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The status and issues of the Institutional Animal Care and Use Committee of Seoul National University: from its establishment to the present day

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Abstract: The Institutional Animal Care and Use Committee (IACUC) of Seoul National University (SNU) plays a key role in monitoring and managing the humane use of animals in scientific research. Here, as one of the pioneers of the IACUC in Korea, we reported SNU-IACUC operations and activities including committee establishment and legal formulation, protocol review, and post-approval monitoring of protocols, which the IACUC has undertaken in the last decade. In addition, legal regulations and improvements were also discussed, and encompassed the limited number of committee members and the single IACUC policy in Korea. As of December, 2020, amendments are on the table at the National Assembly. We also emphasized the independent nature of the IACUC in protecting activities, including approval and monitoring animal experiments, and its public role in narrowing the knowledge gap between society and scientists. Thus, the aim of this report is to help society and scientists understand the operations of the SNU-IACUC and its role in animal welfare.

Key words: animal ethics, animal protocol review, animal welfare, post-approval monitoring, the Institutional Animal Care and Use Committee (IACUC)

Introduction

Despite growing public concern and increasing availability and diversity of alternative scientific methods, animals continue to be used for scientific purposes. The main purpose of scientific studies on live animals is: 1) to gain basic biological knowledge, 2) to investigate drug discovery and development, 3) to investigate vaccine and medical device research, 4) to assess safety testing of drugs, chemicals, and consumer products, 5) to perform environmental research, and 6) to assist with education and training [1]. The Institutional Animal Care and Use Committee (IACUC) of Seoul National University (SNU) plays a key role in monitoring and managing the humane use of animals in research across the univer-

sity campus, and by extension across Korea. This report outlines the activities undertaken by the IACUC of SNU (SNU-IACUC) over the last decade.

SNU-IACUC is one of the early established IACUCs in Korea, and advocates implementation of the 3Rs [2, 3], i.e., Replacement, Reduction and Refinement with respect to animal research, when university researchers propose experiments. In March 2005, the university first launched the Animal Experiment Committee of SNU (SNU-AEC) which later handed over its role to the SNU-IACUC. Three months later in June 2005, the university also established the Institute of Laboratory Animal Resources of Seoul National University (SNU-ILAR) [4] to manage all animal facilities across the campus. The institute supported the operation of the SNU-AEC

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at that time. After launching of SNU-IACUC and SNU-ILAR, the university could collect and evaluate the data related to animal use in the campus, and also could manage animal facilities and train researchers and staffs more professionally. In 2007, the Korean government imposed requirements for an IACUC at all institutions running animal facilities [5], thus 2008, the SNU renamed the committee as the SNU-IACUC, and operation of the new committee was set apart from the SNU-ILAR to guarantee independence. SNU-IACUC specialize its roles to protocol reviews and the monitoring of approved animal experiments while SNU-ILAR is focusing the management of animal facilities and the education and training (Table 1). Although the official name in English is the IACUC, the Korean meaning is closer to “Committee on Animal Research and Ethics,” therefore reviewers focus more on ethical issues when they review a protocol. In October 2008, the SNU-IACUC was finally approved for legal operation by the Animal and Plant Quarantine Agency of Korea (APQA) [6].

Due to complicated legal limitations, the SNU [7] only operates one IACUC. According to the Animal Protection Act (APA) in Korea [8], which regulate all types of

animal use and correct animal experimental conduct, one corporation cannot operate multiple IACUCs, regardless of the scale of its animal use. In addition, the number of committee members who have voting rights is limited to 15. To avoid delays in the reviewing process, the SNU-IACUC has appointed 10 additional professional reviewers who are specialized in the animal study field; however these individuals do not have voting powers. Before reviewing a protocol, the professional secretary (administrator) pre-screens every protocol and conduct associated administrative processes. As a full-time employee, the professional secretary can either be a veterinarian or qualified individual (master’s degree) with experience of animal experiments and/or animal ethics. In 2019, the committee reviewed more than 1,700 protocols, including protocol amendment requests (Fig. 1) [9]. In 2020, to expedite and shorten turn-around times for protocols, the university assigned additional staff to cover this administrative work. In addition to protocol review, committee functions also include regular and occasional post-approval monitoring (PAM). Regular PAM is generally performed in conjunction with the animal facility check, which is conducted by the SNU-ILAR every six

Table 1. The operating bodies related to animal experimentation and facility in Seoul National University (SNU) and their roles over the years*

Roles	Year(s)	–2005	2005–2008	2008–2020	2021–
Legal status of IACUC		N/A	Under preparation of IACUC by MAFRA	Operation of IACUC becomes compulsory to all institutions running animal facilities	
Animal protocol review		N/A	SNU-AEC** (ILAR support its operation including administration)	SNU-IACUC (Operation was set apart from the SNU-ILAR to guarantee independence and its administration is directly supported by Research Affairs)	
Post approval monitoring		N/A	None	SNU-IACUC	
Authority for animal facility management	Each college/facility		SNU-ILAR and each college/facility	SNU-ILAR: animal facilities registered to MFDS	SNU-ILAR
				SNU-IACUC: all other animal facilities	
Education and training for researchers and animal facility staffs	Each college/facility	ILAR (Large facilities also operate their own program)			
		SNU-IACUC operates (re-) education programs for its own committee members			
Veterinary consulting	Each facility has own responsibility				ILAR supports consulting service to small facilities which cannot afford to employ veterinarian
	Large facilities generally employ their own attending veterinarian(s)				
Animal supply (purchase) and disposal		Each college/facility		SNU-ILAR	
Microorganism monitoring		Each college/facility			ILAR plans to integrate

N/A: not applicable; MAFRA: Ministry of Agriculture, Food and Rural Affairs; IACUC: the Institutional Animal Care and Use Committee; AEC: Animal Experiment Committee; ILAR: Institute of Laboratory Animal Resources; MFDS: Ministry of Food and Drug Safety. *The information here is based on the white paper of SNU-IACUC published in 2015 [9], and personal experiences and communications. Official opinion of SNU and organizations mentioned here may differ. **SNU-AEC was launched by SNU Research Affairs in preparation of IACUC planned to be imposed by the government at that time. This committee is regulated by SNU bylaws, not by national laws.

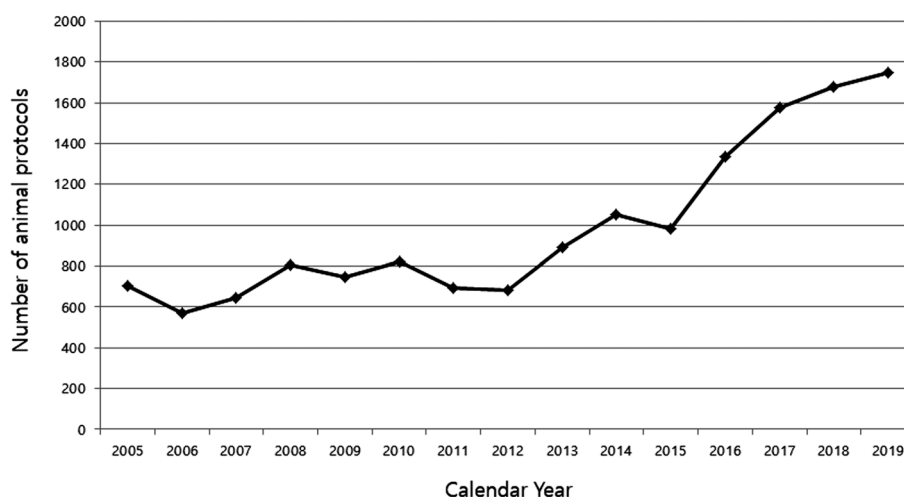


Fig. 1. The number of animal protocols reviewed by the Institutional Animal Care and Use Committee of Seoul National University (SNU-IACUC) from 2005–2019. Data from 2005–2014 were obtained from the SNU-IACUC white paper [9], and data from 2015–2019 were collected from the SNU-IACUC data archives.

months, which is the managing and regulatory body of the animal facilities in the SNU.

From the medical school to the college of engineering, many researchers across the SNU have submitted animal experimental protocols to the SNU-IACUC. Thus, animal research activities at SNU are wide, and ranges from agriculture to translational medicine. To support those research activities, there are 15 animal facilities across the SNU, operated by six colleges and four institutes. Some facilities are located outside the main campus, i.e., medical and agricultural units (Supplementary Table 1). With very few exceptions, most animal experiments in the SNU are performed at one of these animal facilities. In September 2020, the SNU completed a large centralized animal facility, directly operated by SNU-ILAR in Gwanak (main) campus. This facility is forecasted to take over animal housing from small or satellite animal facilities on the main campus, and will also offer several services including consulting by attending veterinarians, embryo preservation and transfer and purchasing of laboratory animals.

Results

Protocol review process of the SNU-IACUC

According to guidelines for the standard operations of the IACUC published by APQA and the Ministry of Drug and Food Safety (MDFS) [10], five pain levels (PLs) exist, and are categorized A to E (Supplementary Table 2). These pain categorizations are similar to the United States Department of Agriculture animal pain and distress categories [11]. The Korean guidelines by APQA and MDFS mostly refer to ‘Guide for the care and use

of laboratory animals’ published by National Research Council of the United States of America [12] and only a specific difference is about the institutional-appointed Attending Veterinarian (AV) in animal facility. According to the Korean guidelines, AV is not compulsory while each animal facility must have an AV in the United States of America and the European Union by law. As the English version of the Korean guidelines are not provided by the authorities, the English outline of the guidelines is presented here as an appendix (Supplementary Information).

A PL-A protocol is generally exempted from the reviewing process. Apart from PL-A protocol review, the SNU-IACUC engages with two types of review system: 1) designated professional review (DPR), and 2) full committee review (FCR). The DPR approach is generally applied to PL-B and -C protocols, while FCR is generally applied to PL-D and -E protocols. From 2020, for dogs, cats and monkeys including primates, FCR is applied to all protocols. Regardless of the type of review system, all committee members regularly confirmed all protocols in committee meeting afterward. The general flow of a protocol review is described (Fig. 2). In the forthcoming paragraphs we introduce the FCR and DPR systems, respectively.

All protocol review procedures from submission to final decision including member voting are conducted online. When a researcher submit a protocol through the online submission system, the administrator pre-screens the protocol to sure all paperwork is correct, including experimental procedures and required animal numbers. Then, the protocol is assigned to a professional reviewer who is expert in that particular research area. The

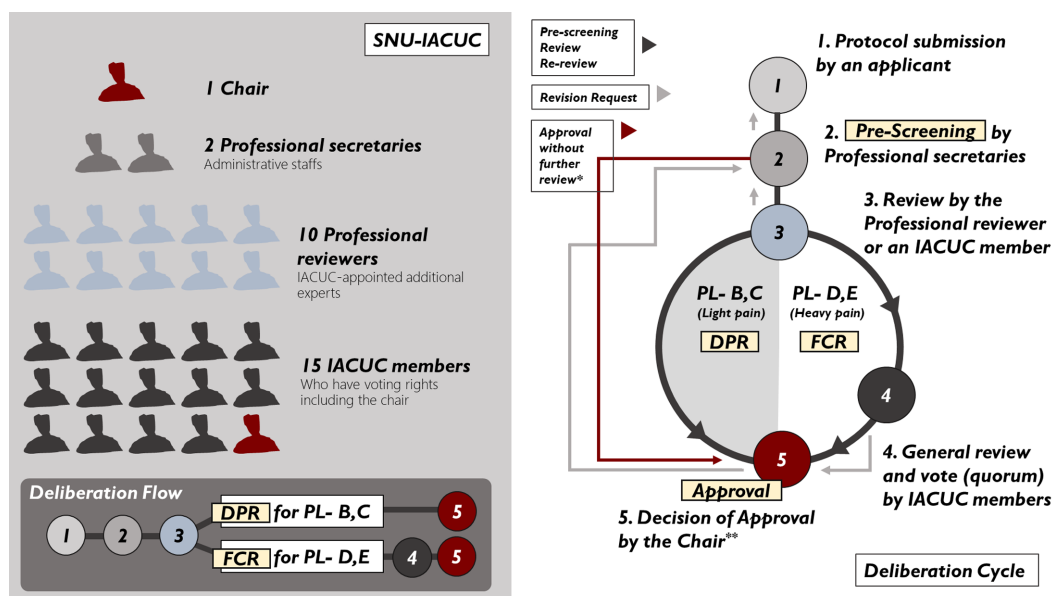


Fig. 2. Schematic of the protocol review process in the Institutional Animal Care and Use Committee of Seoul National University (SNU-IACUC) and the structure of SNU-IACUC. *1) The revised protocol without further issue after the decision of 'conditionally approved with a request for revision', 2) Simple modifications such as address change, replacement of technician, extension of the study period by less than three months, or increased animal numbers by less than 10% (rodents only). **Regardless of the type of review system, all committee members regularly confirmed all protocols in committee meeting afterward. DPR: designated professional review, FCR: full committee review, PL: pain levels.

professional reviewer here includes some IACUC members who are experts in various fields of animal experiments and 10 additional reviewers who are not the IACUC members but experts in the fields not covered by the IACUC members. If a protocol involves a potential conflict of interest with a provisional reviewer, that individual is not assigned to that task. The professional reviewer is obligated to review all animal care and welfare issues and associated scientific animal studies. Once the protocol has been reviewed and approved, a report is delivered to all 15 committee members in order to conduct a general review and vote. The protocol is passed by a majority and is handed over to the IACUC chair for a final decision. At this stage, while most protocols are approved by the committee, if the chair determines any protocol issues, the protocol may be sent back to the applicant, with comments. If the professional reviewer does not approve the protocol, the documents are returned to the applicant with one of the following two decisions, and some revision comments: 1) conditionally approved with a request for revision or 2) re-review after revision. For the former situation (1), the applicant must revise the protocol accordingly. Once the professional secretary receives the revised version and does not determine any further issues, the protocol goes to the chair. For the latter situation (2), the revised version of the protocol is sent to the same professional reviewer for

re-reviewing then goes to the next place, general review and member voting.

In the DPR system, approval of a new or amended protocol may be directly finalized by the chair after professional review, without general review and member voting. The professional reviewing process reflects the FCR system however, if the chair, professional reviewer or professional secretary requests a general review and member voting for specific reasons, the protocol is referred to the FCR process for secure approval. Among the protocol amendment requests, simple modifications such as address change, replacement of technician, extension of the study period by less than three months, or increased animal numbers by less than 10% (rodents only) goes to the chair directly, regardless of protocol PL or the type of review system.

Status of a protocol review by SNU-IACUC Data collection

Although public concern regarding animal experiments is growing, the use of live animals for biomedical research is also increasing in Korea. This scenario at the SNU is no exception. In the next chapter, a decade of protocol reviews across the SNU was collated, and some results were compared with national data from APQA. The SNU-IACUC data were obtained either from the SNU-IACUC white paper published in 2015 [9] or from

SNU-IACUC data archives. National data were collected from the national IACUC portal operated by APQA [13] which open to the public. SNU-IACUC permitted the use of data collected from its data archives as long as the data are in the range of annual report submitted to APQA. There was a limit to our report because the years of data obtained from SNU-IACUC and APQA varied from 2005 to 2015 depending on categories.

The scale of animal protocols

After launching the SNU-AEC in 2005, protocol review numbers increased considerably (Fig. 1). When compared with the national data (Table 2), the scale of animal experimental protocols at SNU accounted for 5–7% of national data. In 2019, the number of institutions registering their own IACUC to APQA was 410, and the average number of protocols reviewed by each active (operative) IACUC was approximately 100. In contrast, SNU-IACUC reviewed over 1,700 protocols or protocol amendments in this period – approximately 20-fold greater than the national average.

Animal numbers, species, and PLs in submitted protocols

Of the approximate 20 animal species, from fish to horses used for animal experiments in SNU, we selected six mammalian species; mouse, rat, rabbit, dog, pig and monkey (including primates), as representative animals for trend analyses of PLs and animal use. Importantly, these six species accounted for more than 90% of all animal experiments performed at SNU, and therefore adequately represented experimental studies and PLs.

As expected, most study animals were mice, followed by rats (Table 3). The numbers of the six representative animal species used for education and research purposes increased from 2.4 million in 2014 to 3.7 million in 2018, nationwide (Fig. 3). Use of the animals across the SNU also increased from 164,409 to 367,205 in the same period, and the proportion of animal use in the SNU has also increased up from 6.8% to 9.9%, when compared with national data during this period. In particular, the proportion of mice and rat use in the SNU was over

10% of total mice and rat use from 359 institutions operating IACUC nationwide in 2018 (Table 3). The increased use of the six representative animal species slowed down in 2019 (Fig. 3), whereas protocol reviews increased in both the SNU (Fig. 1) and nationwide (Table 2). This status reflected a reduction of animal numbers in protocols when compared with the previous year. In the SNU, animal experimental protocols using pigs and dogs were also relatively high as well as mouse and rat protocols. This reason stemmed partly from xenotransplantation studies using mini-pigs [14] and dog cloning [15], respectively. Many scientists are involved in these projects as principal or collaborative investigators. In addition, as the SNU medical school has specific-pathogen-free mini-pig care and breeding facility in its “Biomedical Center for Animal Resource Development,” some protocols are taken over to obtain the permission of the distribution of those pigs and collaboration to share specific mini-pig with other institutions. Rabbits were primarily used for dental and orthopedic implant research in the SNU [16], whereas monkeys were generally used for xenotransplantation [17] or neuroscience [18] research.

As mentioned previously, those protocols assigned to FCR were generally PL-D or -E status but there were exceptions. According to data from 2013 to 2019, the proportion of the representative animal species assigned to FCR review in the SNU-IACUC was 60–70% while the remainder was assigned to DPR (Fig. 4). The reason we compared the number and proportion of “the animals actually used in the protocols” assigned to FCR and DPR, instead of those of “the protocols”, is mainly because the numbers of animals in protocols varies from one to thousands, and the numbers of protocols and the animals in each protocol could be double counted as many researchers apply “Protocol amendment requests” in the same year as well. For instance, in the case of mice for FCR review, numerous protocols were related to cancer or neuroscience research, which traditionally induce high levels of animal pain, while toxicology-related protocols were mainly assigned to FCR review in rats (data not shown).

Table 2. National report of Korea for the animal protocol review from 2015–2019

Number of	2015	2016	2017	2018	2019
Total institutions registered IACUC	351	364	N/A	385	410
Total Institutions operating IACUC ^a	322	326	N/A	359	386
Total protocol review nationwide ^b	22,398	25,053	N/A	33,825	39,244
Protocol review per institution ^{b/a}	63.8	76.8	N/A	94.2	101.7

IACUC: the Institutional Animal Care and Use Committee. Abstracted and translated from the national IACUC Portal [13], operated by Animal and Plant Quarantine Agency of Korea.

Table 3. Trend analyses of animal uses of six representative species in the SNU and nationwide

		2013	2014	2015	2016	2017	2018	2019
Mouse	National			1,893,493	2,212,357		2,739,198	2,851,898
	SNU	136,688	143,192	178,333	181,112	230,958	290,993	309,114
	SNU/National			9.42%	8.19%		10.62%	10.84%
Rat	National			319,519	351,821		320,896	307,577
	SNU	24,445	17,108	25,527	34,141	34,724	32,743	30,631
	SNU/National			7.99%	9.70%		10.20%	9.96%
Rabbit	National			37,178	37,373		34,952	27,001
	SNU	991	652	786	865	818	832	953
	SNU/National			2.11%	2.31%		2.38%	3.53%
Dog	National			9,972	9,897		13,470	12,301
	SNU	857	1,143	522	771	1,571	1,790	824
	SNU/National			5.23%	7.79%		13.29%	6.70%
Pig	National			11,636	11,354		11,808	9,323
	SNU	894	618	488	3,805	2,815	1,551	421
	SNU/National			4.19%	33.51%		13.14%	4.52%
Monkey	National			3,132	2,544		3,084	3,817
	SNU	0	60	127	175	197	110	116
	SNU/National			4.05%	6.88%		3.57%	3.04%

SNU: Seoul National University.

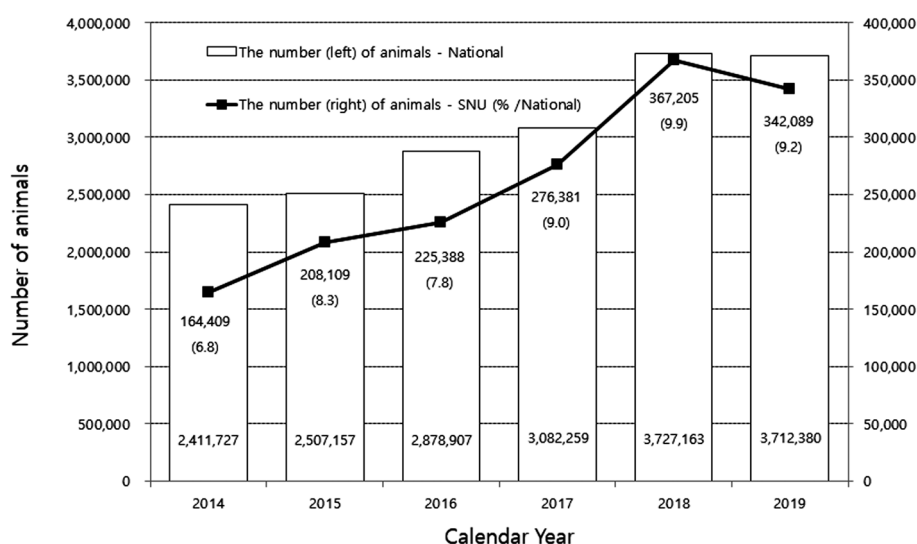


Fig. 3. A comparison of the total numbers of the representative animal species (mouse, rat, rabbit, dog, pig, and monkey) used for education and research purposes in the Seoul National University (SNU) and nationwide, from 2014–2019. SNU data were collected from the Institute of Animal Care and Use Committee (IACUC) of SNU data archives, and national data were collected from the national IACUC portal [13].

Approved, conditionally approved with a request for revision, re-review after revision and rejected

Regardless of PLs, once a professional reviewer examined a protocol, they must assign a decision from the following four categories: 1) approved, 2) conditionally approved with a request for revision, 3) re-review after revision, and 4) rejected. As indicated (Fig. 5) protocol approval patterns were similar to national reports, although SNU-IACUC tended to impose more “re-review after revision” decisions to applicants, as the first decision. In contrast, “rejected” decisions were rare in the

SNU-IACUC. This situation may have been partly reflected by SNU-IACUC strategy. Because some protocols were required to be twice revised to avoid “rejected”, there was a possibility of overlapped aggregation to count “re-review after revision”. Hence, we only showed a tendency here, thus the precise number of original protocols could not be presented. In general, professional reviewers preferred to send back protocols with detailed comments if there were no severe ethical issues, instead of outright rejection.

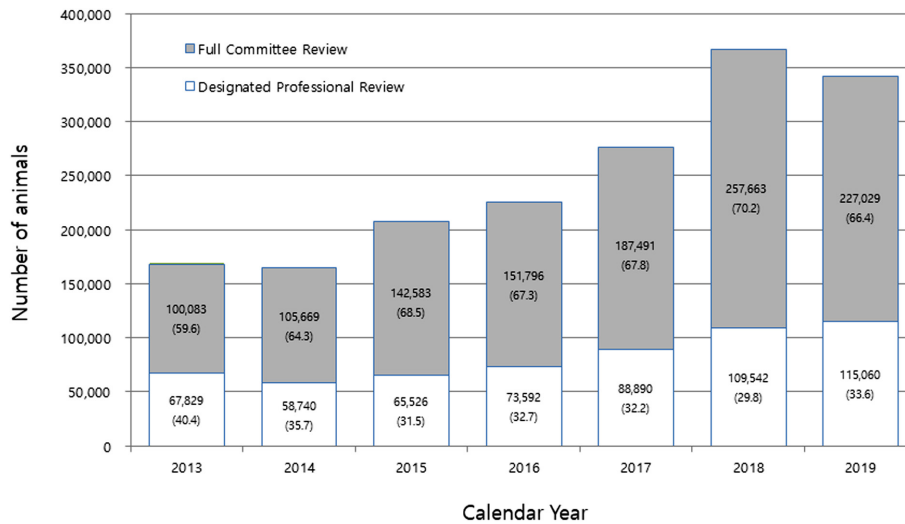


Fig. 4. The numbers and proportions of the representative animal species (mouse, rat, rabbit, dog, pig and monkey) in “full committee review” and “designated professional review” protocols approved by the Institutional Animal Care and Use Committee of Seoul National University (SNU-IACUC), from 2013–2019. The data were collected from the SNU-IACUC data archives.

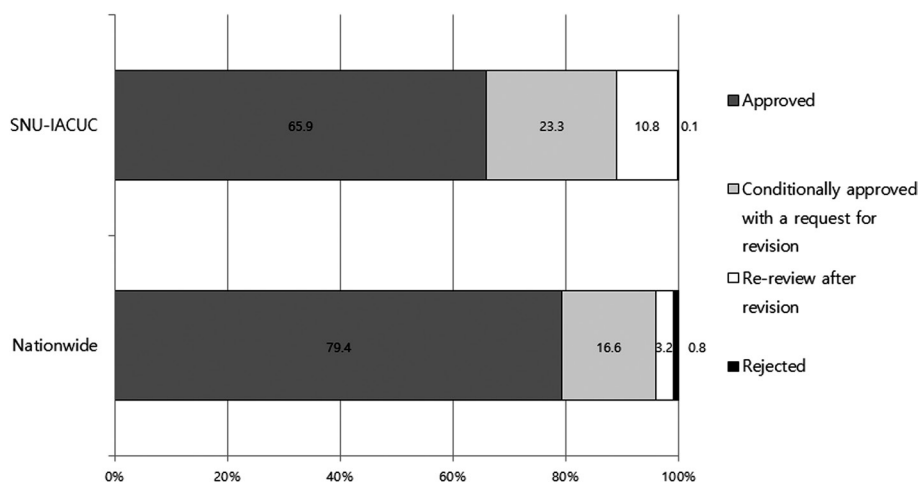


Fig. 5. Comparison of the four approval patterns of protocols reviewed by the Institutional Animal Care and Use Committee of Seoul National University (SNU-IACUC) and nationwide: averages from 2014–2019. SNU-IACUC data were collected from the SNU-IACUC data archives, and national data were collected from the national IACUC portal [13].

Issues with protocol PAM

PAM is an important service of the SNU-IACUC, and is just as vital as protocol review. In performing PAM, the committee ascertains whether researchers have followed all guidelines, and experiments were conducted as approved. In recent years, two important issues were directly observed from PAM activities; 1) overcrowded mouse housing, and 2) concerns related to dog reuse.

During a PAM review in an animal facility, committee members observed an overcrowded cage, which housed a nest of transgenic mice. Unfortunately, the facility had neglected to control mouse populations in cages; therefore, the SNU-IACUC reported this issue to the facility

representative and requested a preventive action report. The facility was then listed in the next PAM schedule. When unsolicited visit was conducted later, the committee found no overcrowded cages.

When reviewing multiple protocols for period extensions by one research group, the professional reviewer observed that several physiological experiments were in progress, but the dog supply for experiments was limited. The reviewer was concerned about the duplicated use of some dogs for different experiments, and reported this issue to the committee followed by PAM. Fortunately no severe violations were observed against dog use; however, no information on “date of birth”, “indi-

vidual number/code”, and “protocol approval number” was observed on cage labels. This lack of vital information could potentially cause researchers to duplicate animal use, or promote incorrect animal use. Hence, the committee requested that researchers update all dog labels, including their respective names for future monitoring. After receiving the action report which was accompanied by the necessary documents, the committee confirmed all required corrections were completed.

Requirement of regulatory amendments

About 2,000 protocols, including protocol amendment requests, are currently under review of the SNU-IACUC. However, as the APA [8] requires that there be only a single committee and restricts it to consist of only 15 or fewer voting members, there are a lot of difficulties operating the IACUC, especially in large institutions such as SNU. In order to address this problem, as of December, 2020, efforts are being made at the National Assembly. Amendments, which would allow the active use of DPR and abolish the limit of the number of voting committee members, are currently on the table. Nonetheless, it remains that the single IACUC policy needs to be revised, and the double regulation imposed upon by the Laboratory Animal Act (LAA) [19] also poses a problem; as the LAA, which regulates animal experimentations for drug development, also limits the number of the committee members to 15 people or less, animal facilities at SNU, including the SNU-ILAR, are required to follow both laws.

APA was primarily focused on preventing abuses of companion animals [20], and now the policy objective and purpose is expanded to enhance public health, sentiment and confidence, through an effective system minimizing animal cruelty and promoting animal welfare, while the purpose of the LAA is to contribute to the development of life sciences and improvement in public health by enhancing the reliability of animal research and testing, through appropriate regulation and oversight of institutions, laboratory animals and animal testing [21]. The animals for testing or experimentation regulated by the LAA (Article 3) should be supplied either by another animal facility, a qualified laboratory animal production facility, or a registered laboratory animal supplier [19]. The categories defined by Article 3 of the LAA is limited to the specific animal testing or experimentation such as the safety and quality controls of foods, functional health foods, medical and pharmaceutical products, non-medical and pharmaceutical products, biomedicines, medical appliances, cosmetics, and narcotics. Although the other types of animal experiments just follow the regulation of the APA which does not limit

the animal supply route, many institutions operating animal facilities are expanding the LAA to most animal experimentations as some experiments are complex and often border the categories. This often makes scientists abandon their animal research at the planning stage because they cannot obtain the animals to use ‘legally’. Reformation of APA and/or LAA including merging these two Acts should be considered instead of repeated amendments of each Act.

To achieve a seamless operation of the IACUC at SNU and in Korea, it seems that simply relying on the possible law reforms is not enough. The most important task seems to be acknowledging and expanding the authority and autonomy of the IACUC.

IACUC, institution and public

Despite ongoing alternative method development to avoid animal experimentation and growing public concern, animal use in scientific research cannot be completely avoided. Hence, it is incumbent that the scientific community communicates with the public to tolerate animal experimentation. This can be done by providing accurate information on animal welfare and clearly demonstrating efforts to reduce animal use in laboratories. In addition, the IACUC and its members should make efforts to narrow knowledge gaps in society, and this includes animal activists and scientists who conduct animal experiments. This strategy can be facilitated by alerting and studying public concerns on animal welfare issues. The IACUC is an autonomous body, and its right to approve and monitor animal experiments and related activities such as PAM are delegated by national authorities. In addition, scientists and veterinarians work together with members or nominees of the Animal Protection Organization (APO) on this committee. Hence, institutions with IACUCs guarantee committee independence and protect their right to approve protocols and other activities. If IACUC decisions are interrupted or intervened by the APO, principal investigators, the national press or social media, then the committee cannot maintain its autonomy.

Discussion

With 15 years’ experience, the SNU-IACUC is facilitating humane animal research and carefully monitoring and controlling experimental animal use in Korea. In this study, as an IACUC pioneer in Korea, we reviewed our SNU-IACUC operations and sought out areas that required improvement. Above all, the operation of a single IACUC policy must be changed to multiple IACUCs for large institutions, which operate mul-

tiple animal facilities e.g., SNU. Needless to say, the institution operating animal facility must secure the authority and autonomy of its IACUC. The authors hope the information provided here will help society understand the operational status of the IACUC in SNU. This applies to those interested in animal welfare, such as IACUC chair and members, administrator, attending veterinarians, principal investigators, institutional officials, government bodies with legal obligations, laboratory animal technicians, and researchers who conduct animal experiments, not only in Korea but also the wider global community.

Disclaimer

The views presented in this article are those of the authors and do not necessary represent the views of the SNU-IACUC.

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