

Report

Human Research Protection Program and IRB review in Seoul National University Hospital

— Interview with Prof. Ock-Joo Kim after observation of IRB*1 —

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Abstract

This is a report of the author's experience in August 2012 of observing the meeting of the IRB (institutional review board) of Seoul National University Hospital (SNUH) and an interview with Prof. Ock-Joo Kim, Department of Medical History and Medical Humanities, SNU, the Director of Center for Human Subject Protection of SNUH.

In South Korea, revision of the Bioethics and Safety Act was passed in February 2012 and enacted in February 2013, which expanded its scope to cover not only human embryo, genetic research but also a wider range of research involving human subjects.

At the IRBs of the SNUH, in 2011 a total of 1,501 new protocols (including 605 full reviews) were reviewed. After the author's visit, the Human Research Protection Program (HRPP) of the SNUH was accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) of the United States.

It was impressive that the discussion of the SNUH-IRB was very efficiently focused on especially important ethical, scientific points, which have been discussed in well-known international guidelines of research ethics. This situation is different from IRBs in Japan which tend to take long time to discuss complicated administrative local issues, and generally IRB members are not familiar with internationally deeply discussed important points of research ethics.

South Korea seemed to lead bioethics in Asia and we Japanese should reconsider our role in the international research community.

Key words

Bioethics and Safety Act, research ethics, institutional review board (IRB), Human Research Protection Program (HRPP), Association for the Accreditation of Human Research Protection Programs (AAHRPP)

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1. Revision of the human subject protection system in South Korea

In South Korea, some IRBs (Institutional Review Boards) review dozens of new protocols in one committee meeting. In recent years, the number of global clinical trials in South Korea has been the highest of all Asian countries. Additionally, South Korea's Bioethics and Safety Act which covers human embryo and genetic research expanded its scope to cover research involving human subjects, generally¹⁾. This revised Act passed in February 2012 and was enacted in February 2013. In May 2012, I visited Prof. San-goo Shin, Department of Clinical Pharmacology and Therapeutics, Seoul

National University, and heard about the above situation from him²⁾. So I strongly wished to observe an IRB meeting and to learn more about the revision of the Act. Prof. Shin introduced me Prof. Ock-Joo Kim (associate professor at this time), Department of Medical History and Medical Humanities, SNU, the Director of Center for Human Subject Protection. Then I visited her and observed an IRB meeting on August 2, 2012 (Photo 1, 2)^{*2}.

2. IRB meeting at Seoul National University Hospital

IRB meetings of SNUH are held in the meeting room in the restaurant on the 11th floor of the Biomedical Research Institute Building (Photo 3), which is next to the hospital. Committee members

Photo 1 Seoul National University Hospital



August 2, 2012, at the time of the author's visit.

^{*2} Related to this article, Prof. Kim and Dr. Ian Chen, Taiwan National University Hospital, which was accredited at the same timing with the Seoul National University Hospital by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) for its Human Research Protection Program (HRPP), both will have lectures at the meeting of Japan Clinical Pharmacology and Therapeutics (Dec 6, Friday, 2013, 9:00-11:00am, Main Hall of Tokyo International Forum) and at the Japanese Association of Pharmaceutical Medicine (Dec 6, Friday, 3:30-6:30am, Conference room of AstraZeneca).

Photo 2 Old building of Seoul National University Department of Medicine



Old building built during the time of Japanese dominion. Now this building is used as a historical museum.

Photo 3 Biomedical Research Institute



IRB meeting was held in the meeting room in the restaurant on the 11th floor of this building.

discuss for about 2 hours while having lunch, so it really looks like a “power lunch” meeting. Prof. Kim promised me to have a 1 hour interview after the IRB meeting; however, while I was waiting at the restaurant, Prof. Kim arrived 20 minutes

before the meeting, and said “Let’s start talk, having lunch before the meeting starts!” Having a very delicious bibimbap, I learned about their IRB procedure and human subject protection system at SNUH. For me it seems that she is a person with a

Photo 4 Interview with Prof. Kim



After the IRB meeting, Prof. Kim explained about ethically important points discussed in the meeting, using the material delivered to the committee member.

very quick mind and never wastes her time. Such an attitude fascinated me. She said that sometimes news media people came to observe the IRB meeting, and from Japan, previously only 1 university researcher came and observed the meeting (Photo 4).

There are 4 IRBs in SNUH, and they review both industry-initiated and academic-researcher-initiated research. Each meeting of the IRB is held on the first and third Thursday and on the second and fourth Wednesday, a total of 4 times a month. Tables 1 and 2 show the number of reviews. It means that, in 2011, there were 1,501 new protocols (including 605 full reviews), and the average

Table 1 Number of protocol reviewed at SNUH IRB in 2011

no. of protocols reviewed at SNUH IRB in 2011

| | exempted | expedited initial review | PMS | initial full board review | re-review full board review | total |
|--------------------|----------|--------------------------|-----|---------------------------|-----------------------------|-------|
| sponsored research | 0 | 11 | 25 | 239 | 8 | 283 |
| academic research | 71 | 863 | 0 | 363 | 18 | 1,315 |
| total | 71 | 874 | 25 | 602 | 26 | 1,598 |

Table 2 Number of protocol reviewed at SNUH IRB by year

initial protocol review (full board review and expedite review) by year

| | '01 | '02 | '03 | '04 | '05 | '06 | '07 | '08 | '09 | '10 | '11 |
|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|-------|
| sponsored research | 54 | 94 | 117 | 106 | 159 | 184 | 229 | 235 | 236 | 252 | 275 |
| academic research | 37 | 45 | 82 | 125 | 202 | 370 | 436 | 666 | 686 | 964 | 1,226 |
| total | 91 | 139 | 199 | 231 | 361 | 554 | 665 | 901 | 922 | 1,216 | 1,501 |

From Table 1, # of exempted; re-review were deleted

expedite review by year

| | '04 | '05 | '06 | '07 | '08 | '09 | '10 | '11 |
|-------|-----|-------|-------|-------|-------|-------|--------|--------|
| total | 722 | 1,502 | 3,132 | 4,747 | 6,135 | 8,363 | 10,569 | 12,187 |

number of new protocols reviewed in one meeting was 12.5, including 5 industry-initiated clinical trials ^{*3}.

Both industry-initiated and researcher-initiated clinical trials are covered by GCP Ordinance, and other categories such as human genetic, embryonic research are covered by the Bioethics and Safety Act, which after the revision, cover 5 general human research. There are exemptions and expedited review procedures for such research with smaller risk. Clinical trials including genetic analysis are covered by both GCP under the Pharmaceutical Affairs Law and the Bioethics and Safety Act. However, these 2 different legal frameworks do not seem to such discrepancy to cause confusion.

3. Quality assurance of research review and the research governance system

The IRBs of SNUH were recognized in 2006 by FERCAP (Forum for Ethical Review Committees in the Asian and Western Pacific Region), and in May 2011, the hospital established the Center for Human Research Protection (CHRP) which oversees the Human Research Protection Program (HRPP) (Fig. 1). This system is compliant with the requirements of accreditation by the United States (US)- Association for the Accreditation of Human Research Protection Programs (AAHRPP). AAHRPP's mission is to facilitate an effective, efficient, innovative human subject protection sys-

tem. It announces through its web-site that SNUH was accredited on December 7, with the name of Prof. Kim as the contact person.

In addition to the CHRP, SNUH has the MRCC (Medical Research Collaborating Center), where 30 biostatisticians and nurses are working to check and refine the design and other scientific aspects of applied protocols. MRCC was established in 2004 and has sufficient experience, but there is no clinician, so Prof. Kim said that primary reviewer's role is important.

Once a protocol is submitted to an IRB, it is allocated at once to primary reviewers, layperson members, an expert secretary, and to the MRCC. Generally, one primary reviewer is assigned to 1 protocol. The primary reviewer is a clinician/researcher whose expertise is suitable to review the assigned protocol. Layperson members are lawyers, clergymen, or social workers, and they are engaged in the review of the informed consent form. The expert secretary is an experienced IRB member, who collects and synthesizes the review results and manages committee meetings supporting the chair of the committee. At the MRCC, a team composed of 1 biostatistician and 1 nurse is assigned to 1 protocol.

4. Efficient management system

The effectiveness of the management activities of Prof. Kim was brilliantly apparent during the meeting (Photo 5). At noon, about 20 committee board members gathered in the meeting room.

^{*3} Postscript by Ock-Joo Kim: In 2012 October, the four panels of the SNUH IRB had been divided into eight. Thus, since October 2012, the SNUH IRB has eight panels each having a smaller number of members. Why did SNUH divide 4 IRBs into 8 IRBs? It is because they wanted to have more time for discussion before making a decision. Previously, the 4 IRBs had an average of 26 members and reviewed an average of 12.5 new protocols per meeting and we had only 5-10 minutes per protocol discussion. Currently the 8 IRBs have an average of 14 members and review an average of 6 new protocols per meeting (i.e., 3 industry trial protocols plus 3 investigator-initiated trials), and we have 15-20 minutes per protocol discussion. I found that IRB members look happier with this smaller number of members and protocols because they can discuss more without any time constraints.

Fig. 1 Organization chart of Human Research Protection Programs in Seoul National University

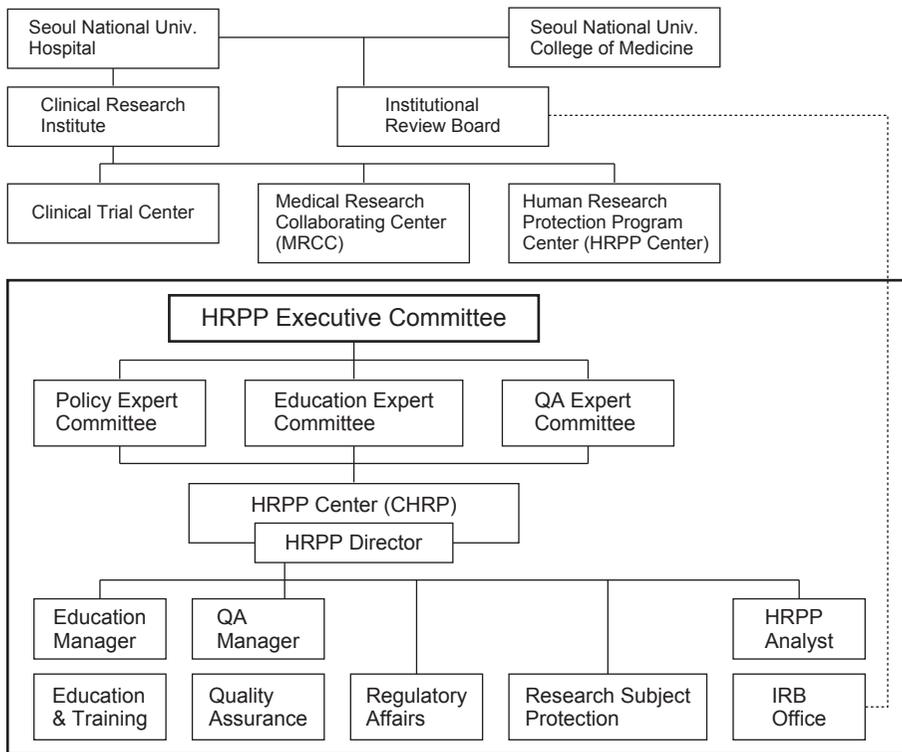


Photo 5 IRB meeting scenery of the Seoul National University Hospital



Right, center is Prof. Kim, facing the chairman of the committee. Two ladies in the back are secretariats; the lady left of them is a biostatistician, team leader of MRCC.

Among them, there were 3 females: Prof. Kim, who manages the meeting as an expert secretary (Photo 6) a layperson member, and a team leader at the MRCC, who is a biostatistician. Other members were males, including the chairman of the committee. The Chairman and Prof. Kim sat vis-à-vis at the center of the table. Just beside Prof. Kim, Dr. Jeong-Hwa Hong sat and supported her. He is a medical doctor, a member of Prof. Kim's department, and majoring in research ethics, and works as the "HRPP analyst" as indicated in the chart of Fig. 1. He is also responsible for regulatory affairs in their center. This kind of name "HRPP analyst" is well known in the US, but the IRB community in Japan is not so familiar with it.

I sat at the end of the table, and the document for review was handed also to me, which should be returned to them after the meeting. Next to me, two secretariat ladies sat, one of whom was engaged in recording the discussion typing on a computer. The other concentrated on the discussion points and made a memo of each decision, and sometimes answered questions from the board members, and

sometimes told me in English the critical points of the discussion. Both of them seemed to have very sharp, quick minds and were very conscientious and honest secretariats. It seemed that Prof. Kim had exerted great care in the selection of the staff. The distributed document was 60 pages and was composed of 16 protocols summarized; review results of primary reviewers for each protocol; and MRCC's review results for high-risk category protocols. For each protocol, the risk level was categorized as minimal, moderate, or high. According to this risk level, reporting requirements were defined as once a year; once every 6 months; or once every 3 months. At the end of the bound documents, there were dates of US-AHRPP's site visit and schedule concerning the accreditation.

Several minutes after starting the discussion, the restaurant staff came to ask for the order of each board member and then lunch was delivered to each: kimchi-fried rice, bibimbap, coffee, orange juice, etc., according to their preference. They continued serious and careful discussion while having their lunch.

Photo 6 Prof. Kim during the meeting discussion



Each protocol was discussed within 5 to 10 minutes and then all the members voted on each protocol raising a hand for approval, conditioned approval, or disapproval. For many of the protocols, 10 to 30% of the members showed their opinions opposite to the majority and some of the protocols were disapproved. More than 80% of the members were assigned the role of primary reviewer of at least one protocol, and gave presentations of their review results. Sometimes, a board member who was a principal investigator of a reviewed protocol left the room, and returned after the vote.

When I told Japanese specialists that dozens of new protocols are reviewed at one time in an IRB meeting in Korea, someone said that they should be easy reviews or should be to the result of a pre-review system. However, the reality is different. They review protocols very quickly, focusing on ethically critical points, and all of the board members express their opinions clearly, and some protocols are rejected. Such a situation cannot often be seen in Japanese IRBs.

5. Actual discussion on protocols

Here, I will introduce how critical points were discussed.

The first protocol of that day's meeting was rejected. This protocol was designed using the retrospective data from a randomized-controlled trial (RCT), which had a quite different purpose from this protocol. The RCT itself had a problem of omission of the signature of the investigator on the informed consent document. The IRB members discussed and decided that to set up the protocol based on the data generated from this RCT was not acceptable both ethically and scientifically. It would be incredible for the Japanese IRB community that this kind of judgment can be done in around 10 minutes.

The second one was a questionnaire survey involving prisoners. The research subjects are classified into 3 groups, including the people with psychiatric disorders. At first, this protocol was assigned to an expedited review as its risk level was regarded to be minimal; however, the expedited review opinion was to reject the protocol. Their SOP defines that a protocol cannot be rejected by expedited review. So this protocol came to be reviewed at a full board meeting. They discussed about the subjects being a vulnerable population, and whether they have the capacity to give informed consent. The review summary included the opinion of a consultant, a psychiatrist of SNU-Bundang hospital who has long experience to provide medical care to prisoners. A lawyer member also expressed his opinion. Finally, the review result was "conditional approval", on condition that a witness is required in the process the informed consent. After the meeting Prof. Kim told me that this kind of additional protection for vulnerable subjects in getting additional opinion of an expert of the special population is a requirement defined in the CIOMS guidelines³⁾. Also she said that they wish to be compliant with US regulations for protecting human subjects, as they were applying for AAHRPP accreditation. In Japan, this kind of additional protection procedure for vulnerable subjects, indicated in the international standard ethical guidelines, is often regarded as difficult to provide.

A protocol submitted from the Department of Radiology caused a discussion concerning the radiation dose of CT examination on healthy volunteers. It was 1 mSv for 1 scan, then totally 10 to 12 mSv. The opinion was concluded to be a "conditional approval". According to the ICRP's recommendation⁴⁾, 1 mSv for 1 scan is categorized as "trivial risk" and 10 mSv for 1 scan is as "moderate risk" which requires substantial benefit generated from

the research results. On the other hand, FDA's regulation⁵⁾ categorizes the research of an annual total dose less than 50 mSv for healthy volunteers to be safe and FDA's authorization of starting the study is not required for some defined category of research of such a lower level of radiation. From the view of these standards, it seemed to be reasonable to conclude "conditional approval" after substantial discussion on such a protocol in which the total radiation dose is 10 to 12 mSv.

There was also stem cell research for Alzheimer's disease patients, combining phase 1 and 2 stages, initiated by academic researchers. It was categorized as high-risk, so 2 primary reviewers who were medical experts were assigned, one of whom was a neurologist, and the other was a stem cell researcher.

Some clinical trials were proposed by global companies, and Prof. Kim explained that such protocols are reviewed by specialists inside the companies and the risk level is not so high generally, therefore, the IRB reached a judgment according to the CIOMS guidelines: Commentary on "multi-centre research" according to the Guideline 2 "Ethical Review Committees": "Generally, to ensure that the results will be valid, the study must be conducted in an identical way at each centre. ... For such studies, local ethical or scientific review committees are not normally authorized to change doses of drugs, to change inclusion or exclusion criteria, or to make other similar modifications. They (ethics committees) should be fully empowered to prevent a study that they believe to be unethical."

As for the protocol of domestic companies, and also for herbal medicine trials, it is difficult for IRB members to evaluate pharmacological aspects, so the MRCC's evaluation is extremely important, she said.

Recent reports by OECD⁶⁾ and US-President

Committee on Bioethics⁷⁾ recommended a research governance system employing a risk-based approach, and also one review opinion for one protocol for a multi-center clinical trial, and SNUH-IRB's discussion seemed to be compatible with such a policy. As for the discussion concerning vulnerable populations and radiation risk, it seemed to be concentrate efficiently on critical points from the views of international standards, so they reached a conclusion in a short time. In Japanese IRBs it often takes time to discuss very detailed administrative issues from view of the local rules of each institute. It was impressive that the discussion of SNUH-IRB is in an opposite way, dynamic and efficient and internationally comprehensible.

6. After the IRB meeting

After the IRB meeting, I interviewed Prof. Kim on her background, and on the revision of Bioethics and Safety Act (Photo 7). During about the 1 hour interview, Jeong-Hwa Hong and other 2 secretariat staff waited for her in the restaurant next to the meeting room, discussing follow-up administrative issues of the IRB meeting. But when we focused on detailed issues of the Act, Dr. Hong came to support her and gave me answers.

Photo 7 Prof. Kim and author



Prof. Kim entered the College of Medicine, Seoul National University, in 1982 and graduated in 1989. She then studied about the History of Medicine in US-Minnesota University and then worked three years as a postdoctoral fellow in the Department of History of Science, Harvard University Faculty of Arts and Sciences (FAS). During this time, she learned from her advisor about social medicine and research ethics. Her husband got his Ph.D. studying public health at the Harvard School of Public Health and they attended the same seminar on research ethics. Together with her husband she came back to Korea and started working at Seoul National University as a research professor. Being granted a scholarship of FERCAP, she learned research ethics as a fellow for 6 months at the Western IRB in US. In 2002 the Korean Association of Institutional Review Boards (KAIRB) was established and Prof. Kim worked as a secretariat for 5 years and her first work at the KAIRB was a questionnaire survey of IRBs nationwide. This survey result was published in 2003⁸⁾ and has had great impact on the research governance framework development. In 2005 there was a scandal of a fabricated publication of ES (embryonic stem) cell derived from a cloned human embryo, and the government came to strengthen research regulations. In 2007, the Korean Government started the project to dispatch experts of research ethics to the US for their learning at IRBs, AAHRPP, OHRP (Office for Human Research Protections), or NIH (National Institute of Health).

I highly regarded the revision of Bioethics and Safety Act as a great achievement of the Korean people, but Prof. Kim, who was a member of the governmental working group of the revision of the Act, said in a non-emotional manner: "We don't know if we can say it is an achievement as there are some objections." Also she said that SNUH's research governance system had covered a wide

range of human research since before the revision of the Act, so there will be no significant expansion of the work after the enactment of the Act. They learned from the US, but developed at SNUH an original system to manage a substantial number of protocols. The categories of low risk research for which a review is expedited is defined in a draft enforcement decree and guidelines of the Act, for which public comments were submitted during the summer of 2012, to be enacted in the spring of 2013.

7. Leading bioethics in Asian countries

After the interview, I had an impression that South Korea will take leadership of bioethics in Asian countries. Prof. Kim was invited to the meeting of the Japanese Society of Bioethics held in Kyoto and gave a lecture on October 30, 2012, so I could meet her again there. Japanese specialists of bioethics were surprised and asked questions how such a kind of revision of bioethics act was possible in South Korea. Prof. Kim answered that there were objections from not only researchers but also citizen's groups with concerns that "ethics" may be replaced by "compliance" because of such an expansion of the range of the Act.

It was just after the fabricated presentation of Dr. Naofumi Moriguchi of iPS cell clinical research after Prof. Sinya Yamanaka's winning the Nobel Prize, so I asked for her comments on this issue. She showed a slide of a Korean national memorial postage stamp of ES cell derived from human cloned embryo. Its design was the figure of a patient standing and jumping from invalid wheel chair. She gave warning to the social trend of appraising hasty translation from basic science to clinical application.

We here in Japan also experienced the same kind

of scientific misconduct; however, it will never stimulate the development of a comprehensible law to regulate human research. In Japan many of the research guidelines are discussed one by one and only in December 2012, there began governmental committee discussion towards integrating guidelines of clinical research and epidemiological research. After that, another issue of scientific misconduct in several number of large-scale multi-center clinical trials of an antihypertensive drug has come to be discussed and the revision of the guidelines is being affected by this scientific fraud.

The situation of South Korea leading bioethics in Asia is worth noting and we Japanese should reconsider our role in the international research community.

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