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The status of central ethical reviewing and challenges regarding its introduction to non-interventional studies in Japan

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ABSTRACT

In 2018, we conducted a study on 121 ethics review committee offices in Japan to examine the state of "central review" in non-interventional studies and discern any challenges regarding its introduction. Of the 452 offices that were invited to participate, 121 responded (26.8% response rate), and 35 (28.9%) had records of furnishing contracting agreements with ethical reviews by other research institutions. The merits of central reviewing include easing the burden on ethics review committees, improving the quality level and consistency of ethical reviews, and enhancing the efficiency in conducting them. The demerits include increased administrative overheads and work for researchers, such as preparing application forms and checking institutional requirements, and a lack of clarity regarding who is responsible for conducting the research, which makes it is less desirable for institutions to have their own ethics review committees. This study revealed that the comprehensive introduction of central review in non-interventional studies continues to encounter many hurdles, and promoting central review requires overcoming these challenges one at a time. The Ethical Guidelines for Medical and Health Research Involving Human Subjects will be revised in 2021 to require central review as a part of ethical reviews for non-interventional studies. In the future, central reviews of non-interventional studies will need to be of high quality and conducted efficiently, and this will require research institutions to utilize relevant central review guidelines and checklists.

Keywords: central review, ethical review committee, non-interventional study, quality of ethical review

Abbreviations:
ERC: ethical review committee
CRB: certified review board
IRB: institutional review board
PI: principal investigator
ARO: academic research organization

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INTRODUCTION

Regulations for research on humans, also known as clinical research, are undergoing rapid transformations in Japan. Wrongdoing in Novartis' clinical trial of an anti-hypertension drug prompted calls for measures to prevent the reoccurrence of such an event and encouraged the Japanese government to strengthen clinical research regulations. Repeated clinical study misconduct damaged the reputation of Japanese clinical studies with unnecessary defrayment in health insurance; therefore, the medical community must change its inappropriate relationship with the industry.[1] One of those measures involved strengthening the functions of ethics review committees (ERCs) that deliberate upon and assess the quality of clinical studies.

Even though clinical research uses sophisticated methods, it is not always clear to researchers what requirements they must meet for ethical review and compliance. Thus, variations in quality have emerged among individual ERCs. As a result, a research proposal could certainly be approved without ensuring the lack of wrongdoing in clinical research, even if there were scientific or ethical problems, or the research did not adhere to laws and ethical guidelines. Thus, the work of ERCs has been reduced to a mere formality. Improving the quality of ethical reviews by ERCs has become an urgent matter.[2] One initiative to promote the development of the ethical review system is the Project for the Certification of Ethical Review Committees, started by the Ministry of Health, Labour and Welfare (MHLW) in 2016 (since 2017, it has been under the authority of the Japan Agency for Medical Research and Development [AMED]). The purpose of this project is to strengthen the functions of ERCs by certifying ERCs that can appropriately judge a certain level of ethical and scientific validity and can serve as models for others.[3]

Due to limited financial and personal resources, it is not realistic for every research institution to establish an ERC to conduct high-quality ethical reviews. However, it is realistic for each research institution to contract its reviews to a capable ERC. In large-scale, multi-site joint research, a principal investigator (PI) compiles the contracting agreements from each participating institution, and subsequently the PI submits a batch application to an ERC that is capable of high-quality reviews. This enables higher-quality and more efficient ethical reviews.

Central review has become an institutional requirement for interventional studies (clinical trials), as they are subject to the Clinical Trials Act[4] and the Act on the Securement of Safety of Regenerative Medicine,[5] which were passed and enacted in 2013 and 2017, respectively. However, the Ethical Guidelines for Medical and Health Research Involving Human Subjects ("Guidelines")[6] do not by law require central reviews; therefore, each research institution conducts its own reviews. The Guidelines include studies that are interventional or invasive (with regard to subjects), and these studies can have consequences for society. For these reasons, central reviews need to be promoted so that studies conducted under the Guidelines can also quickly undergo ethical review.

For studies to be conducted under the Guidelines, the 2015 AMED project, "Program for the Development of a Central Institutional Review Board Model," announced guidelines for central reviews and a requirement checklist for commissioning research institutions ("Checklist").[7] However, regarding non-interventional studies, these guidelines need to be simplified as they include many unnecessary items, such as how to deal with reports of adverse incidents. We conducted a survey of ERC offices in research institutions across Japan to examine the status of central reviews in non-interventional studies and the challenges concerning their introduction. This paper reports and discusses the results.

MATERIALS AND METHOD

Overview of the survey

This survey took place between October and December 2018. We mailed and emailed invitations to participate to a total of 452 ERC offices, which are described below. They were asked to respond via Google Forms. We surveyed the following ERC offices: (1) 80 ERC offices that review non-interventional studies of research institutions and had a certified review board (CRB) under the Clinical Trials Act as of November 2018 ("CRB Offices") and (2) 372 randomly chosen ERC offices within private companies, public interest incorporated associations, and a random selection of medical institutions (excluding privately run clinics) that were registered in the MHLW's reporting system[8] ("non-CRB offices"). Of the non-CRB offices, 313 belonged to medical institutions and 59 belonged to private companies or public interest incorporated associations.

The central reviews in this survey include both *centralized central reviews*, where an ERC office is commissioned to review studies from all participating institutions in a multi-site joint study, and *partial central reviews*, where an ERC office is commissioned to review studies from only some of the participating institutions. When we sent invitations to participate, we informed the potential respondents that the survey would be anonymized and that respondents would not be identifiable. We also mentioned that they would not incur a penalty if they did not respond. The response to the survey was taken as consent to participate.

The survey included questions on (1) the non-interventional studies that they recommended as suitable for central reviews, and (2) the non-interventional studies that were not suitable for central reviews (free response). On contracting others for ethical reviews, the survey asked for: (1) the records of furnishing contracting agreements in 2017 and 2018, (2) the procedure for contracting studies, (3) the enactment of regulations for contracting studies, (4) the merits, and (5) the demerits of central review from the perspective of the contracting institution.

Survey items on *being* contracted to conduct ethical reviews that were only given to CRB offices that we assumed received such contracting agreements included: (1) records of receiving contracting agreements in 2017 and 2018, (2) fees for reviews, (3) procedures for receiving contracting agreements, (4) the application documents required of the contracting institution, (5) the merits, and (6) the demerits of central review from the perspective of the contracted institution.

Research Institutions that Responded

Of the 452 ERC offices invited, 121 responded (response rate of 26.8%), composed of 51 of 80 CRB offices (response rate of 63.8%) and 70 of 372 non-CRB offices (response rate of 18.8%). Of the non-CRB offices, 48 of the 313 offices (15.3%) at medical institutions responded and 22 of the 59 offices (37.3%) at private companies or public interest incorporated associations responded (Table 1).

Table 1 Response to a questionnaire

	Institutions	Questionnaires sent	Response (% rate)
CRB Offices	Institutions that have a CRB	80	51 (63.8)
Non-CRB Offices	Medical institutions	313	48 (15.3)
	Private companies or public interest incorporated associations	59	22 (37.3)
	Total	372	70 (18.8)
	Total	452	121 (26.8)

Table 1 shows the number of questionnaires sent and the response rate in terms of institutions.

RESULTS

Non-interventional Studies Suitable for Central Reviews (Multiple Choice) (n=121)

As many as 58 ERC offices (49.7%) recommended "Studies involving specimen/data on a large scale," 35 (28.9%) recommended "All non-interventional studies," 29 (24.0%) recommended "Invasive studies," 29 (24.0%) recommended "Studies where the criteria for eligibility/exclusion and what will take place in the study are already decided," and 6 (5.0%) recommended "Other" studies.

Non-interventional Studies Not Suitable for Central Review (Free Response)

Respondents cited studies with a variety of characteristics, such as "Studies of an invasive nature with regard to their research subjects," "Studies where there is a conflict of interest because of funding from a private company," "Large-scale studies to be conducted nationwide," "Non-invasive studies that are just analyses of specimen/data," "Studies that have to take the research institution's local circumstances into account," and "Studies with so few subjects that there is a risk that individual subjects could be identified."

Contracting Others for Ethical Reviews

Records of furnishing contracting agreements in 2017–2018 (n=121). While 35 ERC offices (28.9%) had records of furnishing contracting agreements, of which 8 (22.9%) had contracted 10 or more ethical reviews, 86 ERC offices (71.1%) had no such records.

Procedure for contracting studies (n=121). Twenty-nine ERC offices (24.0%) responded that "After the ERC office checks it, the head of the institution contracts it," 29 (24.0%) responded that "The head of the institution contracts it through the ERC office," 15 (12.4%) responded that "The researchers contract it," 1 (0.8%) responded that "It is contracted following a consultation with the academic research organization (ARO)," and 47 ERC offices (38.8%) reported that they had "not contracted any studies."

Enactment of regulations for contracting studies (n=121). Whereas 39 ERC offices (32.2%) responded that they had enacted regulations, 31 (25.6%) said that they did not have regulations but were managed effectively, 12 (9.9%) said that they planned to enact regulations, and 2 said that they used written agreements. The remaining 37 ERC offices (30.6%) responded that they had no regulations.

Merits of central review from the perspective of the contracting institution (multiple choice) (n=121). A total of 72 ERC offices (59.5%) responded that central review "eases the burden on ERCs," 68 (49.0%) said "it makes the quality of reviews more consistent," 45 (37.5%) that "it eases the burden on the ERC office," 30 (24.5%) said that "it makes the task of reviewing more efficient," 17 (14.5%) that "you can get support from the contracted institution," and 3 ERC offices (2.5%) said that "it eases the burden on researchers" (Figure 1).

Demerits of central review from the perspective of the contacting institution (multiple choice) (n=121). A total of 67 ERC offices (55.4%) responded that central review "increases administrative overheads," 58 (39.2%) said that "it increases paperwork such as application forms," 39 (32.2%) that "checking the requirements is a bother," 29 (24.0%) that "it makes it less meaningful for institutions to have their own ERCs," and 5 ERC offices (4.1%) responded that "it increases the expenses involved in doing reviews" (Figure 2).

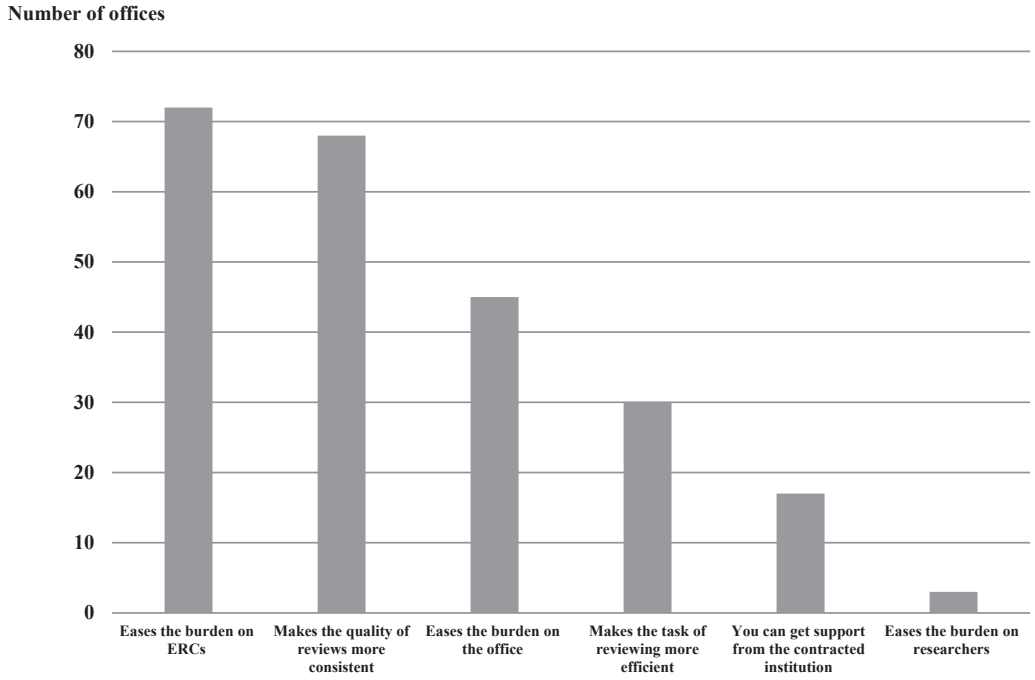

Fig. 1 Merits from the perspective of the contracting institution (n=121, multiple choice)

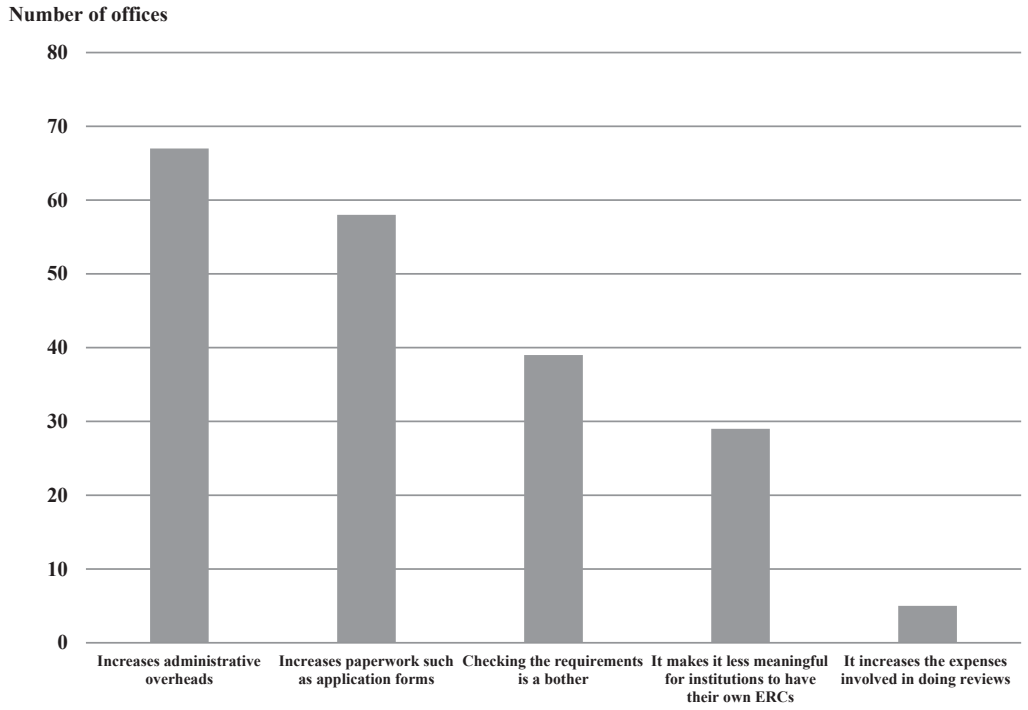

Fig. 2 Demerits from the perspective of the contracting institution (n=121, multiple choice)

Being Contracted for Ethical Reviews

Records of receiving contracting agreements in 2017–2018 (n=51). The items related to being contracted to conduct ethical reviews were only given to CRB offices (ie, offices of ERCs in research institutions that had a CRB) that we assumed received many such contracting agreements. Of the 51 CRB offices that responded, 27 (52.9%) did not have any records of being contracted for ethical reviews of non-interventional studies, whereas 8 offices (15.7%) had been receiving 10 or more contracting agreements for non-interventional studies per year. Looking at the total number of institutions participating in multi-site, joint research studies and the number of those that had been contracted for ethical reviews, there were very few examples of all participating institutions conducting a central review (so-called centralized central reviews); most were partial central reviews, in which some of the participating institutions contracted their studies for review.

Fees for reviews (n=51). A total of 23 CRB offices (45.1%) charged the contracting institution a fee. Of these, 2 (3.9%) charged "¥20,000 or less per review," 4 (7.8%) charged "¥20,001–50,000" per review, 3 (5.9%) charged "¥50,001–100,000" per review, 5 (9.8%) charged "¥100,001 or more" per review, and 9 offices (17.6%) said that the amount they charged depended on the number of contracting institutions.

Procedures for receiving contacting agreements (n=39). Over half of the CRB offices required contracts, with 21 (53.8%) requiring the conclusion of a contract between the contracting and contracted institutions. Of the remaining offices, 17 (43.6%) responded saying that they preferred "going by the review request form," and 1 (2.6%) responded with a reference for "exchanging memos."

Application documents required of the contracting institution (n=51). The CRB offices

required a variety of materials, with 21 (41.2%) requiring "checklists," 19 (37.3%) requiring "standard operating procedures," 6 (11.8%) requiring "a summary of the institution conducting the study," 5 (9.8%) requiring "internal regulations on the safekeeping of specimen/data," 4 (7.8%) requiring "a document enabling outsourcing" and "internal regulations on adverse incidents," and 1 (2.0%) requiring "proof of education/training."

The merits of central reviews from the perspective of the contracted institution (n=51) (multiple choice). A total of 33 CRB offices (64.7%) responded that central review "makes the quality of reviews more consistent," 14 (27.5%) responded that "it improves the quality of ERCs," 12 (23.5%) responded saying that "it bolsters review records," 10 (19.6%) responded that "it makes administrative procedures more efficient," 9 (17.6%) responded that "it increases revenues from review fees," and 4 (7.8%) responded that "it promotes the understanding of ethical reviews among executives" (Figure 3).

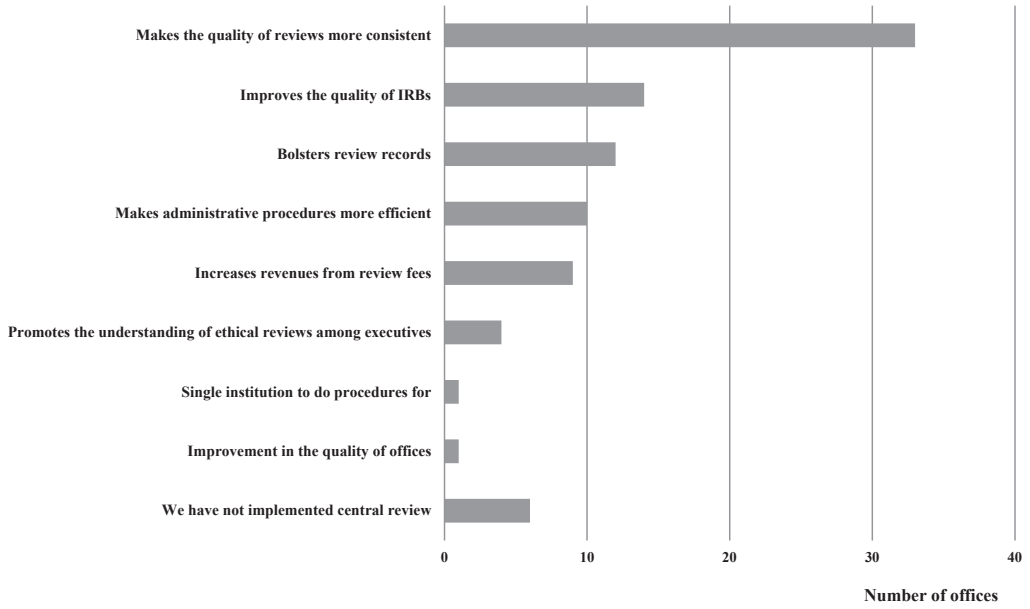

Fig. 3 Merits from the perspective of the contracting institution (n=51) (multiple choice)

The demerits of central reviews from the perspective of the contracted institution (n=51) (multiple choice). A total of 37 CRB offices (72.5%) responded that "the increase in the number of application documents increases administrative overheads," 37 (72.5%) responded that "the increase in the number of review requests increases administrative overheads," 31 (60.1%) responded that "it increases administrative overheads in the form of adverse incident reports, annual reports, etc.," 29 (56.9%) indicated that "it increases the workload involved in helping researchers," 26 (51.0%) responded that"external institutions contact us with greater frequency," 23 (45.1%) indicated that they "bear the responsibility involved in conducting the contracting institution's research," and 15 (29.4%) responded that it "increased overheads involved in improving the system" (Figure 4).

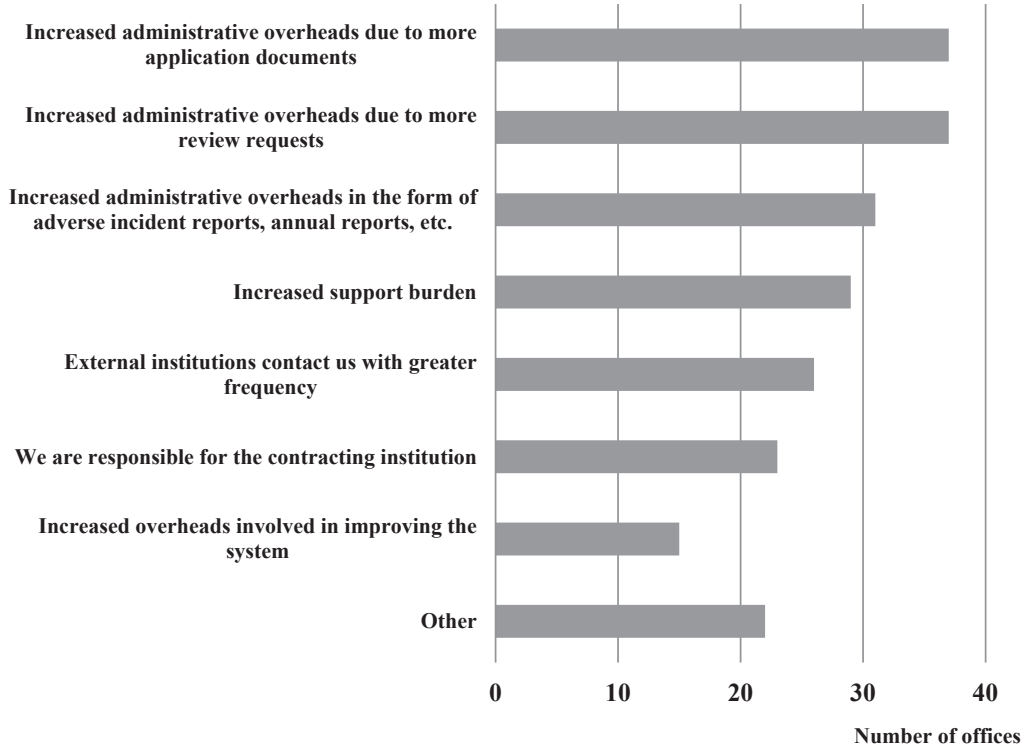

Fig. 4 Demerits from the perspective of the contracting institution (n=51) (multiple choice)

Free Response

Concerns about increased administrative overheads

"The work involved in contracting reviews increases administrative overheads significantly until the central review begins."

"Central reviews under the Guidelines increase procedural overheads such as concluding contracts and exchanging documents to establish the contracting relationship between research institutions. Therefore, research offices must be utilized more effectively."

"The administrative procedures for central reviews must be made more efficient."

"Even though it may reduce overheads for ERCs as a whole, if the contracting institution's ERC office aims to help with the procedures for contracting reviews, it will increase the burden on [ERC] offices."

Issues between research institutions

"Each research institution needs to do its own administrative processing. The work involved in understanding the situation is split between them to the extent that it is not passed through each institution's ERC."

"It is unclear who is responsible in the event that a serious adverse incident occurs at the contracting institution."

"If there are not enough ERCs that can conduct central reviews, then institutions may have to 'wait in line' to contract a review."

"We do not handle a lot of studies like university hospitals do, so central review will decrease the number of studies our institution gets for review and make it difficult for us to maintain

an ERC."
"There may be cases where the central [board] approves a study that an individual institution would not, so institutions ultimately need to conduct their own reviews."
"Central reviews are significant for the use of big data (multi-site, joint research, large-scale clinical research). It is fine if the contracting institution has a certain level of involvement in central review deliberations."

DISCUSSION

The objective of this study was to examine central reviewing in non-interventional studies in Japan to understand the status of the reviewing system, explain the challenges encountered by studies, and determine what can be done to realize more efficient and higher-quality central reviews for non-interventional studies.

Non-interventional studies for which respondents recommended central reviews included "Studies involving specimen/data on a large scale," "Invasive studies," and "Studies where the criteria for eligibility/exclusion and what will take place in the study are already decided." Respondents also recommended central reviews for multi-site studies in which the participating institutions conduct the study under the same conditions; however, there were also many responses to the effect that such studies were *not* suitable for central review, which shows that there is a range of opinions.

At the time of this study, ERCs were not very proactive in contracting or receiving non-interventional studies for central review, with approximately 71% of the ERC offices having no record of contracting and 47.1% of the CRB offices having no record of receiving. One of the reasons cited was that the procedures for central reviews under the Guidelines were complicated and bothersome because they required the heads of institutions to be involved, for example, in contracting studies for review. The Clinical Trials Act and the Act on the Securement of Safety of Regenerative Medicine procedures ensure that a PI compiles the application materials from all participating institutions and submits them to a CRB. In contrast, the Guidelines currently in effect require each researcher to request an ethical review through the head of the institution to which they belong. Thus, submission to the heads of institutions, concluding contracts between institutions, and other complicated administrative procedures must all be addressed when reviewing studies.

Central reviews for non-interventional studies still face some obstacles. Unlike clinical trials (so-called interventional research), plans for non-interventional studies are often written in general terms, and there are various structures for executing them. Sometimes, the participating institutions do not conduct the same studies, but rather take in the patients while others only perform the analysis. Each participating institution has its local rules governing the safekeeping and management of specimens and data, obtaining informed consent, and so on. Rather than each institution touting its own rules, review standards need to be similar so that studies can be conducted uniformly, except when an individual institution needs to conduct its own review of a study already approved by the central board. The format of application materials, such as protocols and explanatory documents, needs to be standardized as well.

When the institution contracted to perform a central review reviews the contracting institution, the former should not be held responsible for how the latter conducts the study and its management systems. The head of each institution conducting a study must be responsible for establishing systems for training the researchers, managing conflicts of interest, and monitoring research progress. The ERC contracted for central review should only have to verify a study

checklist verified by the participating institutions that contracted the review, obviating the need to confirm directly whether or not such systems have been established. Responsibility for conducting the study should be borne by the researchers and the head of the contracting institutions.

It is difficult for ERCs that have been contracted for central reviews to know what systems are in place for conducting studies that are in progress at the contracting institutions, which may also make it difficult to respond adequately should a serious adverse incident occur. To allay such concerns, it is important for the offices of the research institutions involved to foster trusting relationships and share information with each other so that they can respond appropriately and quickly to any adverse incidents and protect research subjects.

In 2016, the US government mandated that clinical studies funded by the National Institutes of Health (NIH) undergo central review by a single IRB and announced the single IRB (sIRB) policy to promote central reviews[9] (in the US, the corresponding term for what is called ERC in Japan is IRB). The National Center for Advancing Translational Sciences has announced its SMART IRB platform to promote single-IRB central reviews by making research institutions adopt and implement the NIH's sIRB policy.[10] However, even in the US, there are challenges for central reviews, such as issues related to the delegation of roles and distribution of responsibilities between IRBs and contracting institutions. The need to overcome these challenges is now a topic of discussion.[11] It has been reported that an IRB that conducts a central review needs to be aware of local information concerning the contracting institutions, such as the status of researchers that belong to them (especially information related to the PI), their institutional guidelines and research management systems, and local cultural and linguistic issues (though that may be particular to the US).[12]

The increase in economic (review fees) and administrative burdens while conducting central reviews of non-interventional studies must be mitigated. Cumbersome paperwork, such as contracts between institutions, must be eliminated, and the most efficient review-contracting procedure possible should be built instead. This study found that approximately half of the institutions contracted for central review did not charge review fees, although from the perspective of building a sustainable central review system it would be necessary to do so. With many non-interventional studies poorly funded, however, there are many studies for which review fees would not be available. Although it has recently become necessary for institutions to charge review fees to maintain their ERCs, such fees should be limited. Furthermore, it should become established practice to include review costs in research grants when applying for them.

Conducting central reviews should reduce the effort involved in ethical reviews while looking at the contracting and contracted institutions altogether because it reduces the effort involved in conducting rapid reviews at each contracting institution. The spread of central reviews may help consolidate ERCs.

CONCLUSIONS

This study revealed that the comprehensive introduction of central review in non-interventional studies continues to encounter many hurdles. Thus, promoting central review for non-interventional studies will require overcoming these challenges one at a time. In 2021 the Ethical Guidelines for Medical Research Involving Human Subjects will be integrated with the Ethical Guidelines for Human Genome Analysis Research, and the new guidelines will introduce a central review on a "one study, one review" basis. In the future, central reviews of non-interventional studies will need to be of a high quality and efficiently conducted, and this will require research institutions to utilize relevant central review guidelines and checklists.

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DISCLOSURE STATEMENT

The authors have no conflicts of interest directly relevant to the content of this article.

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