原 千絵子

放射線医学総合研究所分子イメージング研究センター

2. 韓国における生命倫理安全法

：Hwang Woo-Suk スキャンダルと法の拡大とその影響

Ock-Joo Kim,

College of Medicine, Seoul National University

3. 台湾における人体研究法とバイオバンク法

：同意なき研究と研究規制の改革

Ian Chen

National Taiwan University Hospital

4. 日本における再生医療推進法とその他の研究管理体制

宮田 俊男

特定非営利活動法人 日本医療政策機構

エグゼクティブ・ディレクター

In Korea, there was a scientific misconduct of the report of cloned embryo-derived embryonic stem cell, and Bioethics and Safety Act was developed and expanded through the discussion on this issue.

In Taiwan, there was the ethical issue gathering samples of ethnic group without informed consent, and Human Research Act and Biobank Act had been developed. In Japan, iPS cell researcher won Nobel Prize, and Regenerative Medicine Act was developed. On the other hand, there has been several number of deviations: unauthorized cell therapy for Korean medical tourists; deviation of ethical guidelines; fake presentation of iPS clinical research; scientific misconduct of large size multi-center clinical trials funded by pharmaceutical company; fake data gathering in the registered clinical trials under the Pharmaceutical Affairs Law. We discuss how we should develop research governance framework learning from Asian countries.

(同時通訳なし/日本語解説・講演あり)

Some of the IRBs (institutional review boards) in Korea and Taiwan conduct full review of 10 to 30 first submitted human research protocols in one time committee meeting. Some of Japanese may think it easy way, however, actually, they are introducing human research protection program in the style originally developed in United States and review protocols focusing on ethically scientifically critical points, in efficient way. It is obvious that research review should be conducted from view of "ethics" and "science". Additionally, efficient and appropriate distribution of limited financial and human resources is also prerequisite for sustainable assurance of human subject protection. In this symposium, we discuss with specialists from South Korea and Taiwan who are engaged in Human Research Protection Program at their research hospitals, learning from them about "efficiency", as well as other ordinal issues of human subject protection. We wish to learn more about research ethics in Asian countries, considering world trend where reformation in United States of regulation of human subject protection and in European Union of EU Clinical Trial Directive.

(同時通訳なし/日本語解説・講演あり)

第34回日本臨床薬理学会学術総会「新しい世代の臨床薬理学」

会期：2013年12月4日(水)～12月6日(金)

会場：東京国際フォーラム (東京・千代田区)

会長：内田英二 (昭和大学研究推進室・教授)

学術総会参加者対象

関連シンポジウム

第34回日本臨床薬理学会学術総会 アジアにおける倫理審査・ 被験者保護システムの動向 — 効率性・科学性・倫理性 —

2013年12月6日(金) 9:00～11:00
東京国際フォーラム ホールC

1. Human Research Protection Program and IRB
review in Seoul National University Hospital
Ock-Joo Kim, M.D., Ph.D.

College of Medicine, Seoul National University

2. Human Research Protection Program and IRB
review in National Taiwan University Hospital
Ian Chen, M.D., LL.M., J.S.D.

National Taiwan University Hospital

座長：景山茂、栗原千絵子

even before the expansion of the scope of the Act. After this case was concluded as a fabrication, there was much criticism of Korean researchers in international journals. As there are many researchers with the same family name, these Korean researchers felt pain in their hearts.

From 2006 to 2008, ethical debates shifted from “embryo ethics” to “egg ethics”. Hwang’s research used more than 2,000 eggs, which he obtained through unregulated IVF (*in vitro* fertilization) practice and the black market for human eggs in Korea. Human egg brokers and egg sellers were penalized. The total number of egg donations came to be limited to three times in one’s life, with an interval of more than 6 months. This case caused the expansion of the Bioethics and Safety Act.

(2) Research governance system of the Seoul National University¹²⁾ (Photo)

As the additional information to the already reported Human Research Protection Program (HRPP) of the Seoul National University Hospital (SNUH)^{6,7)}, this report introduces statistical information provided by Prof. Kim to show the scale of research activities and research governance activities of the university. The numbers of the beds of

SNUH are in main hospital: 1,792; SNUBH (Bundang): 1,101; SMG-SNUBMC (Borame Medical Center): 786; totally 3,679. The average number in 2013 of inpatients/outpatients for each site are 1,330/3,909; 1,037/4,516; 713/3,156; totally 3,080/11,581. The numbers of employees (physicians) are 5,943 (1,149); 2,111 (715); 1,432 (323); totally 9,486 (2,187). Numbers of investigators/research staff are 729/2,413; 179/856; 98/260; totally 1,006/3,529. Numbers of IRB panels/members/staff of these sites are 8/1,124/6; 4/67/3; 2/26/3, totally 14/217/11. Numbers of HRPP members/staff are 10/5; 5/4; 5/2; totally 20/11.

The total amount of research funding has increased from 27.9 m USD (million United States Dollars) in 2007; 52.6 in 2008; 57.1 in 2009 to 76.0 in 2012. The number of publications in the SCI (science citation index) journals was 1,485 in 2009 and 2,205 in 2012. The number of clinical trials conducted in main hospital is 36 phase 1s; 54 phase 2s; 91 phase 3s in 2012. There has been no specific change (increasing) in this number through 2008 to 2012. The number of the sponsored PMS (post marketing study) reviewed in 2011 was 25. The total numbers of initial protocol reviews by SNUH IRB increased from 901 in 2008 (sponsored: 235; academic: 666) to 1,501 in 2011 (sponsored: 275; academic: 1,226).

There was no specific research funding for establishment of a quality assurance system of this scale of research activities, responding to the expansion of the Bioethics and Safety Act. Governmental funding was provided for experts to learn about bioethics or research ethics while staying at the IRB in US.



Lecture by Prof. Ock-Joo Kim on AAHRPP-accredited system of the Seoul National University Hospital, at the meeting of the Japanese Society of Clinical Pharmacology, Tokyo, December 6, 2013

4.2 Human Research Act and Biobank Act in Taiwan and AAHRPP-accredited HRPP in National Taiwan University

The article by Prof. Chen¹⁾ in this journal introduces in detail the Human Subject Research Act and Human Biobank Management Act in Taiwan. This article provides some additional information summarized from the lectures by Prof. Chen in December and discussion before and after.

(I) Social debate concerning anthropology research led the new Acts¹³⁾ (Photo)

Taiwan research regulations had been composed of ethical guidelines by Ministry of Health for each of collection of human specimen for research use; on human embryo and embryonic stem cell research; on human subject research. Covering all the research in these categories, the Human Subjects Research Act of 2011 and the Human Biobank Management Act of 2010 were established. One of the triggers for the establishment of these Acts was the social debate on anthropology studies on indigenous people. The details of the contents of these Acts and

background story are described in Chen's article. In the question and answer session of his lecture, it was impressive that the debate is not because of the "lack" of informed consent of the research subjects, but because of "insufficient" informed consent, which means not telling the exact purpose of these research studies to find the genetic origins of these people.



Lecture by Prof. Ian Chen on the Human Subject Research Act and Human Biobank Management Act, at the seminar of the Association of Pharmaceutical Medicine (JAPhMed), Tokyo, December 6, 2013



National Taiwan University Hospital, New building, August, 2012

(2) Research governance system of the National Taiwan University¹⁴⁾ (Photo)

Here, this report introduces statistical information provided by Prof. Chen to show the scale of research activities and research governance activities of his university.

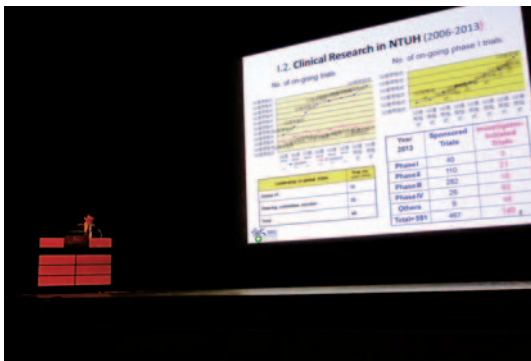
The number of the beds of National Taiwan University Hospital is 2,200 and there are 6,000 employees including 600 physician specialists and 600 medical residents, serving 2,000 inpatients and 8,000 outpatients per day. The number of ethics

committees and its members and structure in 2012 is shown in Table 1.

Numbers of the new protocols of full review: 1,507/expedited review: 1,824 and exemption: 95 in 2011 and this numbers increased to 2,011/2,004/136 in 2012. The numbers of clinical trials are shown in Fig. 1, 2 and Table 2. Their ranking of the total number of publications in the Asian-Pacific area is shown in Table 3.

5. Conclusions and issues for Japan

As reported above, a wide range of laws to regulate research involving human subjects have been established in Korea and Taiwan, and leading research institutes have acquired accreditation of AAHRPP, in order to not only prepare for domestic regulatory inspection but also for conducting clinical trials funded by global companies and associated US-FDA's inspections. This kind of research governance system is established on the basis of the JCI-accredited governance system of daily medical practice. These efforts are not only for obtaining a leading position among the world research institutes but also for responding to prob-



Lecture by Prof. Ian Chen on AAHRPP-accredited system of the National Taiwan University Hospital, at the meeting of the Japanese Society of Clinical Pharmacology, Tokyo, December 6, 2013

Table 1 Number of committee members of NTUH Research Ethics Committees (2012)

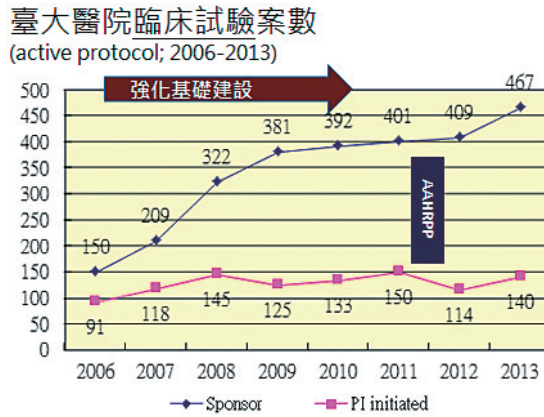
Jurisdiction *1	Committee A Sponsored trials	Committee B Investigator initiated trial	Committee C Expedited review	Committee D Investigator initiated trial
Non-scientific Member	7	8	6	7
Scientific Member	12	12	9	10
Non-affiliated Member	8	8	6	7
Total *2	27	28	21	24

* 1 The jurisdictions of each committee have been the same since 2013. It means each committee can review all kinds of research protocols.

* 2 Total number of the members: 100

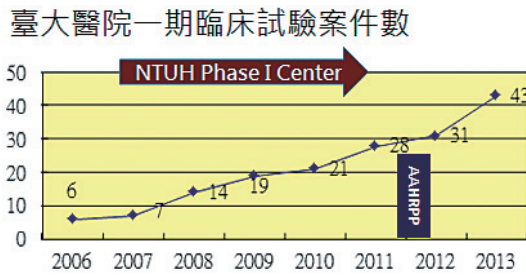
Provided by Chen I

Fig. 1 Number of active protocols of clinical trials in National Taiwan University Hospital from 2006 to 2013



Provided by Chen I

Fig. 2 Number of active protocols of Phase I clinical trials in National Taiwan University Hospital from 2006 to 2013



Provided by Chen I

Table 2 Number of active protocols of each phase and category of clinical trials in National Taiwan University Hospital in 2013

臺大醫院在臨床試驗的global leadership與案件類型分布

Leadership in global trials	Trial no. (2007-2013)
Global PI	15
Steering committee member	25
Total	40

Year 2013	Sponsored Trials	Investigator-Initiated Trials
Phase I	40	3
Phase II	110	21
Phase III	282	10
Phase IV	26	62
Others	9	44
Total=	467	140

Provided by Chen I

lematic cases or scandals, which happened at these leading research institutes. They felt pain in their hearts, and struggled with difficulties at several stages. Additionally, in such situations where med-

ical expenditure is strictly suppressed, medical professionals in Korea came to be regulated for restriction of rebate taking, and the relationship between companies and researchers are coming to

Table 3 Institution rankings in clinical medicine research of NTU (Asia-Pacific, 2007-2011)

Rank	Institution	Country	Total Papers	Total Citations	Citations per Paper
1	Univ Sydney	Australia	5,934	51,109	8.61
2	Univ Melbourne	Australia	5,870	52,093	8.86
3	Seoul Natl Univ	Korea	5,713	27,888	4.88
4	Univ Tokyo	Japan	4,563	33,362	7.31
5	Natl Taiwan Univ	Taiwan	4,343	23,802	5.48

Source: Essential Science Indicators
Provided by Chen I

be more and more strictly regulated. They pose objections to such restrictions of the government and at the same time fight to establish credible research governance system. Funding of the government is not for establishment of this kind of quality assurance system but for achieving improvement of the ethics review.

In Korea, a social debate was arisen concerning the possibility that women had provided more than 2,000 eggs. In Japan, there is no such debate concerning the possibility that 4,436 patients of hypertension may have been exploited in the five unfair clinical trials and may have received inappropriate treatment. In Japan there is no such case as in Catholic University to suspend all the research at the institute after some deviations were found. In Japan there are still pros and cons on the establishment of laws to regulate clinical research. There is no institute in Japan to get AAHRPP accreditation at this moment; of course it is obvious that majority of medical professionals would protest against stricter rebate restrictions.

This report does not include the rebate regulations in Taiwan. I only heard from another Taiwan researcher about the situation: In his university, it is possible to have a lecture meeting supported by a pharmaceutical company where lunch is provided by the company. In this kind of meeting, when a lecturer speaks even just a little bit about the

information not included in the approved label, sales staff of the company stop it and correct the information which should not be mentioned in this meeting. Sometimes Japanese researchers tend to regard "If the conflict of interest is disclosed any kind of relationship between researcher and company can be promoted". This kind of idea should be corrected. Common sense in the world about what is right and what is wrong may not be in common in Japan.

We should avoid such a situation in which the Japanese research community is derided by the international research community for such lack of common sense about the regulations of clinical trials and conflict of interest management.

Acknowledgement

The author deeply appreciates and respects all of the interviewees and lecturers of Korea and Taiwan to provide precious information of their experience to establish an excellent research governance system in their country and their institutes; and to review each part of this manuscript.

The author also appreciates Rinsho Hyoka Kankokai Inc. to fund the program to invite lecturers from Korea and Taiwan in December 2013 and Astra Zeneka to provide meeting venue for JAPhMed seminar. There is no any other financial support for all of these surveys.

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(Published October 30, 2014)