Revision of Bioethics and Safety Act in South Korea

— Comprehensive system of human research subjects protection and quality assurance of research, comparing with Japan —*

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Abstract

In South Korea, the Bioethics and Safety Act initially enforced in 2005 was revised and is to be enforced from February 2013. This Act was legislated to regulate biotechnologies utilizing human embryo, cells and genes but now its scope is expanded to general research involving human subjects. Clinical trials of drugs and medical devices are separately regulated by GCP (Good Clinical Practice) Ordinance under the Pharmaceutical Affairs Law. Covered by these research governance frameworks, research review committees are to be accredited, inspected, educated and evaluated by the regulatory authority. Additionally, research review experts are dispatched to the United States (US) for training and then they introduce US-style Human Research Protection Program into their own institutes. Based on such improvement and assurance of human subject protection, government and research institutes take some measures to streamline some administrative procedures.

In this article the author describes the background and actual situation of the revision of the South Korea's Bioethics and Safety Act, comparing them with the situation in Japan, where research governance frameworks are composed of many separate guidelines without sufficient legal bases for them.

Key words

bioethics, protection of human research subjects, clinical trial, Good Clinical Practice (GCP), ethics committee

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1. Introduction

In South Korea the Bioethics and Safety Act was established in January 2004 and enforced in January 2005, and its entire revision was announced in 2012, and is to be enforced from February 2013 [1]. The Act was initially legislated covering advanced life science and biotechnology, utilizing human embryos, cells, and genes. Clinical trials of drugs and medical devices have been covered by GCP (Good Clinical Practice) regulations under the Pharmaceutical Affairs Law, compliant with ICH-GCP. This time, revision of the Bioethics and Safety Act expands its scope widely covering research involving human subjects, except clinical trials under GCP. Its scope covers not only "medical" research involving human subjects, which is covered by the Japanese "Ethical Guidelines for Clinical Research" or the World Medical Association (WMA)'s "Declaration of Helsinki", including research to use individual-identifiable human material as well. The Act also covers human material banking and any research not limited to medical areas if the research has interventions to or interactions with humans. The categories of research covered by the Act and minimal-risk research for which an ethics review can be expedited are to be defined in the draft proposals of the Enforcement Decree [2] and Enforcement Rule [3] which have called for public comments.

In South Korea, a comprehensive research governance framework under the Bioethics and Safety Act and GCP Ordinance under the Pharmaceutical Affairs Law is to be established and ethics committees are going to be accredited, inspected, educated, and evaluated by the regulatory authority, more intensively than previously. In such a regulatory environment, the leading research hospitals have been dispatching experts in research ethics, funded by the government, to the United States (US) for training. They come back to implement a US-style Human Research Protection Program, and also a US-style-applied primary reviewer method for the ethics review. By means of such methodology, they sometimes review dozens of new protocols at one time in a review meeting. Additionally, the regulatory authority is going to implement such a system that streamlines their inspection at the institutes that have their own quality assurance system.

This article describes the background and actual situation of the revision of the Bioethics and Safety Act in South Korea, comparing it with the situation in Japan. The focus is especially on the comprehensive design of the Act and system of human research subject protection, but not on detailed issues of advanced technologies such as human embryo, genetic related research, transplantation, regenerative medicine, and cell therapy.

2. Background of the revision of Korean Bioethics and Safety Act (Table 1) [6 ~ 52]

2.1 Initial legislation of the Bioethics and Safety Act and its revision

The initial legislation of the Bioethics and Safety Act was realized in January 2005, after the first proposal of outlines in 2001. Both the citizens groups and bioethicists concerning rapid development of life science and the industries and government bodies seeking rapid development of science and technology proposed with congress members each draft bill, and after all the surveys and several committees' discussions, the Act was established [4, 5]. Touched off by the birth of cloned sheep Dolly in 1996 [17], international society required legal control to prohibit human cloning [19, 30]. Responding to such a trend, the scope of the initial

Table 1 Historical background of human research governance framework development in South Korea comparing world and Japanese trend

World trend	South Korea	Japan
1946 Nuremberg Code [6] 1962 US Kefauver-Harris Amendment Act to regulate drug clinical trial 1964 WMA Declaration of Helsinki [7] 1966 UN International Covenant on Civil and Political Rights [8] 1974 US National Research Act		
1982 CIOMS Guidelines for Biomedical Research 1988 French Act for Biomedical Research [9, 10]	1987 First IRB at Catholic Medical School	1982 First ethics committee at the Tokushima University for in vitro fertilization 1989 GCP guidelines (Notification)
1990 EC-GCP [11] 1991 US Regulations for Protection of Human Subjects became Common Rule through the Departments [12] 1991 CIOMS Guidelines for Epidemiological Research [13] 1993 CIOMS Guidelines for Biomedical Research (Ver. 2) [14] 1994 French Act on Bioethics [9] 1995 WHO-GCP [15] 1996 ICH-GCP [16] 1996 Publication of cloned sheep Dolly [17] 1997 Council of Europe Convention on Human Rights and Biomedicine [18] 1997 G8 Agreement on prohibiting human cloning [19] 1997 UNESCO Declaration on Human Genome [20] 1998 Netherlands Act on Medical Research involving Human Subjects [21] 1998 ICH-E5 (Ethnic Factors) [22]	1995 GCP guidelines 1998 Accreditation system of drug clinical trial institutes started (since 2006 for device clinical trial) [23]	1997 GCP Ordinance, compatible with ICH-GCP [24]
2001 EU Clinical Trial Directive [25] 2002 CIOMS Guidelines for biomedical research (Ver. 3) [26] 2003 Sweden Human Research Ethics Review Act [27] 2003 UNESCO Declaration on Human Genetic Information [28] 2004 EU Human Cells and Tissue Directive [29] 2005 UN Convention Against Reproductive Human Cloning [30] 2005 UNESCO Declaration on Bioethics and Human Rights [31] 2008 WMA Declaration of Helsinki (Ver. 7, at General Assembly at Seoul)	2000 Korean GCP revised for being harmonized with ICH-GCP [32] 2001 Outlines of initial Bioethics and Safety Act was proposed; Bridging concept (ICH-E5) was introduced 2002 Separate of IND from NDA; Establishment of Korean Association of IRB (KAIRB) [33] 2003 Publication of the KAIRB's survey on IRBs in Korea [34] 2004 Start of Regional Clinical Trial Center [35] (Until 2012, 20 Centers including 15 Core Center have been designated) [36] by the Ministry of Health 2005 Establishment of Bioethics and Safety Act; Scandal of fabricated report of human-cloned embryo derived stem cell lines 2006 Accreditation by KFDA of medical device clinical trial institutes started [37] ; Leading hospitals are starting to get accreditation of WHO and/or US-AAHRPP [36] 2007 KFDA started New Inspection Program [38] on clinical trial institutes and project of KoNECT [35] ; Ministry of Health started training program to dispatch ethics review experts to US IRB, OHRP, AHRPP, NIH (to stay 2, 3 ～ 6 months) 2007-8 GCP was revised to enable joint IRBs [39]	2000 Act on Human Cloning [40] 2001 Guidelines for Specified Embryo [41] ; Embryonic Stem Cell Derivations and Utilization [42] ; Genetic Analysis Research [43] 2002 Guidelines for Gene Therapy Research [44] ; Epidemiological Research [45] 2003 Revision of GCP Ordinance to enable doctor-initiated clinical trial; Guidelines for Clinical Research [46] 2006 Guidelines for Human Stem Cell Clinical Research [47] 2007 10 Clinical trial core hospitals; 30 (later decreased to 20) clinical trial bases institutes; and 7 Translational Research Centers are selected and funded by the government. (There are also several other infrastructure development projects.) 2008 GCP was revised to enable joint IRB; IRB registration started 2009 Guidelines for ES cell were separated for "Derivation and Distribution" [48] and for "Utilization" [49]
2011 OECD Report on non-commercial clinical trials [50]	2010 KAIRB began to evaluate IRB initiated by Ministry of Health 2012 Announcement of total revision of Bioethics and Safety Act [1] (to be enforced from 2013)	2010 Guidelines for Creation of Reproductive Cells from iPS Cells [51] 2010 Guidelines for reproductive medicine creating embryo [52] 2011 5 Early phase clinical trial centers were designated 2012 5 Clinical research core centers, 2 Japan-oriented global clinical research centers were designated

Act focused mainly on prohibition of human cloning and expanded its scope covering assisted reproduction technology and regenerative medicine. Also responding to the completion of the human genome project at the beginning of this millennium and international declarations to prohibit discrimination based on genetic information [20, 28], the Act covered genetic tests, gene therapy, and gene banking, as well. The Act established the system of registration of institutes to conduct these kinds of medical technologies on human; and also established the National and Institutional Bioethics Committees; and defined the requirements of informed consent and other ethics and safety assurance measures, all in this single Act. In May 2005, establishment of human cloned embryo (SCNT (somatic cell nuclear transfer) embryo)-derived stem cells was reported by Hwang Woo-Suk, who used to be a professor at the Seoul National University, which was investigated and concluded in January 2006 by the University to be fabricated results. This scandal also facilitated further strengthening of research governance in South Korea.

The revision of the Act was discussed by the committee under the Ministry of Health, Welfare and Family (hereafter called "Ministry of Health"). There have been deservedly objections from the view of academic freedom to such wide ranging comprehensive regulations. However, the above mentioned scandal promoted opinions that it is irrational to protect the embryo but not to protect human subjects generally. People also have recognized that international norms such as the Declaration of Helsinki [7] and European Convention on Human rights and Biomedicine [18] require legal protection of human dignity and human rights, which leads to a consensus for revision of the Act. Additionally, the following activities toward assurance of ethical and sound scientific clinical trials under GCP regulations have contributed to consensus development.

2.2 GCP and clinical trial infrastructure development

Besides the Bioethics and Safety Act, in the area of drug clinical trials, responding to the trend that EC (European Community)-GCP [11] in 1990 and WHO (World Health Organization)-GCP [15] in 1995 had been issued, Korean Food and Drug Administration (KFDA) under the Ministry of Health issued GCP guidelines in 1995, which later was revised in 2000 [32] to be compliant with 1996 ICH-GCP [16], and then became an Ordinance in 2011. In South Korea, domestic clinical trials had not been required for marketing approval of drugs already approved in foreign countries but ICH-E5 guidelines for bridging studies [22] were implemented in 2001, and since 2002 IND (Investigational New Drug application) and NDA (New Drug Application) came to be separate. Since then, a comprehensive legal framework of drug clinical trial, not limited to the ones aiming at NDA, has been established composed of the Pharmaceutical Affairs Law; the laws enforcing it; and guidelines for GCP, IND, and for accreditation of clinical trial institutes.

In 2002, the Korean Association of Institutional Review Boards (KAIRB) was established in cooperation with researchers, industries, and regulatory authorities [33], which later in 2007 became funded by the Ministry of Health. KAIRB conducted a questionnaire survey on IRBs throughout the country and its results were reported in 2003 [34]. Among the 74 IRBs, 63 responded to the survey (response rate: 85.1%), among which 72% review only 1 protocol per month, covering only clinical trials under GCP, which was regarded not to reach the internationally required level. The report concluded that it was necessary to facilitate IRBs' association, development of an educational program, and introduction of an audit system.

2.3 Capacity development of conduct and review of research

Since then, in both research governance frameworks based on the Bioethics and Safety Act and based on GCP under the Pharmaceutical Affairs Law, a system of accreditation and inspection of research institutes and research review committees and education programs have been developed.

In 2004 the Ministry of Health set up regional clinical trial centers designating 2 centers [35], which expanded in 2012 to designate 20 centers including 15 core centers [36]. In 2006, KFDA's accreditation on clinical trial institutes which started in 1998 expanded its scope to medical devices [37]. In 2007 KFDA started a new inspection program of clinical trials [38]. In Japan, inspection is conducted only after NDA, but in South Korea inspection is conducted both during and after conduct of a clinical trial. Also in 2007 KoNECT (Korea National Enterprise for Clinical Trials) was established being funded by the Ministry of Health, with its mission to develop an infrastructure of clinical trials nationwide [35].

Since around 2006, leading research hospitals started to receive recognition/accreditation by WHO FERCAP (Forum for Ethical Review Committees in the Asian and Western Pacific Region) and US AAHRPP (Association for the Accreditation of Human Research Protection Programs) (Table 2) [36]. AAHRPP's accreditation requires not only a standard research review system but also a comprehensive high standard and efficient human research protection program. In 2007, The Ministry of Health started a program to fund experts of ethics review to study in the US and stay 2 or 3 to 6 months at Western IRB (private IRB); OHRP (Office of Human Research Protection) of the Ministry of Health and Welfare; AAHRPP; and National Institute of Health (NIH). Additionally in 2012, KFDA issued a guideline that they may

Table 2 Trend of acquiring authorization of US-AAHRPP and WHO-FERCAP/SIDCER in South Korea *1

AAHRPP accredited	WHO-FERCAP/SIDCER*2 recognized
2006 Samsung Medical Center (Seoul)	2006, 2009 Seoul National University Hospital (SNUH) IRB (Seoul) 2006, 2009 Asan Medical Center IRB (Seoul)
	2007 Kangnam St. Mary's Hospital IRB (Seoul) 2007, 2010 Chonnam National University Hospital IRB (Gwangju) Inje University Busan Pail Hospital IRB (Busan) 2008 Kyung Hee University Hospital IRB (Seoul) 2008, 2011 Halym University Sacred Heart Hospital IRB (Gyeonggi-do); Daegu Catholic University Medical Center IRB (Daegu); Ajou University Hospital IRB (Gyeonggi-do) 2009 Inha University Hospital IRB (Incheon); Kangbuk Samsung Hospital IRB (Seoul); Chungnam National University Hospital IRB (Daejeon); International Vaccine Institute IRB (Seoul)
2010 Severance Hospital (Seoul); Yonsei University College of Medicine (Seoul); The Catholic University of Korea Catholic Medical Center (Seoul) (Under application) 2012 SNUH; Bundang SNUH; Borame SNUH (Seoul)	2010 Keimyung University Dongsan Hospital IRB (Daegu); Kyungpook National University Hospital IRB (Daegu); Yeungnam University Medical Center IRB (Daegu); Kangdong Sacred Heart Hospital IRB (Seoul); National Cancer Center Hospital IRB (Seoul); CHA Bundang Medical Center IRB, CHA University (Gyeonggi-do); Busan Dong-A University Hospital IRB (Busan); Anam Hospital IRB, Korea University Medical Center (Seoul) 2011 Soon Chun Hyang University Bucheon Hospital IRB (Gyeonggi-do); Korea University Guro Hospital IRB (Seoul); Gachon University Gil Hospital IRB (Incheon)

*1 : Revised from the material provided by Prof. Goo Shin [36], according to the web-sites of AAHRPP and FERCAP.
*2 : SIDCER : Strategic Initiative for Developing Capacity in Ethical Review

abbreviate inspection of a clinical trial site if the institute has its own quality assurance system. Well designed and managed Human Research Protection Programs may be relevant to the conditions of this standard.

Through these processes, leading research hospitals have voluntarily developed their own system to cover not only clinical trials under GCP and embryonic, genetic research under the Bioethics and Safety Act but also research involving human subjects to be reviewed by their IRBs or ethics committees.

2.4 Common review system

Not only expanding the regulatory framework, but also streamlining procedures based on capacity development has been facilitated.

GCP regulations were revised in 2007 to 2008 to enable "joint IRBs" [39] and in 2010 the pilot project of the Ministry of Health to establish a public common IRB. At this moment, this public common IRB can review only phase 4 clinical trials of already approved drugs. Also in the revised Bioethics and Safety Act, the "Common Institutional Bioethics Committee" was defined and detailed procedures are described in the draft proposal of Enforcement Decree and Enforcement Rules of the Act.

The number of multi-national clinical trials in South Korea is around the largest among the Asian countries [36]. For such multi-national trials, the number of domestic subjects required for establishment of evidence is not so large compared to the case of single-national domestic trials. Furthermore, Korean leading hospitals have 1,500 to 3,000 beds. Therefore, the necessity of a common IRB is not so urgent compared to Japan. However, expansion of a joint review system in South Korea is expected in the near future, reflecting the revision of the Act.

2.5 Human Research Protection Program and "primary reviewer" system (In the case of the Seoul National University Hospital)

Some leading hospitals in South Korea use research review systems to review dozens of new protocols at one time during a committee meeting, which is similar to the "primary reviewer" system in the US. Such a system can be developed based on an enhanced institutional framework of research subject protection. In the case of Seoul National University Hospital (SNUH), Center for Human Research Protection (CHRP) manages the Human Research Protection Program (HRPP), and it is applying for AAHRPP accreditation. The CHRP has not only an IRB office but also separate teams each engaged in quality assurance; education; regulatory affairs (policy and SOP (standard operating procedure) development); and being research subject advocates. The author had an opportunity to observe an IRB meeting on August 2, 2012.

In SNUH, each of the 4 IRBs has a meeting once a month so a total of 4 IRB meetings are held every month, and more than 10 to around 30 new protocols are reviewed in each meeting. In 2011 a total of 1,501 new protocols (275 industrial sponsored research projects and 1,226 academic ones) were reviewed in full committee and 12,187 expedited reviews were conducted. When a new protocol is submitted to the IRB, it is assigned to MRCC, a primary reviewer, a layperson and expert secretary at the same time. MRCC (Medical Research Collaboration Center) is composed of about 30 biostatisticians and nurses who review scientific aspects such as design and statistical power of the protocol; each protocol is assigned for review to a team composed of 1 biostatistician and 1 nurse in MRCC. The primary reviewer is usually one clinical M.D. scientist for one protocol, whose expertise is suitable to review the protocol, and the layper-

son member – lawyers, clergymen, or social workers – review the informed consent form. The expert secretary is an experienced IRB member, who collects and synthesizes the review results and leads the presentation of the review of the protocol at the board meeting.

At the full meeting, summaries and primary reviewers' opinions of all the protocols are distributed in printed material, and each protocol is discussed in 5 to 10 minutes efficiently focusing on ethically and scientifically critical points. Then all the members vote each protocol raising a hand.

In many of Japanese IRBs, SOPs define that the protocol should be approved by a majority vote of more than 1/2 or 2/3 members, and in reality approval seems to be unanimous but many of the members do not show their real opinions. Such scenes cannot be seen in SNUH-IRB and all members indicate their opinions by raising their hands for approval; conditional approval; or disapproval. For many of the protocols 10 to 30% of the members show their opinions opposite to the majority and some of the protocols are disapproved.

3. Outlines of revision of the Act

Table 3 shows the main points of the revision of the Act compared with the related points of Japanese research regulations. Fig. 1 shows the organization of research governance bodies after the revision of the Act.

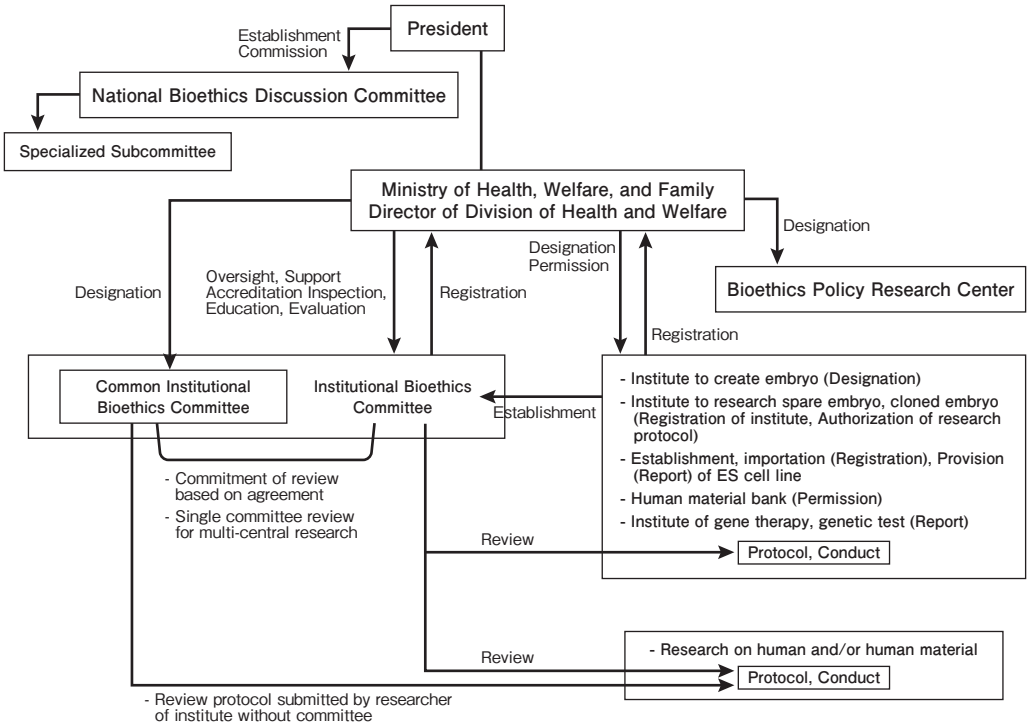
South Korea's Bioethics and Safety Act has clear objectives to protect human dignity, to prevent harm to human, to assure bioethics and safety and to improve people's health and quality of life. It expanded its scope from advanced technology and research utilizing human embryo and gene, to research involving human subjects with interven-

Table 3 Points of the revision of South Korea's Bioethics and Safety Act and related Japanese research regulations

Korean Bioethics and Safety Act		Related Japanese research regulations
Before the 2012 revision (Source: the version of 2008 revision [53])	After the 2012 revision [1]	
【Objective】 - Protect human dignity, prevent harm to human. - Assure bioethics and safety, improve people's health and quality of life.		- The wording such as human dignity, human rights, development of medicine and improvement of quality life are included in each of the separate regulations, not perfectly and the legal bases are not sufficient.
【Definitions (related to scope of the Act)】 - "life science and biotechnology" refers to science and technology using human embryo, cells, and genes.	- "research involving human subjects" refers research with intervention in or interaction with human; to use individual-identifiable data.	- Guidelines for "Clinical Research" [46] and "Epidemiological Research" [45] limit the scope of these terms to research in medical area. In addition, there are specific guidelines for embryonic [48, 49, 52], genetic [43, 44], stem cell [47~49, 51] research, but there is no governmental guideline for social behavioral research.
- "embryo", "spare embryo", "SCNT", "SCNT embryo"		- The terms related to embryonic research are defined in the Act on Cloning [40]; Guidelines for Specified Embryo [41]; Embryonic Stem Cell [48, 49] Research. There is no specific consideration for monogenetic reproduction.
	- "spare oocyte", "monogenetic reproduction" are added.	
- "stem cell lines"	- Changed to "embryonic stem cell lines".	
- "genetic information", "genetic test", "gene therapy"		- There are guidelines for Genetic Analysis (limited to germline mutation or polymorphism related) [43] and for Gene Therapy [44] but for Genetic Test, there are only industry/academia-initiated guidelines but no governmental guidelines.
	- "human derived material", "individual-identifiable information", "individual information" are added.	- Human-derived material and individual-identifiable information are defined in each of the separate guidelines. Because the Act of Protecting Individual Information excludes academic research, each guideline includes text of this Act in it.
- "gene bank"	- Expanded to "human derived material bank".	- There are no specific guidelines for human-derived material bank.

Korean Bioethics and Safety Act		Related Japanese research regulations
Before the 2012 revision (Source: the version of 2008 revision [53])	After the 2012 revision [1]	
【Responsible Authority】 - The Authority responsible for registration, authorization, licensing is the Ministry of Health, Welfare, and Family (The Ministry of Health).	- In the revised Act, the Authority responsible for registration, authorization, licensing is the Director of Division of Health and Welfare under the Ministry of Health.	- 1 to 3 among the Ministries of Education, Health, or Economics issue the guidelines and the Ministry which issued guidelines is the responsible authority of the topics covered in the guidelines.
	【Bioethics Policy Research Center】 - Designated by the Authority, its mission is policy study and education on bioethics.	- There is no governmental establishment of institute specialized in bioethics policy research or education.
【National Bioethics Discussion Committee】 - Designated by the President, discuss about national bioethics policy and the following issues:		- Bioethics Specialized Survey Committee is designated by, as one of sub-committees, the General Science and Technology Committee (designated by the Prime Minister). This Committee has been discussing intensively about human cloning, specified embryo, and embryonic stem cell research, but for other categories of research or ethical issues, discussion is limited and fragmentary. For other guidelines, separate ad hoc committees are created and they discuss about revision of each of the guidelines.
- Issues concerning spare embryo, SCNT, genetic test, gene therapy.	- Issues concerning spare embryo, embryonic stem cell line, genetic test.	
	- Work of Common Institutional Bioethics committee; Exemptions of review of human research, human material research; Retention and disclosure of information.	
- Other important issues.		
【Institutional Bioethics Committee】 - Should be established at the institutes where embryonic or genetic technologies defined by this Act are conducted as research or medical practice. - Should be registered to the Authority. - Each institute has responsibility to provide education to the committee.	- Should be established at the institutes where research involving human subjects; embryonic or genetic technologies; or human material banking, that defined by this Act, are conducted as research or medical practice. - Should be registered to the Authority. - The Authority has responsibility of education, evaluation, inspection of the committee.	- There are systems of registration of research review committees under regulations of GCP [24], Clinical Research [46], Genetic Analysis [43] Research. - Responsibility of education is committed to each institute. Evaluation and inspection by the Authorities have not actually been conducted for review committees.
- Review research and practice utilizing human embryonic, genetic technologies defined by this Act.	- Additionally to the left, review any research involving human subjects and human material banking defined by this Act (not including GCP-regulated clinical trials).	- Issues to be reviewed are defined in each guidelines.
	【Common Institutional Bioethics Committee】 - Each institute can submit a review to the Common Committee based on agreement. - Researchers who do not belong to research institute/hospital can submit to a Common Committee. - Single committee can be selected as a Common Committee in case of multi-central research.	- Guidelines for Genetic Analysis [43] and for Epidemiological research [45] define that in case an institute does not have a review committee it can submit a review to an outside committee. - GCP Ordinance [24] and Guidelines for Clinical Research [46] define that even in case an institute has its own committee it can submit a review to an outside committee. - Other guidelines do not allow outside committee review.
【Human subjects protection】 - Human subject protection rules are defined only for subjects of the technologies under this Act (i.e., embryonic, genetic technologies).	- Following rules of human subject protection come to be applied for all the research and practice defined by the Act: Protocol review; Informed consent; Proxy consent; Safety measures; Compensation for loss; Individual information protection; Retention and disclosure of information.	- These provisions for protecting subjects are included in each guideline. - Only for GCP [24] -covered clinical trials and for the "Interventional Clinical Research" using drug or device under Guidelines for Clinical Research [46] are obligated to provide compensation for research-related injury.
【Human embryonic and assisted reproductive technologies】 - Prohibition of human reproductive cloning and reproduction of human-animal hybrid individual. - Restriction of artificial fertilization for gender selection; or using reproductive cells of non-living human; or of under-aged except the cases of after marriage.		- Prohibition of human cloning and human-animal hybrid being are defined in the Act on Cloning [40] and Guidelines for Specified Embryo [41]. - There is no regulations for fertilization for gender selection, for using reproductive cells of non-living human or of under-aged.
- Designation of embryo producing institute by the Authority; Registration of spare embryo research institute to the Authority; Authorization of spare embryo research by the Authority; Registration of embryonic stem cell line to the Authority. Same rules are applied to SCNT embryo. - Comprehensive regulations of assisted reproductive medicine and medical research utilizing reproductive cells.		- For Specified Embryo [41]; ES cell [48, 49]; reproductive cell creation from iPS cell [51]; reproductive medicine creating embryo [52], there are registration systems of individual plans submitted to the Authority. There is no registration system of institute.
【Gene bank】 - Should be licensed by the Authority and conduct of research and management of human gene material is regulated.	【Human material bank and research】 - Human material bank should be licensed by the Authority and conduct of research and handling of human material is regulated.	- There is no specific guideline for "human-derived material bank". - In each guideline there are some provisions concerning depository and disposal of human-derived material.
【Genetic test, genetic research, gene therapy】 - Prohibition of discrimination based on genetic information and forcing others to take genetic test. - Restriction of genetic test on reproductive cells or fetus. - Restriction of gene therapy allowing only in defined serious cases. - Report/registration of genetic test and gene therapy institute.		- There is no governmental guideline for genetic test. There is no legal provision to prohibit discrimination based on genetic information. - Gene Therapy guideline [44] defines registration of each protocol to the Ministry.
【Penalty】 - Criminal and administrative penalties are defined for each specified violation.		- Provisions of penalties are defined only in the Act on Cloning [40]. Other guidelines do not have provisions of penalties but other administrative documents define that in case of serious violation public funding should be withdrawn.

Fig. 1 Organization of research governance designed by the revised South Korea's Bioethics and Safety Act



tion in or interaction with human and human-derived material banking activities. In an explanatory document, categories of research and activities are described to be not only general human research but also human material banking, epidemiological research, questionnaire surveys, social and behavioral research, sports physiological research and educational research.

The activities which are controlled in South Korea by 2 legal frameworks: GCP Ordinance under Pharmaceutical Affairs Law and the Bioethics and Safety Act are controlled in Japan by 3 legal rules and 9 regulations without acts or law to define them: GCP Ordinance under Pharmaceutical Affairs Law (limited to clinical trials aiming at NDA)[24]; Act on Cloning[40] and Guidelines for Specified Embryo[41] under this Act; 3 separate administrative guidelines related to ES cell[48, 49] and iPS cell[51] research; other separate administrative guidelines for reproductive medicine involving creation of embryo[52]; human genome analysis[43]; gene therapy[44]; epidemiological research[45]; clinical research[46]; and human stem cell clinical research[47].

Additionally, what are established in South Korea but not in Japan are: legal rules on genetic testing; human material banking; human research outside medical areas; legal authorized organizations engaged in bioethics research survey and policy development; regulatory authority's system of registration, accreditation, investigation, evaluation and education for research institutes and research review committees; legally explicit rules on common/joint review for multi-central research; and legally explicit penalty clauses.

4. Conclusion

The design of the revised Korean Bioethics and Safety Act is a kind of combination of the French Act on Biomedical Research [9, 10] and French Act on Bioethics [9, 54], and the actual Korean system of research governance and research review is similar to US system. Leading hospitals in South Korea often set a goal to become a "global leader" and this revision of the Act seems to be consistent with such a goal.

On the other hand in Japan, a substantial number of administrative guidelines without explicit legal bases have been developed and such a situation has been regarded to be problematic for a long time. Sometimes much time and human resources are consumed for solving the questions concerning which guidelines apply to specific issues; to update each guideline to follow rapid development of science and technology; and to explain to foreign collaborative researchers about complicated Japanese regulations.

For promotion of internationally collaborative clinical trials and clinical research under internationally common ethical and scientific principles, it is desired that harmonization and mutual understanding of research regulations are facilitated.

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