ISSN 2433-8443

CBEL REPORT

Interdisciplinary Bioethics Research in Japanese and English

Volume 7
Issue 1

CBEL Report Volume 7, Issue 1

By The University of Tokyo
Bioethics Collaborative Research Organization
(BiCRO)

CBEL Report Volume 7, Issue 1: Contents

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Regular Article

Throwing the Baby Out with the Bathwater: The Debate on Heritable Human Genome Editing in Japan in the Aftermath of the He Jiankui Affair

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Abstract

This article advocates for a bolder stance on the part of scientists and other academics in Japan on the issue of therapeutic heritable human genome editing (HHGE). The article's contention is that the current moratorium on HHGE science is unlikely to be broken until the moral scruples that the public has on this subject are addressed and resolved. After reviewing literature that highlights the untenability of the popular objections to HHGE, the article goes on to describe the bold pronouncements made in the aftermath of the 2018 He Jiankui affair by Western scientists and contrast these with the silence, or half-hearted endorsement of HHGE, on the part of the Japanese scholarly elite. The article then ends with a discussion on the role that society and social debate have to play in guiding the advancements in technology and science. Drawing parallels with technological developments in other areas, I finish with an urging towards Japan's scientific elite to play a more proactive role in educating the public on this matter.

Keywords: heritable human genome editing; Japan; debate; He Jiankui; reproductive therapy; science

1. Introduction

Although this is not popularly known, Japan is the place where the idea was born that led to the United States (US)-led Human Genome Project. As has been described in a number of academic publications (Cook-Deegan 1994; Ito 2005; Kishi 2004; Sasaki 2019), it was a University of Tokyo molecular biologist, Akiyoshi Wada, who pioneered in the 1970s the idea of developing technology to allow the rapid sequencing of deoxyribonucleic acid (DNA). Indeed, in 1975, having the vision of an automated rapid DNA sequencing machine, he applied for government funding to try to establish a project whereby he could build one. Alas, this visionary's contemporaries in Japan lacked the prescience to see the value of what he was proposing. Wada's initial request for funding was rejected, and even when some funding was granted to him a while after his initial application, the sum was so insignificant that he decided the next best way to proceed in order to see his vision realized was to try to set up an international collaborative project, with his foreign academic counterparts bringing the necessary funds. Crossing the Pacific, he went to the US to talk to James Watson—one of the scientists who had been credited in 1962 with the Nobel Prize for the discovery of the structure of the DNA. By that time, under the auspices of Wada's minor national

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project at home, two other Japanese scientists, Yuzuru Fushimi and Hideki Kambara, had invented technologies that would later become critical to the success of the Human Genome Project . Regrettably for Wada and his team, however, since Japan and the US were in the midst of a trade war, Wada's initiative would be misinterpreted by the Americans as a threat, with the upshot being that the government there would refuse Wada funding, only to expend the most generous sum of $120 million to Watson to lead his own version of the project of sequencing a human's entire genome. Ultimately, as has been opined many a times in Japanese science circles, when a draft of the first human genome sequenced was published in 2001, merely 6% of it was done by Japanese scientists, whilst the contribution to it by the US and the UK was 59% and 31% respectively. The idea started from Japan, but in the end the fanfare over success happened in the US and the UK, with Wada, Fushimi and Kambara becoming the "unsung heroes" of the Human Genome Project.

Against the background of how cutting-edge Japan had been in the field of molecular biology in the 1970s/1980s and how a lesson was contained therein for the country to advance research ideas generated domestically, it is conspicuous that, as of today, no Japanese research exists that seeks to wield control over the genome—such research seems still very much neglected here. In particular, it stands out that the number of scientific papers reporting experimental work on heritable human genome editing (HHGE) is at zero. As a search on databases such as Google Scholar, PubMed, and Researchmap (which is operated by the Japanese government), would reveal, as of 17 March 2023, science seeking to manipulate the human genome, even only for research purposes, is virtually non-existent here. Given that the country continues to be a powerhouse for research and innovation in many other areas, this failure to engage with HHGE is quite notable.

With regards to HHGE, what ought to be noted is that on a normative level the debate has greatly advanced in recent times, with a great many bioethicists and legal scholars advancing the argument that using HHGE, at least in the case of reproductive therapy, is justifiable. Although a number of works can be cited that do this (e.g., Gyngell et al. 2019, Johnson 2021, and Thaldar 2022), it is perhaps worth singling out the argument developed by the Stanford University's Henry Greely, who refutes the fundamental premises of the objections made to HHGE. Greely explains, for example, that there is no such thing as "the human germline genome", which is sacred and in need of preservation for posterity; in fact, he points out, there are 7.3 billion human germline genomes, because every living person has a 'germline genome'' and "each one is different" (Greely 2021: 209). Furthermore, ad hoc genomic changes, he highlights, occur all the time anyway, both inadvertently and as a result of deliberate actions on our part. To cite one of Greely's examples that illustrate this point, the use of synthetic insulin has boosted over time the number of people with DNA variations leading to diabetes, since those with this condition who would have died as a child in the past now live long enough to reproduce. Similarly, the transition from hunting to farming centuries ago resulted in a greater number of copies in our gene pool of starch-digesting genes.

To return the focus on HHGE in Japan, with a view to pushing this country to play its part in the development of a responsible path for therapeutic HHGE, the

present article seeks to put the spotlight on this regrettable state of affairs. Some discussion already exists that sees the absence of HHGE science in Japan as a result of confusing and contradictory regulatory rules in this area. In particular, as it will be elaborated on later in the article, the Hokkaido University scholar Tetsuya Ishii has pointed out how the Japanese situation is regulated by a multitude of administrative guidelines, as opposed to by a clear single law, and that although some people might interpret this bureaucratically drawn framework to permit genome editing of human embryos, as long as it is at the laboratory level and not for use in reproduction, it is also possible to come to a conclusion from certain earlier-installed rules that this is not the case (Ishii 2020). Even though, since Ishii's submission of his manuscript, it is also possible to point to the instalment in 2019 of the "Guidelines for Research Using Gene-altering Technologies on Human Fertilized Embryos", which permits genome editing on surplus embryos, and the revision in 2021 of the "Ethical Guidelines for Assisted Reproductive Technology Research that Involves the Generation of Human Embryos", which permits genome editing on new embryos), the existence of these earlier-dating regulations Ishii mentions could be said to make HHGE still a grey area in Japan. Against this backdrop, the present article seeks to advocate for a bolder and more proactive stance by the scholarly community here, just as has been the case elsewhere, in interacting and communicating with the citizenry about what the science involves and what issues are at stake. In seeking to advance this agenda, the article joins Nakazawa et al. in arguing for a vibrant grassroots-level domestic discussion on this subject, with social scientists and humanities specialists taking the leadership role (Nakazawa et al. 2018). Whilst promulgating clear rules would also be beneficial, ultimately, I argue, the way to break the stalemate in Japan's HHGE science is through helping the public overcome the moral scruples it has about it.

2. The global state of HHGE debate after the He Jiankui storm

In May 2015, precisely 17 months since China claimed the monkey in the global race to gene-edit mammals (Niu et al. 2014), a team of 16 Chinese scientists reported the first experimental work of this kind in human embryos. Although the embryos used in this experiment were non-viable, since the world was far from having reached a consensus that clinical HHGE would be morally acceptable, the authors had found it difficult to take their manuscript to print. Indeed, prior to being accepted by Protein and Cell—a journal established in 2010 with an editorial board comprising predominantly of China-based scientists—they had received rejections from both Nature and Science. As for the results presented by the paper, they demonstrated an astonishing lack of fidelity: of the 71 embryos that survived intervention with the clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 to correct the mutation causing the lethal heritable blood disorder beta thalassemia, 28 were cleaved, and only 4 contained the replacement genetic material, but with regards to these 4 embryos, a great many off-target mutations were found, and still more were envisioned (Liang et al. 2015).

Two years after this paper, another manuscript of this nature emerged, this time making it to Nature, from within the American community of scientists. In this

second study, the team of the developmental biologist Shoukhrat Mitalipov at the Oregon Health and Science University in Portland made the landmark claim that his team had managed to rid human embryos of the disease mutation giving rise to the deadly condition known as hypertrophic cardiomyopathy. "By modulating the cell cycle stage at which the DSB [double-strand break] was induced", the team stated, "we were able to avoid mosaicism in cleaving embryos and achieve a high yield of homozygous embryos carrying the wild-type MYBPC3 gene without evidence of off-target mutations" (Ma et al. 2017). Asserting in this way that they have corrected the pathogenic gene mutation whilst avoiding problems such as mosaicism, Ma et al. advocated the use of HHGE as a complementary therapeutic measure to preimplantation genetic diagnosis (PGD), only to be immediately thereafter challenged to provide a validation of their conclusions (Egli et al. 2017).

With little else being reported in the way of research on applying CRISPR/Cas9 for human reproduction at the time of the Second International Summit on Human Genome Editing in 2018 in Hong Kong, the announcement by the Chinese biophysicist He Jinkui came as a shock that he had gone on to apply this technique clinically. Although, as elaborated by Stanford University legal scholar Henry Greely (Greely 2019), there are numerous other levels at which He's action was condemned, the criticism of his decision to employ in humans a tool for which there was no demonstrable unequivocal evidence that it is safe and effective was overwhelming. The resulting furore, which has been widely covered in the media and academic circles, saw calls for a moratorium coming from various directions, including from leading scientists (Lander et al. 2019; Wolinetz & Collins 2019; Getz & Dellaire 2019; Baylis 2019; see also Welcome Sanger Institute 2019; Royal Society 2019; SCIMEX 2019).

As the dust was settling from the He announcement, however, the voice was raised from within the Western academic community that the missteps committed by a few rogue scientists should not divert us from the goal of acquiring technical competency in HHGE so as to respond to the unmet medical need of certain patients. Although all of Harris 2018a & 2018b, Steffann et al. 2018, Gyngell et al. 2019, Brokowski & Adli 2019, Hammerstein et al. 2019, Lovell-Badge 2019, Rasnich 2020, and Greely 2021 could be cited as expressions of this idea that there is a moral imperative to act upon HHGE science, one particularly strong exposition of it is found in a 2019 essay entitled After the Storm—A Responsible Path for Genome Editing and penned by the influential trio of geneticists George Q. Daley of the Harvard Medical School and the Boston Children's Hospital, Robin Lovell-Badge of the United Kingdom (UK)'s flagship for discovery research in biomedicine—the Francis Crick Institute, and Julie Steffann of Paris University and the Necker-Enfants Malades Hospital (Daley et al. 2019). Daley, it is worth noting, had previously individually gone as far as outlining what a responsible pathway for clinical translation of HHGE would look like (Daley 2018; also cited in Daley 2020). Included in this outline were both: a list of safeguards for ensuring faithful implementation, with a special focus on the chief concern about mosaicism, and a hierarchy, developed on principles of medical triage, of "disease indications that might represent a gradation of medical necessity, and thus permissibility" (Daley 2020: 8). However, it was here in this joint essay that Daley argued most forcefully

against making a reflex reaction to He, citing the extent to which patients stand to benefit from HHGE. Apart from the couples where both partners carry homozygous recessive disease alleles, or those where one of the members is homozygous for an autosomal dominant disease allele such as that for Huntington's disease, there are all those couples, a significant majority, the trio of authors argued, who are affected by an autosomal recessive or dominant genetic disease and whom pre-implantation genetic diagnosis (PGD) has failed (Daley et al. 2019: 899).

Today, whilst caution is still very much the watchword when it comes to HHGE, a moratorium on it has increasingly come to be seen as too extreme a measure. To elaborate, as evident from the analysis of the wealth of ethics reports and statements issued on HHGE by 2018 by various national and international bioethics bodies (Brokowski 2018), there is a consensus that clinical HHGE should be banned at present. On the other hand, however, the common conclusion of the three arguably highest profile national bodies that have issued documents on HHGE—namely, those of the US, the UK and Germany—was that no categorical ethical barriers exist for its use for reproductive purposes. To illustrate the tenor of one of these texts, the US National Academies of Sciences, Engineering and Medicine (NAS), for example, states that:

> Heritable genome-editing trials must be approached with caution, but caution does not mean they must be prohibited. If the technical challenges were overcome and potential benefits were reasonable in light of the risks, clinical trials could be initiated if limited to the most compelling circumstances, if subject to a comprehensive oversight framework that would protect the research subjects and their descendants, and if sufficient safeguards were in place to protect against inappropriate expansion to uses that are less compelling or less well understood. (NAS 2017: 134)

To go back to George Daley—the Dean of Harvard Medical School—though, even at the 2018 Summit where He Jiankui made the revelation that provoke widespread immediate outrage, he made the step of asking for HHGE not to be ruled out in principle. Daley, who, by his own admission, had been involved in reviewing the above-mentioned first HHGE scientific papers, stressed that the feasibility for HHGE is here and that the ethical considerations can no longer be put off. To quote him:

> … a number of groups have applied gene editing now to human embryos in the context of in vitro fertilization and attempting to determine variations of a protocol that would enhance the fidelity and reduce mosaicism. I think there has been an emerging consensus that the off-target problem is manageable, and in some cases even infinitesimal. There are some interesting proofs of principles, like diseases such as beta-thalassemia that could potentially be approached with this strategy (Daley 2018).

This was followed by him laying down the details of the procedure through which embryos can be effectively assessed for what he calls "fidelity of genome editing safety" (Ibid.). Included in this outline were both: a list of safeguards for ensuring faithful implementation, with

a special focus on the chief concern about mosaicism, and a hierarchy, developed on principles of medical triage, of 'disease indications that might represent a gradation of medical necessity, and thus permissibility' (Daley 2020, 8).

3. The current state of the debate in Japan: Too limited

Whilst strong admonitions, such as the ones by Daley, Lovell-Badge and Steffann mentioned above, were made in the West against knee-jerk reactions to He Jiankui, in Japan, by contrast, the atmosphere was one of complete condemnation of HHGE, even as an idea. Nobody was seen to argue here the case for a responsible path forward for HHGE or to uphold the principle that if it were technically possible for us to change our germline genome safely and effectively, there might be cases where it would be compelling to do so. Nor did anyone take the challenge of pointing out the flaws that underpin the common objections to HHGE and highlighting the responsibility to continue pursuing mastery of the technique for the sake of those currently without a therapeutic reproductive option. Even today, the difference is striking between the record of firm affirmations made in the aftermath of the He announcement by scientists and bioethicists in other countries of the prospective value of prudently implemented HHGE, and the silence, on the other hand, that remains in Japan on this subject.

In the midst of this silence on the part of the academic community, it is no wonder that public support for HHGE was found to drop in the aftermath of the He Jiankui fiasco. Indeed, in the absence of counterforces, the episode of the botched HHGE experiment in China only damaged the populace's view of this procedure in a way that further inhibits debate. To cite concrete evidence of this, through a sequence of questionnaires from the three years of 2016, 2018 and 2019, it was shown in the context specifically of Japan that the widely publicised 2018 HHGE scandal led to a significant decline in the acceptance of the use of the genome editing technology in general, and particularly so for human reproduction (Watanabe et al. 2020). More specifically, the surveys, which asked questions about the acceptability of genome editing in a range of fields, from fishery to agricultural breeding, to human reproduction, revealed in the final sample year a stark rise in disapproval of the technology's utilization of fertilized human eggs—from 12% in 2018 to 29% in 2019. Moreover, respondents on whom use in fertilized human eggs made the strongest impression were found to have risen from 15.9% in 2018 to 20.4% in 2019, with this being interpreted by the trio of scientists that had conducted these surveys as "suggesting the news of the twin babies in China had a substantial influence on the Japanese public," raising public awareness of the genome editing methods, but also damaging their reputation. Whilst this is merely a speculation, it is possible to consider that this documented change in public opinion in Japan will make leading public figures, including politicians, and prominent scientists more hesitant when it comes to discussing HHGE. Ultimately, this can only restrict the public debate, meaning that the ethical challenges surrounding the technology would remain unexamined, with the moratorium in science continuing to the detriment of those who need HHGE.

Recently, an attempt was made by Hokkaido University's bioethicist Tetsuya Ishii to create momentum

for the enactment of a law on HHGE, which he saw as the most appropriate approach to breaking the moratorium on this science. In particular, lamenting the virtually non-existent HHGE science, Ishii pointed to is the confusion and uncertainty that must exist amongst Japanese scientists as to whether they are free, i.e. without the threat of being penalized, to engage in such work. "When it comes to research involving human germline genome modification", he elaborated, "the Japanese regulatory framework [as created by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Ministry of Health, Labour and Welfare (MHLW)], is characterized by gaps and inconsistencies" (Ishii 2020: 442), with the definitions used in it "often [being] at odds with scientific understanding" (Ibid.: 448). "What Japan needs [he concluded] is a coherent, up-to-date, fundamental law that governs both basic research and medical use of human germ cells as well as embryos, one that is discussed in and approved by the Diet, Japan's bicameral legislature, instead of by a Cabinet Committee, to ensure broad social understanding of, and support for, scientifically important research on human germline (Ibid.: 463).

Apart from this discussion by Ishii, what needs to be added is that following the approval to use human embryos in genome editing research in China and the United Kingdom in 2015 and 2016 respectively, the Japanese community of scientists and other academics, or more specifically the Science Council of Japan (SCJ)—an organization of over 2,200 members representing Japan's academic community—issued a call to the government to enact legislation. The SCJ stated in its call that HHGE science is acceptable if the goal is to learn about the natural reproductive process (pursuing it for the purpose of developing a therapy for people with intractable diseases was deemed unacceptable), and it wanted to see a law promulgated to this effect (SCJ 2017). In the meantime, at the government level, deliberations had already begun as to whether regulatory action is needed. In particular, an investigative committee set up within the Council for Science, Technology and Innovation (CSTI) operating under the Cabinet Office had been discussing the ethical issues since 2016. With the academics' recommendations being issued, the further step was taken of establishing a Task Force under the CSTI to review the policy on handling of embryos. During the deliberations within this Task Force, the view was expressed by a number of Japanese scientific Societies (e.g., the Japan Medical Association, the Japan Society for Gene and Cell Therapy, the Japan Society of Human Genetics, the Japan Society of Obstetrics and Gynecology, and the Japan Society of Reproductive Medicine) that there is a limit to which they can self-regulate and that the promulgation of a law on HHGE is necessary in order to prevent misuse of the technology (Nakazawa et al. 2018; Kato 2020). However, when the CSTI released draft guidelines for HHGE research, it became clear that the SCJ's and various Societies' plea for a law would not be granted, and that, if anything is done at all, then that would be a revision of the existing ministerial-level guidelines. Indeed, rather than making a higher-level policy recommendation, the report simply urged the two bureaucratic bodies with jurisdiction over this matter, namely the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Ministry of Health, Labour and Welfare (MHLW) to update their existing guidelines (CSTI 2018, 2019 & 2021). As for the content of the update, this also departed from the

SCJ recommendations in that approval for basic HHGE research was proposed, albeit in two separate stages, for both—the acquisition of knowledge about embryogenesis and for reproductive therapy—with so far only the former being acted upon jointly by the ministries (MEXT & MHLW 2019).

Disapproving of both of these departures from its suggested policy, the SCJ felt compelled to issue in 2020 another set of recommendations (SCJ 2020). In it, it stated unambiguously that 'basic research aimed at clinical application should also be prohibited' (Ibid., 7). Three justifications that were offered in the way of explaining this stance were that: 1) the message might be sent 'to the people presently living with disabilities or with intractable diseases that they should not have been born'; 2) 'a woman who accepts the pregnancy and childbirth could be [sic.] persuaded into not giving birth to a child with a disease or disability', with this 'result[ing] in an unacceptable endorsement of eugenics and a pattern of thinking that is the same as in the old [coercive] eugenics'; and 3) the right to self-determination of future generations would be violated (Ibid., 5-6).

Despite this tone of the SCJ with regards to HHGE research for reproduction, they clearly expected the science to happen for the purpose of understanding embryogenesis. That this is the case could be gauged from a chapter on Japan by Ishii, who served on both scholars' committees, which was included in the above-mentioned 2020 volume Human Germline Genome Modification and the Right to Science. To discuss again with focus on Isshii, whilst his proposal for a reinvigoration of the parliamentary debate is valid and goes some way in the direction of addressing the glaring absence of discussions on the subject, Ishii only goes half the distance. This is because, firstly, he falls short of advocating HHGE for reproductive therapy, arguing that the science should be conducted only insofar as to open the "black box" of conception, full stop. Secondly, he advocates for the criminalization of Japanese nationals who might in the future go and seek HHGE abroad. In an effort to motivate the politicians to enact a law in this area, Ishii suggests that the latter is necessary as a deterrent to Japanese patients who might want to flee for treatment abroad. "[I]n the era of cross-border reproductive medicine", he seems to write in alarm, "some prospective parents might choose to go abroad to seek germline modification as the last-resort remedy for their infertility problems, or to treat a genetic disease in their offspring" (Ibid.: 465). To prevent this from happening, he argues, "[a] national law is needed, one with extraterritorial reach", because ministerial guidelines would not be enough to stop such patients (Ibid.: 465).

Although this issue is tangential to the main one discussed in this article, it is worth arguing that the criminal sanctions that Ishii has in mind in such a scenario would be best directed at charlatan service providers and not the patients who act out of desperation. Indeed, condemnation of couples to domestic reproductive exile, which a law that promises to penalize a national who returns from HHGE therapy on foreign soil is, would perhaps be too much of a draconian measure to have.

4. A call for a bolder stance by Japanese scientists and other academics

How many people in Japan share the knowledge, with Greely above, that there is no such a thing as "the human germline genome" that passes unaltered from generation to generation? And, how many people share

the knowledge that each of our genomes changes, as a result of what we do as well? And how many people realize that the proposed CRISPR-induced changes for reproductive therapy simply change the frequency with which a particular, already common gene variant, is seen in the population?

Instead of urging reflection on such questions, whatever limited debate there exists in Japan on this subject stops at the level of the dogmatic, unquestioning acceptance of the view that HHGE is a line that should never be crossed. This situation seems regrettable. Japan has a lot to contribute technologically to the therapeutic HHGE project, and a societal debate here is a necessary precondition for science to happen. Society indeed has a key role to play in the development of such a technology, impacting the path that science takes. Feeding into policy decisions as it does, societal debate potentially serves as a powerful factor in guiding science, and the two need to march hand in hand. There exist numerous examples where this has hitherto been the case. Take, for example, the way society directed the development of nuclear technology. If it were not for political and war considerations in the US in the 1940s, the so-called Manhattan Project would have never been launched to develop the nuclear bomb. True, nuclear technology might well have developed independently of that Project at some later point in time. However, to say that those scientists operated in a void, taking an initiative of their own, would be a gross misrepresentation. To make the same point with an example where the reverse has happened (i.e., the lack of social support for a technology making the associated science stagnate), it must be remembered what happened with human embryonic stem cell research in the late 1990s and the 2000s. In the US—arguably the leading global scientific powerhouse, the ban during the era of the Bush Administration on the use of federal funding for research using human embryonic stem cells on all but a limited number of cell lines already in existence led to many opportunities for developing cures of intractable illnesses being lost, as scientists had no choice but to choose alternative directions in which to spend their time and efforts. In Japan too, the work involving the manipulation of embryonic stem cells that began at the turn of the century never took off, precisely because the widely held public view of this as a taboo precluded the debate from deepening. Ultimately, in this jurisdiction, resources became focused on using induced pluripotent stem cells, despite the apparent short-term technical advantages, for the development of therapeutics at least, of embryonic stem cells.

As these examples suggest, HHGE science cannot progress in an ethical emptiness. A vibrant public debate is needed to direct it. It is time that Japanese scientists and other academics stepped up and fulfilled their role of enlightening the public.

Acknowledgement

Financial support for this research was received from the Japan Society for the Promotion of Science (Project No. 20K01446 & Project No. 21KK0221).

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Received 1 July 2023
Accepted 22 February 2024
Published online 12 July 2024

Regular Article

Development of Case-Based Rubrics to Assess the Achieved Competencies and Performance of Novice Research Ethics Consultant Trainees through Case-Scenario Discussions

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Abstract

Background: Recently, the need for research ethics consultation services has increased worldwide, but the number of experts who can provide those services (research ethics consultants: RECs) remains quite limited. We have been developing educational materials and training programs for novice REC trainees, aiming to help them acquire competency and appropriate performance skills as expert RECs. However, there was no tool to assess their achievements. This paper reports on our attempt to develop rubrics for novice REC training based on exercises with case-scenarios.

Methods: A case-scenario, developed according to an authentic consultation case, entitled "an observational research study with a conflict of interest (COI)," was used to make rubrics.

Results: A preliminary general scoring guide rubric, a task-specific scoring guide rubric, and a task-specific four-level scoring rubric were developed for the case-scenario. The general scoring guide rubric comprised seven preliminary dimensions for assessment, while the task-specific rubrics developed according to the general one comprised the six dimensions.

Conclusion: The developed task-specific scoring guide rubric and the four-level scoring rubric appear to be useful for assessment of educational achievement in terms of competencies and performance skills as an expert REC.

Keywords: Research ethics; Consultation; Training; Case-scenarios; Rubrics

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Introduction

In clinical research involving human subjects, researchers are required not only to collect scientific data, but to do so while protecting their research subjects appropriately [1]. Almost all ethical guidelines for medical research involving human research subjects require an ethics review board (ERB) to make the final "go/no-go" decision regarding scientific and ethical aspects of the research. As such, as defined in formal documents, the ERB plays a regulatory role. Notably, research ethics consultation services are, more or less, voluntary and non-regulatory activities, in which a research ethics consultant (REC) with expertise in clinical research ethics provides requesters or clients many of whom are clinical researchers with professional advice on ethical and to some extent, scientific aspects of a research project. For example, advice may be offered on how to protect research subjects appropriately, or how to plan the study to ensure better a reduced risk of the research; this insight is given from a perspective that is independent from that of the ERB. In addition to those brought up at the time of research planning, REC consultation covers a wide range of topics [2] that range from basic biomedical science at the bench through clinical experimental studies, and from giving advice on how to respond to comments by an ERB to an issue on publication ethics after research completion, to name just a few. Therefore, to a great extent, RECs are expected to support researchers and clinical research institutions in order to promote ethical conduct in research activities.

However, REC activities represent relatively new practices in medical ethics, and the number of expert RECs is still quite limited in many countries. Therefore, developing the human resources for those eligible to provide REC services is necessary. Unfortunately, underdevelopment of educational curricula and effective training methods for RECs seems to be an issue across the globe. This begs the question of how potential RECs should be trained to become competent RECs, and how the acquisition of their expertise and performance should be evaluated.

In order to function professionally as a REC, REC trainees must acquire sufficient competencies. Matsui et al. have proposed a model list of core competencies required of RECs [3]; these core competencies for an expert REC include 61 items in three major domains: knowledge, skills, and personal characteristics. Of these, 35 competencies are minimal requirements for REC functioning at a basic level (**Appendix 1**), and trainees are expected to acquire at least those 35 competencies to become a competent "novice REC." Our research project group (designated AMED Matsui Group in the present article), funded by the Japan Agency for Medical Research and Development (AMED), has been developing teaching materials/programs for research ethics education, and has been conducting novice REC training workshops since 2017 as part of the project [4]. The workshops aim to help participants acquire competencies that enable them to respond professionally to research ethics consultation requests; namely, to identify ethical issues inherent in the consulted medical research studies involving human subjects, to analyze the issues, to find solutions, and to advise or recommend appropriate/better/best courses of action by their own efforts. To this end, workshop participants perform training exercises with case-scenarios which were developed based on authentic prior research ethics consultations, and discuss in a small group, as reported elsewhere [4].

The basic structure of novice REC training programs for workshops is well established, although significant challenges remain with regard to assessment of both trainee acquisition of the required core competencies and their performance as competent RECs. Use of a rubric is one way to evaluate such items; as noted by Stevens and Levi, "At its most basic, a rubric is a scoring tool that lays out the specific expectations for an assignment [5]." Thus, we have developed rubrics to assess competencies and performance of our workshop participants as REC trainees through the workshop programs. The purpose of this article is to describe the rubric development process and provide example rubrics for use in novice REC training programs based on case studies, so that other institutions or groups of people engaged in REC education might be able to modify and implement them for their own REC training programs.

Methods

Underlying REC training workshop programs

As of 2019, when rubric development was initiated, the AMED Matsui Group consisted of 17 members, some of whom were RECs and/or ERB members, and whose areas of expertise included medicine, pharmacology, nursing, public health, law, philosophy, bioethics, research ethics, education, and medical education. During 2018-2019, those members led the novice REC training workshops, which consisted of a lecture (50 min sessions) and 2-4 case-scenario discussion sessions by small groups (90-180 min sessions, 150 min average), held over one or two days. We prepared two case-scenarios for the one-day workshop (an example agenda for the one-day workshop is reported elsewhere [4]) and three or four for the two-day workshop. Scenarios to be used vary for each workshop to ensure that attendance at multiple workshops will not result in redundant discussions. During case-scenario discussions, questions are posed based on the model of core competencies. However, not all core competencies are included in a single case-scenario.

Workshop participants (REC trainees)

Because the goal of the workshops was to train potential novice RECs with the minimum necessary (basic) abilities, regardless of their fields of specialization, our established conditions for participation were that one has some basic knowledge of and experience in bioethics and/or medical ethics, and that one is likely to or hopes to be in charge of research ethics consultation and education. Therefore, workshop participants had a variety of occupations, comprising medical doctors, nurses, clinical laboratory technicians, medical representatives at pharmaceutical companies, academic researchers/teachers, research ethics committee office staff, and so forth.

Table 1 Consultation case about "an observational research study with a conflict of interest (COI)"

Case description:

We received the following consultation request from a researcher at a university hospital.

"I was thinking of doing research on a new image analysis method to help diagnose a particular disease using images obtained from past medical treatment," he said. "The research would use new image analysis software recently developed by a company and compare it with conventional image analysis software. The company was going to provide us with the necessary software and research funds. I have done many similar studies in the past, but an issue was raised for the first time by the ethics review board (ERB). In past similar studies, I was allowed to use an opt-out method without obtaining individual informed consent. However, when I underwent the ethical review this time, I was told by the ERB that this research was not an academic research study, and that they would not allow me to use an opt-out method. I was puzzled by this response from the ERB, as it was different from that in the past. I am now unable to conduct the research study as planned. What should I do?"

Q1: What are the laws, regulations, and guidelines that may be relevant to this consultation case? List the ones that come to mind, and research in advance the content of the written clauses and regulations that you think should be followed particularly in this case.

Q2: When we asked the researcher about the conflict of interest (COI) policy of his university hospital, he said:

"When we do a joint research project with a company, we are supposed to submit a COI sheet to our hospital. I wrote down how much research funding I would receive for this research and which software I would receive. I completed the documentation for this the same way I have done in the past, and there should have been nothing special about this research. Also, there is a COI Management Committee in our hospital, where conflicts of interest in research are reviewed."

As a research ethics consultant (REC), is there any additional information that you need to extract from the researcher?

Case description (cont.):

The initial information that the client gave us was insufficient for us to give thoughtful advice. Accordingly, we asked the following questions:

"Would you tell us a little more about the research plan? The way the research will be handled will depend on the content of the research plan and the research partnership, including the form of the contract with the company. Also, could you give us more specific details about the comments you received from the ERB?"

In response to the consultant's question, the client replied as follows:

"First of all, I plan to use the new software to reanalyze image data to look into the differences between the new software images and the conventional images. If this research is successful, the new software may improve disease diagnostics. Of course, the impact of clinical use of the software needs to be examined in another study, but I believe that it will help us to make more accurate diagnoses. Also, I will only ask the company to provide equipment and research funds at a basic level, and I will not let them have any input into the analysis or interpretation of the research results. Although I was going to sign a joint research agreement with a company, I was planning to obtain consent from the research subjects via an opt-out method, as all of the images I will be using were derived from previous diagnostics work."

Regarding the comments received from the ERB, the client responded as follows:

"Apparently, the review raised the issue of conflict of interest. I have conducted other joint research studies with the same company. If you add up all the research funds I have received from this company, it is indeed a considerable amount, but the oldest research was done 10 years ago, and I have been reporting conflicts of interest accordingly. Besides, the amount of the funding I will receive for this research is not very large. Even at a high estimate, it is expected to be around 500,000 yen (or 4,500 US dollars) per year."

Additionally, he noted the following:

"The other problems seemed to be the adjustment of the software and the preliminary conference for publication of the paper. Adjustment means that the company sets the parameters for the analysis software before the analysis. This is done by sending anonymized diagnostic images to the company using a correspondence table. According to the person in charge at the company, this work can be completed within a day. Nevertheless, because of this adjustment work, I was told that this research was joint research with a company. The preliminary conference for publication of the paper means that I will report the contents of the paper to the company once before publication and obtain their consent before publication if there is a possibility that the company will be disadvantaged. I believe that this is a common agreement in joint research studies like this one. According to the ERB, this study did not ultimately qualify as an academic research study overall, and they said that I needed to obtain individual informed consent, as the research study could not be conducted using the opt-out method among the research subjects. But I'm not convinced. I designed the research project myself, and I will conduct the image analysis and the comparative evaluation. If this is not considered an academic research study, then would they argue that every other study I have conducted in the past may not be considered academic research either? More importantly, this research will use imaging data from about 1,000 patients; it will be impossible to obtain informed consent from all 1,000 patients."

Table 1 (cont.) Consultation case about "an observational research study with a conflict of interest (COI)"

Q3: Considering the responses from the researcher, which part of Japan's ethical guidelines for medical research is relevant to the conclusions of the ethics review?
Q4: Speculate why the ERB made this decision.
Case description (cont.):
At the end of the consultation, the researcher said: *"In all honesty, I just want to do this research, regardless of whether it is considered academic research or not. I've already negotiated with the company on this research, and I can't say that I can't do it now at this stage. In the end, what do I need to do to be allowed to conduct this research?"*
Q5-1: If, on the one hand, the goal is to conduct the research as "an academic research study," how would you, as a REC, suggest modifying the research plan?
Q5-2: On the other hand, if the goal is to conduct the research as "a product development research," how would you, as REC, suggest modifying the research plan?
Q6: Based on the above analysis, come up with your final advice to the researcher.

A case-scenario

In this article, we created rubrics for the consultation case shown in **Table 1**, tentatively entitled "an observational research study with a conflict of interest (COI)." In research ethics consultation, issues of research integrity such as conflicts of interest may also be addressed in addition to issues of clinical research ethics centered on human subject protection [6]. We therefore chose this case as a good case that includes both of the above issues.

The scenario pertained to a research situation involving collaborative development of medical imaging analysis software by academic researchers and a company, and involved potential ethical issues related to a financial COI. As is evident in **Table 1**, this case-scenario was structured in multiple layers in the form of a dialogue: (1) the initial case description/explanation of the situation and ethical problems which a requesting researcher encounters in his/her research project, followed by several subsequent questions of concern (Q1, Q2); (2) dialogue on additional information between the requester and a REC; with time, the dialogue revealed further details of the situation, along with several concerning questions (Q3, Q4); and (3) the last case description and relevant questions were offered by a REC to develop final advice for researchers (Q5, Q6). The goal of this case-scenario was to train participants to develop competency in understanding research design/protocol, to discover relevant regulations including institutional policies and seek necessary additional information through dialogue with the requester, to identify and analyze ethical issues pertaining to this case, and to create final advice that would be ethically better/best.

REC performance assessments and rubrics

With some exceptions, research ethics consultation is generally conducted as a team [7], because it deals with various ethical issues as well as areas of biomedical research projects involving human subjects whose characteristics inevitably require review and analysis at a multi-disciplinary level [8]. By functioning effectively and practically regardless of whether as individuals or as a team, RECs are expected to improve the overall ethical quality of a consulted research project, thus, maximizing social benefits and protecting research subjects – namely, minimizing risks to the research subjects who

must solely bear all of the risks pertaining to the research project [8]. Therefore, RECs need to be equipped not only with sufficient knowledge of research ethics but also research ethics reasoning skills and the ability to translate the consequences of this reasoning into practical advice or feasible recommendations for the requesters [9-12].

Rubrics are often used by teachers as a tool to evaluate student performance in terms of such higher-order thinking and its subsequent outputting (practical performance) skills; in the general context of bioethics education, the use of rubrics has recently increased in popularity [10, 12]. Rubrics can also be used as a tool for self-assessment. As stated by Stevens and Levi (2013), "By encouraging students to think critically about their own learning, rubrics can inspire precisely the pattern of 'self-assessment and self-improvement' intrinsic to creating the kind of motivated, creative students we all want in our classes.[13]" Usually, a rubric is presented in the form of a table with descriptions of the characteristics corresponding to each level of achievement, according to the multiple assessment levels of performance (e.g., four levels). A rubric that shows only the descriptions of the highest level of performance for each dimension is called a scoring guide rubric [14]. In many cases, the knowledge, understanding, and skills required by a performance task are divided into multiple, more detailed dimensions, and each dimension is then assessed. Thus, the dimensions of a rubric represent the components of a performance task.

Rubrics development processes

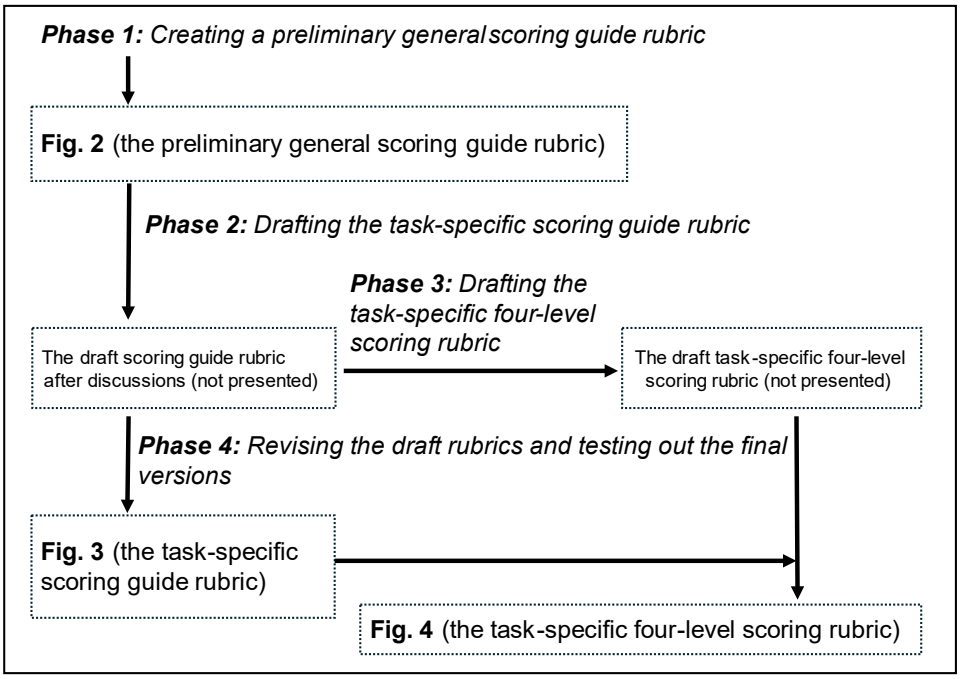
A scoring guide rubric and a four-level scoring rubric have advantages and disadvantages respectively. For instance, according to Stevens and Levi (2013), while a scoring guide rubric requires extra time for scoring and giving narrative feedback, it takes a relatively short amount of time to create, and has the advantage of allowing flexible, individualized assessment for each learner. A four-level rubric allows for quick scoring and detailed formative feedback by simply checking and circling [15]. Therefore, we thought that creating a four-level rubric would compensate for the downside of the scoring guide rubric, which requires extra time for scoring and giving feedback. From these reasons, we created not only a scoring guide rubric, but also a four-level rubric, with the goal of increasing the efficiency of the evaluation in the workshop.

Two experts experienced in research ethics consultation (KM, KY), two researchers of education (KK, AY), and one medical education/ethics expert (AN) in the AMED Matsui Group joined the other Group members in the meetings to lead the rubric development process for the above-mentioned consultation case. The author of the case-scenario (US) in the Group also participated in some of the team meetings to explain and confirm key ethical issues pertaining to this case. The rubric team discussed how to create and draft rubric prototypes, and made several revisions to them via group e-mails, which followed the face-to-face discussions in which a consensus was reached about the rubrics.

Following these discussions, the team and the Group decided to create a scoring guide rubric and a four-level scoring rubric for REC trainee performance self-assessment. In summary, the rubric creation processes comprised the following four phases (**Fig. 1**): 1) create a preliminary general scoring guide rubric; 2) develop the draft task-specific scoring guide rubric;

3) develop the draft task-specific four-level scoring rubric; 4) revise the draft rubrics and test out the final versions in actual REC training workshops.

Fig. 1 The rubrics development processes



1) Creating a preliminary general scoring guide rubric

To create a preliminary general scoring guide rubric, the rubric team utilized as performance examples the reports on three different consultation case-scenarios including the present case, which were submitted by eight participants of one of our workshops held in 2018. As the very first step, these reports were used for consideration of the dimensions of the performance tasks (a breakdown of the core competencies involved in the performance tasks). Members also referred to explanations and model answers for each consultation case provided by the case-scenario authors, using these as resources to think about the dimensions of the preliminary general scoring guide rubric. Following careful examination of the reports submitted by the participants and the explanations and model answers of the case-scenarios, and having discussed the dimensions involved in the tasks, the team created a preliminary general scoring guide rubric for novice RECs (**Fig. 2**). This preliminary rubric was not a task-specific rubric for assessment of performances specific to a particular task, but a general one that can be applied to many different tasks [16]. Accordingly, the task description became very general, i.e., "Analyze ethical issues involved in the assigned consultation case and prepare your own final advice to the client." As a scoring guide rubric, the preliminary rubric contained only the descriptions of the highest level of performance in each dimension.

Fig. 2 The preliminary general scoring guide rubric for novice research ethics consultants

Task Description: Analyze ethical issues involved in the assigned consultation case and prepare your own final advice to the client. You, as a research ethics consultant, are expected to do the following:
_____.

	Preliminary Dimensions	Descriptions of the highest level of performance	Assessment Highest (4) <=> Lowest (1)
I	*Identifying issues (points of interest)*	• Identifies all points that contain ethical issues. • Sufficiently understands the correlations among the points of interest.	4 3 2 1
II	*Understanding and knowledge of relevant laws, regulations, guidelines, and other rules (by governments, academic societies, etc.)*	• Points out the relevant laws, guidelines, regulations, and other rules. • Sufficiently understands the contents of the relevant laws, guidelines, regulations, and other rules. • Understands the normative nature (existence, strength, etc. of the binding force) of the relevant laws, guidelines, regulations, and other rules.	4 3 2 1
III	*Understanding and knowledge of relevant research ethics principles, concepts, discussions, etc.*	• Correctly points out relevant research ethics principles, concepts, discussions, etc. • Sufficiently grasps the contents of the relevant principles, concepts, discussions, etc.	4 3 2 1
IV	*Hearing additional information*	• Correctly determines whether or not obtaining additional information is necessary. • Sufficiently hears additional information needed to analyze ethical issues. • Comprehends the client's policies and thoughts, research conditions, and limitations in practice.	4 3 2 1
V	*Analyzing ethical issues*	• Adequately analyzes all ethical issues. • Provides sufficient justification for each issue and reasons why it cannot be justified.	4 3 2 1
VI	*Devising and presenting best recommendations and alternatives (second best recommendations, etc.)*	• Devises the best solution as an ideal one. • Adequately devises alternative solutions (e.g., second best one). • Presents the best practical solution based on the client's policy and thoughts in accordance with the conditions and feasibility of the research.	4 3 2 1
VII	*Appropriateness as advice*	• Appropriately selects the analysis results that should be disclosed (or not) to the client. • Uses appropriate expressions in Japanese. • Expressions are easily understood. • Clearly indicates that the answers from the research ethics consultant constitute only advice or recommendations, and not instructions or orders.	4 3 2 1
Overall evaluation: ☐ **Expert level (4)** ☐ **Advanced level (3)** ☐ **Basic level (2)** ☐ **Below basic level (1)**			
Comments:			

2) Drafting the task-specific scoring guide rubric

The rubric team provided the created preliminary general scoring-guide rubric for assessment to the members of the AMED Matsui Group, including the author of the case-scenario in question (US). We then attempted to evaluate the original reports with the general scoring guide rubric and discussed where there might be variation in performance of workshop participants, and areas in which evaluation using the general rubric might have been difficult for members. Thus, we examined its suitability as a tool to assess case-based performance.

However, after hours of discussion, we concluded that the general scoring guide rubric developed through three different case-scenarios was too abstract to fit each specific ethical issue raised by each case-scenario. Consequently, we decided to develop task-specific scoring rubrics based on the general scoring guide rubric, rather than revising the general rubric and continuing to use it.

The case-scenario author was asked to draft a prototype of a task-specific scoring guide rubric in accordance with the specific case-scenario. Once a task-specific scoring guide rubric was drafted by the author, we re-examined its dimensions and the suitability of the dimension descriptions.

3) Drafting the task-specific four-level scoring rubric

We set a matrix of four scale levels for a task-specific scoring rubric. The case-scenario author was also asked to draft a prototype of a four-level scoring rubric in accordance with the specific case-scenario. In parallel with the revision of the task-specific scoring guide rubric, the dimensions of the four-level scoring rubric prepared by the author were also examined, along with descriptions of what constitutes each level of performance in each dimension. Specifically, we set the dimensions according to the task-specific scoring guide rubric that had been developed. Then, after deciding on the labels for each scale level, we wrote down the content for each description of performance used in the matrix.

4) Revising the draft rubrics and testing out the final versions

Following the examinations described above, we asked the author to revise the task-specific scoring guide rubric and the task-specific four-level scoring rubric. We also asked him to reexamine whether or not there was any discrepancy with the aim of the case-scenario or the points for evaluation with regard to the rubrics, and whether or not the expressions were suitable from his own perspective. After the author made minor revisions to the descriptions of each level of performance of each rubric, we completed the tentative final versions of both rubrics, which comprised six dimensions.

At a separate venue in which we were given another opportunity to conduct a REC training workshop using the relevant case-scenario, “an observational research study with a conflict of interest (COI),” we presented the tentatively finalized task-specific scoring guide rubric to workshop participants and asked them to self-assess their performance using the rubric. Because the workshop could provide only 15 minutes to the attendees for an opinion-and-evaluation survey, we used a task-specific scoring guide rubric which enables them to read through in a shorter amount of time. Twenty-two workshop participants completed this self-evaluation.

Results

1) Creating a preliminary general scoring guide rubric

Fig. 2 shows the preliminary general scoring guide rubric. The seven preliminary dimensions developed for this rubric were basically ordered according to the flow of consultations common to research ethics consultation services described elsewhere. Briefly, when a consultation request comes from a client, the REC will first listen to the client and identify points that involve or potentially raise ethical issues. During the conversation, s/he will identify relevant regulations, ethical principles and/or, if any, global discussions in the field of research ethics concerning the case. If s/he thinks that more information is necessary for analysis, s/he will ask the client for the detailed and/or additional information. Then, s/he will analyze ethical issues identified in the case, and develop and recommend several better/best options of optimal countermeasures, in consideration of practical conditions and feasibility of the research project.

Accordingly, preliminary dimensions were arranged as follows: Dimension I: "Identifying issues (points of interest)"; Dimension II: "Understanding and knowledge of relevant laws, regulations, guidelines, and other rules (by governments, academic societies, etc.)"; Dimension III: "Understanding and knowledge of relevant research ethics principles, concepts, discussions, etc."; Dimension IV: "Hearing additional information"; Dimension V: "Analysis of ethical issues"; Dimension VI: "Devising and presenting best recommendations and alternatives (second best recommendations, etc.)"; and Dimension VII: "Appropriateness as advice."

2) Drafting the task-specific scoring guide rubric

Fig. 3 shows the finalized version of the task-specific scoring guide rubric prepared for the consultation case, entitled "an observational research study with a conflict of interest (COI)." At the top of the table, the task description reads, "Analyze ethical issues involved in the assigned consultation case and prepare your own final advice to the client. You, as a research ethics consultant, are expected to *be able to provide advice on an observational research study with a conflict of interest, taking into consideration both the opinions of an ethics review board and the intentions of the client/researcher.* The underlined words are specific to this consultation case, and the rest are common statements used in task description of other cases. This rubric adopts a scale of four levels of performance corresponding to each dimension, with levels ranging from 1 to 4 (lowest to highest); notably, while the preliminary scoring guide rubric presented these in descending order, we inverted this in this rubric.

To represent the components of the performance task (i.e., knowledge, understanding, and ethical reasoning skills), our rubric assesses the following six dimensions: I: Understanding of the contents of a requested consultation; II: Understanding and knowledge of relevant laws, regulations, guidelines, and other rules (by governments, academic societies, etc.); III: Recognition of additional information to be collected from the client; IV: Understanding and knowledge of relevant research ethics principles, concepts, discussion, etc.; V: Analysis of ethical issues; and VI: Devising and providing countermeasures. Appended to each of those dimensions are corresponding question numbers in the concerned case-scenario, and corresponding dimension-specific

descriptions of the performance task are presented. Because this is a scoring guide rubric, those descriptions exemplify the highest level of performance and are therefore often allowed to contain 'judgmental' terms, such as "appropriately" or "properly."

Fig. 3 The task-specific scoring guide rubric on "an observational research study with a conflict of interest (COI)"

Task Description: Analyze ethical issues involved in the assigned consultation case and prepare your own final advice to the client. You, as a research ethics consultant, are expected to *be able to provide advice on an observational research study with a conflict of interest, taking into consideration both the opinions of an ethics review board and the intentions of the client/researcher*.

	Dimensions	Descriptions of the highest level of performance	Assessment Lowest (1) <=> Highest (4)
I	*Understanding of the contents of a requested consultation* (All questions)	• Properly understands the contents and circumstances of a consultation case.	1 2 3 4
II	*Understanding and knowledge of relevant laws, regulations, guidelines, and other rules (by governments, academic societies, etc.)* (Q1)	• Knowledgeable about the *Ethical Guidelines for Medical and Health Research Involving Human Subjects* ("The Guidelines"), and *the Guidance* of the Guidelines. • Knowledgeable about the Act on the Protection of Personal Information (Act No. 57 of May 30, 2003/Article 76(1)(iii): Exclusion of academic studies from application). • Understands "clinical research" and "specific clinical research" as defined by the Clinical Trials Act (Act No. 16 of Apr 14, 2017). • Knowledgeable of some of the official guidelines and rules regarding COI (e.g., *"The Guidelines for Formulation of Conflicts of Interest Policy for Clinical Research," "The Report of the Working Group on the Conflicts of Interest," "The Guidelines for Managing Conflicts of Interest (COI) in Health, Labour and Welfare Science Research by the Ministry of Health, Labour and Welfare," "The Japanese Association of Medical Sciences COI management guidelines,"* etc.).	1 2 3 4
III	*Recognition of additional information to be collected from the client* (Q2)	• Recognizes that additional detailed information should be collected with regard to the research plan, including the contents of the research, the research team, and the contract with a collaborating company. • Recognizes that additional detailed information on the comments by the Ethics Review Board should be collected.	1 2 3 4
IV	*Understanding and knowledge of relevant research ethics principles, concepts, discussions, etc.* (Q3, Q4)	• Understands "collaborative research" and "collaborative research implementing entity" as defined in the Guidelines (Guideline 2(9), (10); Guidance p.14, Explanation 5). • Understands the concept of "existing information" and the requirements when providing existing information to other research implementing entities (defined in Guideline 12-1(2), (3)). • Understands the concept of "conflicts of interest." • Understands the difference between academic and non-academic research (e.g., commercial/for-profit research).	1 2 3 4
V	*Analysis of ethical issues* (Q3 to Q5)	• Appropriately analyzes the rationale behind the decisions by the Ethics Review Board in relation to the relevant laws, regulations, guidelines, and/or other rules. • Appropriately analyzes the justification for conducting the research as "academic research," and understands its merits and demerits. • Appropriately analyzes the justification for conducting the research as a "commercial/for-profit research," and the merits and demerits therein. • Appropriately focuses analysis on the important ethical issues, in addition to listing issues involved in the consultation case. • The issues being analyzed are properly reflected in the proposals/recommendations.	1 2 3 4
VI	*Devising and providing countermeasures* (Q5, Q6)	• Appropriately considers the ideal research plan. • Appropriately considers a feasible research plan. • Respects the client's intentions, and appropriately devises how the research plan should be modified or revised in accordance with the conditions and feasibility of the research. • Appropriately selects which analysis results should be told to the client (or not).	1 2 3 4

Below, a column for comments is prepared, in which evaluators can list the good points of the workshop participant responses and explain the grounds for the evaluations of each dimension of their performance.

Comments:

Dimension I represents a participant's ability to grasp the contents and circumstances of the consultation case from a bird's-eye view. Dimension II represents whether the participants of the workshop have sufficient knowledge of laws, guidelines, regulations, and other rules related to the particular case. For instance, *The Ethical Guidelines for Medical and Health Research Involving Human Subjects,* the then-effective non-binding ethics guidelines jointly issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare (2014), were one of the then-most important governmental research regulations on medical research (and relevant for most cases). Equally important and relevant was the then-Act on the Protection of Personal Information, which deals with the handling of personal information in Japan and thus relates to most consultation cases. At the very least, anyone who wants to be a REC is commonly expected to have a good understanding of these basic regulations, and of any specific regulation such as an institutional COI policy. Dimension III represents a participant's ability to seek and find additional necessary information to be collected from the client in order to develop good advice or recommendations. Dimension IV represents the understanding of the principles and concepts of research ethics relevant to the case, such as COIs and the difference between academic research and product development. Dimension V represents the assessment and analysis skills of the participant on ethical issues involved in the particular case, such as critical thinking about ethical concerns relevant to the research project raised by the ERB. It also represents their ability to identify or appreciate any rationale for and behind a particular case brought for consultation. Dimension VI represents whether the participants can develop appropriate and practically feasible advice or recommended courses of action for the client.

3) Drafting the task-specific four-level scoring rubric

Based on the finalized task-specific scoring guide rubric, we have developed a task-specific four-level scoring rubric (**Fig. 4**). As was done to develop a preliminary general scoring guide rubric, we completed the description of each dimension of the four-level rubric by referring to the model answers in the relevant case-scenario and the sample answers from workshop participants. The task-specific rubric adopts a scale of four levels of performance. The terms used to describe the four levels are unacceptable (1), not yet competent (2), competent (3), and exemplary (4). As the Scale Level 4 (Exemplary) is the highest level of performance, the description of the Level 4 corresponds to that of the task-specific scoring guide rubric.

Fig. 4 The task-specific four-level scoring rubric developed for the consultation case

Task Description: Analyze ethical issues involved in the assigned consultation case and prepare your own final advice to the client. You, as a research ethics consultant, are expected to *be able to provide advice on an observational research study with a conflict of interest, taking into consideration both the opinions of an ethics review board and the intentions of the client/researcher*.

	Dimensions	Unacceptable (1)	Not yet competent (2)	Competent (3)	Exemplary (4)
I	Understanding of the contents of a requested consultation (All questions)	Has many misunderstandings about the contents and circumstances of a consulted case.	Has slightly misunderstood the contents and/or circumstances of a consulted case. Alternatively, does not have a concrete understanding of the contents and circumstances of a consulted case.	Has some concrete understanding of the contents and circumstances of a consulted case without any misunderstanding.	Fully understands the contents and circumstances of a consulted case in a correct and concrete manner.
II	Understanding and knowledge of relevant laws, regulations, guidelines, and other rules (by governments, academic societies, etc.) (Q1)	Lists only one of the following:	Lists two of the following:	Lists three of the following:	Lists all of the following:
		(1) *The Ethical Guidelines for Medical and Health Research Involving Human Subjects, and their Guidance* (2) *The Act on the Protection of Personal Information (Article 76)* (3) *The Clinical Trials Act* (4) *The official guidelines and rules regarding COI*			
III	Recognition of additional information to be collected from the client (Q2)	Recognizes none of the following:	Recognizes only one of the following:	Recognizes to some extent both of the following:	Recognizes fully both of the following:
		(1) *the necessity of additional detailed information regarding the research plan (the contents of the research, the research team, the contract with a collaborating company, etc.)* (2) *the necessity of additional detailed information on the comments by the Ethics Review Board*			
IV	Understanding and knowledge of relevant research ethics principles, concepts, discussions, etc. (Q3, Q4)	Understands none or only one of the following:	Understands two of the following:	Understands three of the following:	Understands all of the following:
		(1) *"collaborative research" and "collaborative research implementing entity" in the Guidelines* (2) *"existing information" and the requirements when providing existing information to other research implementing entities* (3) *the concept of "conflicts of interest"* (4) *the difference between academic research and non-academic research*			
V	Analysis of ethical issues (Q3 to Q5)	Analyzes none or only the second of the following: (1) the rationale behind the decisions by the Ethics Review Board in relation to the relevant laws, regulations, guidelines, and other rules; or	Analyzes to some extent the following: (1) the rationale behind the decisions by the Ethics Review Board in relation to the relevant laws, regulations, guidelines, and other rules, while focusing analysis on the important ethical issues;	Appropriately analyzes the following: (1) the rationale behind the decisions by the Ethics Review Board in relation to the relevant laws, regulations, guidelines, and other rules, while focusing analysis on the important ethical issues;	Appropriately analyzes both of the following: (1) the rationale behind the decisions by the Ethics Review Board in relation to the relevant laws, regulations, guidelines, and other rules; and
		(2) the justification both for conducting the research as "academic research," and for conducting the research as a "commercial/for-profit research," and their respective merits and demerits.	but insufficiently analyzes (2) the justification both for conducting the research as "academic research," and for conducting the research as a "commercial/for-profit research," and their respective merits and demerits.	but appropriately analyzes only one of the following: (2a) the justification for conducting the research as "academic research" and its merits and demerits, and (2b) the justification for conducting the research as a "commercial/for-profit research" and its merits and demerits.	(2) the justification both for conducting the research as "academic research," and for conducting the research as a "commercial/for-profit research," and their respective merits and demerits, while focusing their analysis on the particularly important ethical issues, and appropriately relating the issues to the proposals / recommendations.
VI	Devising and providing countermeasures (Q5, Q6)	Considers none or only one of the following: (1) the ideal research plan, and (2) a feasible research plan.	Devises some modifications toward a feasible research plan that is as close to the ideal as possible, but does not respect the client's intentions fully.	Fully respects the client's intentions, and devises modifications toward a feasible research plan that is as close to the ideal as possible, but excessively emphasizes issues that are not important in this consulted case, and/or insufficiently points out important issues.	Fully respects the client's intentions, devises modifications toward a feasible research plan that is as close to the ideal as possible, providing adequate countermeasures without excess or deficiency.

Below, a column for comments is prepared, in which evaluators can list the good points of the workshop participant responses and explain the grounds for their evaluations of each dimension of their performance.

Comments:

4) Revising the draft rubrics and testing out the final versions

There are several differences in the dimensions and the evaluation forms between the preliminary general scoring guide rubric and the task-specific scoring guide rubric. First, the task-specific rubric for the case-scenario, "an observational research study with a conflict of interest (COI)," lacks the dimension labeled "Identifying issues (points of interest)," which appears in the preliminary general rubric as its preliminary Dimension I. That is because, in contrast to many other case-scenarios, this particular one is not structured to ask workshop participants to identify issues (points of interest) for examination; as such, the dimension of "Identifying issues (points of interest)" is retained in those other task-specific rubrics.

Second, Dimension I of the task-specific rubric ("Understanding of the contents of a requested consultation") does not appear in the general rubric. We have added this dimension not only to the case of concern, but also to all other rubrics, regardless of the scenario, because several reports on three consultation cases submitted by our workshop participants revealed a lack of understanding about the contents and circumstances of consultation cases which cannot be reduced to poor performance in other dimensions.

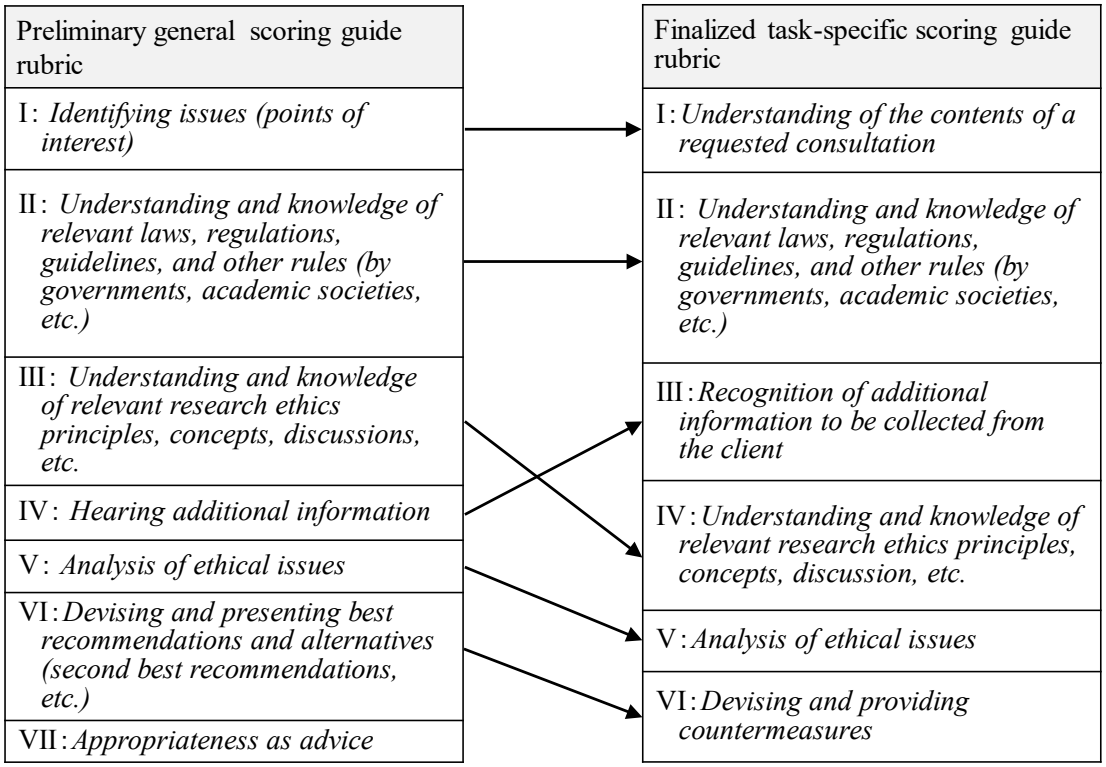
Third, we omitted "Overall evaluation" of performance from the task-specific scoring guide rubric, which is prepared for the preliminary general scoring guide rubric. The reasoning behind this was that, although REC trainees are expected to achieve the minimum standard on each dimension in order to develop good advice for a specific consultation case, giving an overall evaluation score, or grade, for a particular scenario may lead them to misunderstand their true overall competency as a REC. A comprehension test is often given at the end of the training session, for the purpose of measuring the level of achievement in knowledge and is graded as correct or incorrect; in contrast, a rubric evaluates the performance qualitatively, not as correct/incorrect. However, this comprehensive evaluation may lead to incorrect perceptions. Therefore, we concluded that the task-specific rubric should simply function for REC trainees as a tool for self-assessment and self-awareness of their current competency, but not as a pass/fail judgement.

Fourth, the title of Dimension III ("Recognition of additional information to be collected from the client"), equivalent to the preliminary Dimension IV in the preliminary rubric, was renamed from "Hearing additional information," because the ability to recognize what additional information needs to be collected from a consultation requester is more essential than the mere ability to hear this from the requester.

Finally, the preliminary Dimension VII ("Appropriateness as advice") in the preliminary rubric was ultimately excluded from the task-specific rubric, because it was considered similar to and likely to be absorbed into the preliminary Dimension VI ("Devising and presenting best recommendations and alternatives (second best recommendations, etc.)"). Accordingly, the description, "Appropriately selects the analysis results that should be disclosed (or not) to the client," which appeared in the preliminary rubric, was transferred into the preliminary Dimension VI so as to form Dimension VI, "Devising and providing countermeasures," of the task-specific rubric. The remaining descriptions in the preliminary Dimension VII were eliminated, as we decided

to focus more on the quality of the final advice itself, rather than the external formality of the language or expressions. Those changes of dimensions are illustrated in **Fig. 5**.

Fig. 5 Dimension changes



Next, we asked our twenty-two workshop participants of the five groups to self-assess their individual performance in each group using the finalized task-specific scoring guide rubric (**Table 2**). We found that three groups marked several scores with a high standard deviation (SD) of 0.8 or higher, and that such high standard deviations were observed mainly in Dimensions III and IV. The high standard deviations suggested the possibility of a wide range in participant self-assessment skills in some groups, and/or that the descriptions of Dimensions III and IV might have been inappropriately developed.

Table 2 Self-assessed scores (mean ± SD) of the workshop participants by the task-specific scoring-guide rubric

	Dimension I	Dimension II	Dimension III	Dimension IV	Dimension V	Dimension VI
Group 1	2.5±0.6	2.5±0.6	**2.3±1.0**	**2.8±1.0**	2.5±0.6	2.5±0.6
Group 2	**3.0±0.8**	2.7±0.5	3.0	**2.8±1.0**	2.5±0.6	2.5±0.6
Group 3	3.2±0.4	2.8±0.4	3.2±0.4	2.8±0.4	2.6±0.5	2.6±0.5
Group 4	3.0±0.7	3.0	2.6±0.5	2.8±0.4	2.6±0.5	2.6±0.5
Group 5	2.8±0.5	2.8±0.5	**3.0±0.8**	2.8±0.5	**2.0±0.8**	2.5±0.6
All members (n=22)	2.9±0.6	2.8±0.4	2.8±0.7	2.8±0.6	2.5±0.6	2.6±0.5

Assessment score: from the lowest (1) to the highest (4)
SD: a standard deviation

At the draft development stage, when considering the descriptions of four levels of performance in the Dimension II ("Understanding and knowledge of relevant laws, regulations, guidelines, and other rules (by governments, academic societies, etc."), we had set "Can refer to an institutional COI policy" as Scale Level 3 (Competent). However, most of our workshop participants were rated as Level 1 (Unacceptable) because they did not think of it at all. This could have been due to the complicated regulatory circumstances in Japan regarding COI, wherein medical and healthcare researchers must refer to several relevant official regulations in addition to the COI policy at their own institutions; these include The Clinical Trials Act (2017), *Ethical Guidelines for Medical and Health Research Involving Human Subjects* (2014), *Guidelines for Managing Conflicts of Interest in Health, Labour and Welfare Science Research by the Ministry of Health, Labour and Welfare* (2008), and *The Japanese Association of Medical Sciences COI Management Guideline* (2017). When practicing research ethics consultation, the REC is expected to be knowledgeable of at least those complicated sets of regulations. Because of such a flood of relevant regulations, our participants seemed to be ill-prepared for appropriate referencing to their own institution's policies. Accordingly, although we discussed whether or not to set the description of "Can refer to an institutional COI policy" as one of the descriptions in Dimension II, we ultimately decided not to use it as a description because some people noted that some facilities have not created such institutional COI policies.

Discussion

We have developed the task-specific scoring guide rubric and the four-level scoring rubric to be used in self-assessment of higher-order thinking acquisition and practical performance skills as a competent REC through an educational training workshop with exercises by case-scenarios. As mentioned above, although we began by creating a preliminary general scoring guide rubric, our end products became task-specific rubrics for the particular case-scenario, entitled "an observational research study with a conflict of interest (COI)."

Our goal with rubric development changed following the workshop, as we realized that consultation cases used for discussion will differ by workshop and that relevant ethical issues will also be case-dependent. One advantage of a task-specific rubric is that it can provide clear and concrete matters as focal points through the specific case-scenario discussion, allowing for easier (self-)assessment of performance. As Brookhart notes [16], it is easier for evaluators to apply task-specific rubrics because appropriate application of general rubrics takes longer to learn. On the other hand, one of the advantages of a general rubric is that it can be distributed to workshop participants *before* any case-scenario discussion, because it simply provides what should be achieved in an abstract way in an assignment in general, without giving away answers to questions. In addition to this merit, Brookhart also raises four other advantages of a general rubric: it can be used with many different tasks with the same learning outcome, focusing participants on the knowledge and skills they are developing over time; it describes participant performance in terms that allow for many different paths to success; it focuses the instructor on developing participants' learning of skills instead of task completion; and it does not need to be rewritten for every assignment [16].

In contrast, one—and probably the most prominent—disadvantages of a task-specific rubric is that we cannot provide workshop participants with it before the case-scenario discussion, as it would reveal all the answers to the workshop participants. Therefore, it is important to acknowledge the advantages and disadvantages of each kind of rubric and prepare accordingly, keeping in mind the purpose of each project. For the purposes of our workshop, which were to train and assess achievements of novice RECs, we consider a task-specific rubric to be more appropriate than a general one.

Our task-specific rubrics developed for the consultation case, entitled "an observational research study with a conflict of interest (COI)," cover many of the required core competencies for novice RECs listed in Appendix 1 [See Additional File 1]: (1), (4), (5), (7) through (10), (12), (15), (17) through (19), (22), (28), (30), (34), (37) through (39), (48), (51) through (53), (56), and (57). Although it is generally considered difficult to assess competencies directly, especially when we consider personal characteristics such as open-mindedness (51) and empathy (52), they can be assessed indirectly through participant performance during the workshop. Our rubrics have been developed through repeat expert reviews; as such, they may have sufficient content validity and are reasonable, even though there is certainly room for further improvement. One of the primary difficulties in creating the rubrics was translating one's expertise as a REC into words and sharing these with others. In other words, this rubric development process required us to spell out what goes through the mind of an experienced REC during an actual consultation service.

Appendix 1 Core competencies required for novice research ethics consultants (RECs) [3] (excerpted)

Competency domains and intermediate categories		REC level
		Basic
Domain 1:	Knowledge	
(1)	**History of research ethics, historical cases**	●
(2)	Three principles of research ethics/basic theory	●
(4)	**Medical research—basic design and methods**	●
(5)	**Domestic laws related to medical research (e.g., personal information law, clinical research law, regenerative medicine law, next-generation medical infrastructure law)**	●
(7)	**Japanese administrative (ethical) guidelines for medical research (e.g., medical guidelines, genome guidelines)**	●
(8)	**Institution policies/regulations on medical research and in-facility REC/IRB, related departments (e.g., REC/ IRB, clinical research support center, medical information, medical safety)**	●
(9)	**Basic terms and concepts related to medical research and medical care**	●
(10)	**Japan's medical insurance system, medical/biomedical policy**	●
(11)	Basic matters related to research expenses (public and private)	●
(12)	**Basic matters of research integrity (e.g., research misconduct, authorship)**	●

Appendix 1 (cont.) Core competencies required for novice research ethics consultants (RECs) [3] (excerpted)

Competency domains and intermediate categories		REC level
		Basic
Domain 2-1:	Ethics assessment skills	
(15)	**Research protocol reading skills**	●
(16)	Skill of distinguishing between medical care and research	●
(17)	**Skill of distinguishing legal matters from non-legal matters governed by ethical norms**	●
(18)	**Logical thinking/analytical skills**	●
(19)	**Eliciting (or understanding) the true intentions of consultees/researchers**	●
(20)	Identification of ethical, legal, and social issues (ELSI) related to the consultation case: (1) Identification of problems related to the fair selection of subjects	●
(21)	Identification of ethical, legal, and social issues (ELSI) related to the consultation case: (2) Identification of problems related to risks and benefits	●
(22)	**Identification of ethical, legal, and social issues (ELSI) related to the consultation case: (3) Identification of problems related to consent**	●
(28)	**Search and collect necessary information, supplementary information, and materials relevant to domestic situation**	●
Domain 2-2:	Management and procedural skills	
(30)	**Dividing roles and purposes between REC/IRB review and consultation**	●
(34)	**Issuing appropriate warnings to terminate, abandon, or modify issues, matters, or practices that cannot be legally or ethically permitted/justified**	●
(35)	Appropriately connecting and consulting with related departments (e.g., REC/IRB, medical information, medical safety, research integrity audit office) in facility as necessary	●
Domain 2-3:	Interpersonal skills	
(37)	**General communication skills (e.g., listening, clarity, non-verbal communication)**	●
(38)	**Accurate and clear expression skills in Japanese language**	●
(39)	**Ability to first answer required questions**	●
Domain 2-4:	Educational skills	
(48)	**Ability to explain in plain language**	●
Domain 3:	Personal characteristics	
(50)	Self-discipline skills	●
(51)	**Open-minded attitude**	●
(52)	**Empathic attitude**	●
(53)	**Neutral/independent-minded attitude, fair mindedness**	●
(54)	Honesty, integrity	●
(55)	Reflective/self-knowledge attitude	●
(56)	**Perseverance, diligence**	●
(57)	**Coherence, logicalness**	●
(58)	Calmness, prudence	●

Some of the dimensions of the task-specific scoring guide rubric are more easily applied than others. For example, for Dimension II ("Understanding and knowledge of relevant laws, regulations, guidelines, and other rules (by governments, academic societies, etc.)"), its descriptions of the highest level of performance refer to four items, the understanding of which is required of RECs. As is the case with the four-level rubric, it is natural to apply Dimension II mathematically in accordance with the grades assigned in the workshop: when participants enumerate all of four items, then it is rated as 4; when they enumerate three out of four items, then it is rated as 3, and so forth. However, our participants' self-assessment results revealed two groups with an SD of 0.8 or higher for both Dimensions III and IV. These two dimensions are more difficult to apply, as their descriptions cannot be used in a simple mathematical way to assess participant answers. It is premature to conclude, therefore, whether or not the high SDs resulted from the unavoidable nature of these dimensions, inadequate assessment abilities among our workshop participants, and/or the inappropriateness of our developed descriptions of performance. Further examination of the reliability and validity of our developed rubrics is needed, through repeated use and, if necessary, repeated revision at actual training workshops.

The highest level of performance for the case of interest is illustrated by the model answers to the case-scenario questions. Through repeated collection and assessment of workshop participant answers to the questions pertaining to this case, we can expect to identify "anchors" for other lower levels of performance, defined as "[s]amples of work or performance used to set the specific performance standard for each level of a rubric [17]." The identified anchors for lower levels would contribute to scoring reliability. Anchor identification may also lead to revision of the task-specific rubrics which we have developed this time. Generally speaking, as rubrics need continuous refinement, we are ready not only to modify the descriptions of performance, but also to continue with identification of better anchors.

No single consultation case used in our training workshop covers all the core competencies required of a novice REC. Therefore, it is necessary to consider the optimal combinations of consultation cases so that the widest possible range of core competencies can be assessed throughout the workshop.

The general scoring guide rubric created this time remains in a preliminary stage and further revisions based on the task-specific scoring guide rubric, developed here for the case of interest, are needed. However, as it stands now, it will serve as a model for the development of task-specific scoring guide rubrics for other consultation cases. Providing participants with the revised general rubric before the workshop would make self-assessment easier because the general rubric helps workshop participants to conceptualize a high level of performance for a novice REC.

On the other hand, providing participants with the task-specific scoring guide rubric after the case study can serve as a form of feedback. Ideally, task-specific four-level scoring rubrics would allow us to provide detailed feedback and point out relevant descriptions of performance. Unfortunately, development of four-level rubrics requires more time and effort than that required for scoring guide ones. Since our training workshops do not utilize the same consultation cases repeatedly, the

burden of developing task-specific four-level rubrics becomes greater with every additional case that is used. Currently, we have 20 consultation case-scenarios created for the REC training and will need to develop similar rubrics for other cases in the future. Realistically, feedback could be provided by assigning grades for each dimension of the task-specific scoring guide rubrics and circling the relevant descriptions of performance.

Conclusions

We have developed a task-specific scoring guide rubric and a task-specific four-level scoring rubric for an authentic ethics consultation case as tools that can be used to assess the achieved competencies and performance skills of novice RECs at REC training workshops. Our goal in writing this paper was to share our experience and insight with others who are, or will be, engaged in REC training activities, which will inevitably require good educational materials, methods, and tools to assess participant competencies.

Looking to the future, we hope to find ways to further the growth of intermediate RECs as well, as they are expected to teach novice RECs, medical researchers, and ERB members. Knowledge and skills required of intermediate RECs are much broader in scope, deeper in content, and more challenging than those required of a novice REC. The know-how and model procedures obtained through the process of developing rubrics for a novice REC will likely be useful in creating rubrics for self-assessment of competencies and instructional performance skills among intermediate REC trainees.

Abbreviations

AMED: The Japan Agency for Medical Research and Development

COI: A conflict of interest

ERB: An ethics review board

REC: A research ethics consultant

SD: A standard deviation

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Acknowledgements

We would like to express our deepest gratitude to the workshop participants and the members of The Research Group of the Development of the Comprehensive Higher Education Programs on Research Ethics and Integrity for Medical Sciences (the AMED Matsui Group) for their contributions to this study. In particular, we would like to thank Dr. Ukyo Shimizu for authoring the original case-scenario in Japanese discussed in this paper.

Authors' contributions

A.N.: analysis, developing the rubrics, prepared **Table 2**, and writing the first draft manuscript with K.K.. K.K.: analysis, leading the development of the rubrics,

and writing the first draft manuscript with A.N.. K.Y.: analysis, developing the rubrics, and giving critical intellectual inputs to the first draft manuscript. A.Y.: analysis, helping the rubrics development, and revising the first draft manuscript. K.M.: study conceptualization, analysis, developing the rubrics, and revising the draft manuscripts, tables, and figures. All authors read and approved the final manuscript.

Funding

The study was financially supported by the grant of Japan Agency for Medical Research and Development 2019-2021/2022-2024 Research and Development Program for Enhancement of Research Integrity (e-Rad no. JP19190204, and JP22727134), and a Grant-in-aid for Scientific Research by Japan Society for the Promotion of Science (Kiban-kenkyu (A), no. 19H01083). These funding bodies did not play any role in the design of the study, analysis, interpretation, or writing.

Received 12 April 2024
Accepted 30 August 2024

Invited Article

日本における IVF 多胎妊娠の現状と今後行うべき方策について

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Abstract

生殖補助医療が急速に普及する今、様々な倫理問題が発生している。本稿は、体外受精によって発生する多胎妊娠をテーマとしている。第 1 部では、複数胚を母体に戻す DET が妊娠率の向上に寄与する一方で、多胎妊娠率の上昇により母体や胎児のリスクが増大する点を議論し、特に児の負うリスクが親の希望によって軽視されがちである点を指摘した。また、体外受精による多胎妊娠率を減少させる際の目標値を、自然発生率に設定した。第 2 部では、その目標を達成するための具体的なアプローチについて、ベルギー、スウェーデン、イタリア、オーストラリアなどの諸外国の事例を参考に考察した。日本においては、法制化によって移植胚数に厳しい制限を加えるよりも、日本国内の IVF 実施施設の認定基準強化や、保険制度における移植胚数の明確化、過度な「自律尊重」の原則に対して施設が適切に拒否を示すことの妥当性をガイドラインで保証することなどの対策が優先されると考えられる。

キーワード：生殖補助医療、体外受精、複数胚移植、単一胚移植、多胎妊娠

As assisted reproductive technology (ART) rapidly spreads, various ethical issues arise. This paper focuses on the issue of multiple pregnancies resulting from in vitro fertilization (IVF). In the first part, we discuss how double embryo transfer (DET), which involves transferring multiple embryos back into the mother's womb, can increase pregnancy rates but also significantly raises the risk of multiple pregnancies, thereby increasing risks for both the mother and the fetus. Particularly, the risks to the fetus tend to be overlooked in favor of the parents' wishes. Furthermore, I propose setting the target for reducing the rate of multiple pregnancies caused by IVF to match the natural occurrence rate. In the second part, we explore specific approaches to achieve this goal by examining cases from countries like Belgium, Sweden, Italy, and Australia. In Japan, instead of enforcing strict legal restrictions on the number of embryos transferred, it is considered more effective to prioritize measures such as strengthening the accreditation standards of IVF facilities, clarifying the number of embryos transferred under the insurance system, and ensuring that the guidelines support the legitimacy of facilities appropriately refusing excessive patient demands under the principle of "respect for autonomy.".

Keywords: assisted reproductive technology (ART), in vitro fertilization (IVF), double embryo transfer (DET), single embryo transfer (SET), multiple pregnancy

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イントロダクション

生殖補助医療（ART；assisted reproductive technology）は急速に普及している。実際に、ART の一種である、体外受精（IVF；in vitro fertilization）や顕微授精（ISCI；intracytoplasmic sperm injection）といった技術によって、2021 年には 69,797 人の児が誕生している。これは、2021 年の出生数 81 万 1604 人のうち実に 8.6%を占めている。

生殖補助医療を巡っては、様々な倫理的問題が存在する。それは登場人物の多さに由来するものであると考えている。第三者の精子や卵子あるいは子宮を利用することの倫理的問題点はよく議論されるところである。しかし、遺伝上の／法律上の両親だけではなく、出生する児も重要な登場人物である。児は自らの希望を表明できないため、生殖補助医療を巡る問題は複雑化する。

本稿のテーマは、体外受精による多胎妊娠であり、本文は

第 1 部 体外受精によって作成した胚を子宮内に戻す際の適切な個数についての、日本の現状を踏まえた考察

第 2 部 第 1 部で定めた目標を達成するための方策についての、諸外国の事例を通した考察

によって構成されている。

第 1 部

体外受精によって作成した胚を、子宮内に 1 つのみ戻す方法を単一胚移植（SET；single embryo transfer）、複数戻す方法を複数胚移植（DET；double embryo transfer、TET；triple embryo transfer など）と呼ぶ。DET を選択することには、全体的な妊娠率の向上というメリットがあるものの、多胎妊娠率の上昇による母体と胎児のリスク増加というデメリットもある。

まずは、方法としての SET と DET、結果としての単胎妊娠と多胎妊娠について議論する。

多胎妊娠のリスクについて

多胎妊娠、分娩は、自然妊娠の文脈ですら高リスクとされる。胎児については、胎児発育不順、子宮内発育制限、双子の片方または両方の子宮内胎児死亡、先天異常、奇胎、双胎間輸血症候群などのリスクが上昇／発生する[1]。子宮内発育制限に関しては、単胎での基準を適用すること自体が正当でない可能性があるが[2]、脳性麻痺のリスクは双胎児において単体児の 4 倍に、1 歳までの死亡リスクは 7 倍になると報告されており[1]、見逃すことはできない。また、多胎妊娠した母体については、早産のリスクが単胎妊娠の約 4 倍に増加するほか、子癇前症や子癇を発症するリスクや、貧血、尿路感染症、分娩後出血、産褥感染症の発生率が有意に増加するとされている[3]。

IVF で発生する双胎妊娠は、DET による DD 双胎のケースが多く、双胎間輸血症候群などは厳密には問題にならないケースもある。かといって、IVF で発生する多胎妊娠が自然妊娠でのそれと比較して、必ずしもリスクが低くなるわけではない。母体の年齢、BMI、分娩数で調整後、妊娠高血圧、分娩前出血、妊娠糖尿病、帝王切開、肺成熟のためのステロイド使用、子宮内発育制限、先天異常のリスクが有意に上昇するという文献も存在する[4]。一方で、DD 双胎に限って比較すれば、新生児の平均出生体重が低い以外は新生児転帰に有意な悪影響はなかったとする文献も見られる。しかし、この文献には先天異常や脳性麻痺などの項目が登場せず、新生児に対する長期的な影響を見落としている可能性がある[5]。とあるメタアナリシスでは、母体リスクは上昇するものの絶対的な数値として

は低く、IVF は安全に妊娠し出産するという目的を達成するための手段としてリスクよりも有用性が勝ると主張されている一方で、新生児に関しては、呼吸窮迫症候群、先天異常、NICU 入室のリスクが高まると記載されていた[6]。

また、vanishing twin という現象が存在する。これは、多胎妊娠が確認された後、妊娠の途中で片方の胎児の発育が止まってしまい、もう片方のみが出生するという現象である。IVF で出生する単胎児の 10 人に 1 人は双胎妊娠に由来するとしている文献すら存在する[7]。同文献では、妊娠 8 週以上で起こる減少は超低出生体重児、極低出生体重児などのリスクを高めるとされているほか、妊娠中期、後期に vanishing twin が発生すると、妊娠初期に発生する場合と比較して、出生児の神経学的後遺症のリスクが高くなることが観察されている。メタアナリシスにおいても、14 週後に vanishing twin が発生した場合は、早産、低出生体重児となるリスクが高くなると述べられている[8]。壊死した胎盤組織が再吸収されると、炎症性サイトカインとプロスタグランジンの放出が増加し、生存している胎児への血流が変化して一時的に栄養補給が減少することなどが原因と考えられている。

そして、双子を持つ家庭では虐待率が増加するという報告もある。幼い乳幼児を 2 人育てることによるストレスの増大や、母親の分娩数が多いこと、そして双子では周産期合併症の発生率が高いため母子分離が長くなることが、虐待有病率の上昇に関与しているのではないかという仮説が立てられていたが、回帰分析によって、双生児であることそれ自体が虐待に与える影響は、分娩数、母子分離の長さ、出生体重、アプガースコアが与える影響よりも大きいという結果が導かれていた[9]。

SET と DET について

1 周期の SET と DET の効果を比較するメタアナリシスによれば、生児出生率は SET に比べて DET の方が有意に高かった（OR 0.78, 95%Cl 0.71-0.85）[10]。同じく生児出生率に関して、年齢別のサブグループ解析を行ったところ、35 歳未満、35 歳以上 40 歳未満では SET に比べて DET の方が有意に高かった（35 歳未満：0.71,0.61-0.84, 35 歳以上 40 歳未満： 0.80, 0.69-0.94）が、40 歳以上ではその差は有意ではなくなった（0.87, 0.54-1.40）。

一方、新鮮周期の SET と凍結周期の SET を組み合わせた場合（連続 SET）と、新鮮周期に 1 回 DET を行った場合を比較するメタアナリシスによれば、累積の生児出生率について、連続 SET が DET を有意に下回ることはなかった（0.85, 0.62～1.15）[11]。

これらのことから、同一期間で比較した場合、40 歳未満の女性については DET がより有効ということになるが、胚の個数を揃えて比較した場合は、連続 SET が DET と同等に有効であるということになる。単に「子どもが欲しい」という目的を達成するためだけであれば、先に挙げたような多胎妊娠に関連する母体・胎児のリスクを鑑みて、SET を選択することが合理的であると考えられる。しかし、実際にはかかる周期の数も体外受精を受ける患者にとって重要であるようだ。体外受精を受ける患者は、年齢が高く、不妊歴が長く、何度か治療に失敗している可能性があり、出来るだけ早く妊娠したいと強く願っていることもある[12]。また、周期が増えることは、治療を受けるために仕事を休まなければならなかったり、治療本体の費用がかさんだりするなどの心理的、社会的、経済的負担に繋がっていると考えられる。良好胚が 2 個以上利用可能であった 36 歳未満の女性についてのスウェーデンの多施設共同研究[13]では、妊産

婦の医療費総額の平均については、SET 群で 6857 ユーロ、DET 群で 6767 ユーロであり、主に凍結周期の追加によって、確かに SET 群の方が高くなる結果となった。しかし、妊娠中の病欠は DET 群で有意に多く、休業にかかる費用は 1602 ユーロ対 2359 ユーロと、SET 群で有意に低かった。また、女性 1 人あたりの小児医療費と、その子どもの最初の 6 ヵ月間の再入院に要した医療費の平均は、2445 ユーロ対 5551 ユーロと、こちらも SET 群で有意に低かった。この研究では、出生児 1 人あたりの費用では、DET 群の方が有利であったが、SET による単胎妊娠を 2 回行う場合と DET による多胎妊娠を 1 回行う場合では、新生児治療費の関係で前者の方が少ない費用で済むとする研究も存在する。なお、無作為化された女性 1 人当たりの医療費は SET 群で 9309 ユーロ、DET 群で 12318 ユーロであり、個人ではなく国単位で見ても SET は有用な戦略であると言える。

また、体外受精を受ける患者の中には、双子を妊娠することを理想的な結果であると考える人もいるようである[12]。産休や育休を取ることの負担を考えると、1 度の妊娠で 2 人の子どもを設けることを、「コスト／タイムパフォーマンスが良い」と感じるのも無理はないだろう。実際に、メタアナリシスにおいて、DET を 1 周期受けた女性が多胎妊娠する確率は 16.7%（8314/49, 645）である一方、SET を 1 周期受けた場合の確率は 0.7〜1.0%となることが示唆されている[10]。40 歳以上の女性に 1〜3 個の胚を移植する試験においても、40 歳と 41 歳については、DET を 1 周期行った場合の双子出産率が 10%を超える結果となった[14]。

こうした背景があり、双胎妊娠に関する情報を与えても依然として DET を選択する患者が存在する[12]。医師による口頭説明で双胎妊娠に関する情報を受けとった場合、双胎妊娠に関する知識を得たと回答した患者の割合が 10〜20%から 95%に増加し、双胎妊娠に関する肯定的感情が減少、否定的感情が増加し、SET を好む患者の割合は有意に増加した（女性では 7.1%から 24.3%、男性では 20%から 37.1%）が、依然として DET を選択する患者が多くいた。

日本の現状

1995 年の周産期委員会報告で、解析対象 820 例のうち双胎の 32.4%、3 胎の 80.4%、4 胎以上の 100%は生殖補助医療によるものであると報告された[15]。これを受けて、日本産科婦人科学会（日産婦）は、翌 1996 年、会告において、人工授精については排卵誘発剤としてのゴナドトロピン製剤の周期あたりの使用量を可能な限り減量すること、体外受精については胚移植数を 3 個までとすることを求めた。しかし、体外受精による多胎率は減少せず（**Figure 1**）、2000 年過ぎに、多胎児によって NICU のリソースが圧迫され、たらい回しが生じて批判が生じた[16]。2007 年には日本生殖医学会倫理委員会から、「多胎妊娠防止のための移植胚数ガイドライン」が公表され、これを踏まえて日産婦は、翌 2008 年に、「生殖補助医療における多胎妊娠防止に関する見解」の改訂に至った。その内容は、「生殖補助医療の胚移植において、移植する胚は原則として単一とする。ただし、35 歳以上の女性、または 2 回以上続けて妊娠不成立であった女性などについては、2 胚移植を許容する」というものである。この見解が示されて以降、多胎率は著名に減少した（**Figure 1**）。これは、日本において胚凍結の技術が進んでおり、新鮮周期で複数の卵子を採取した場合に、その周期では単一胚移植を行い、残りの胚を凍結周期に回すという選択が

一般的であること、そして、各体外受精実施施設が見解をよく守っているということが理由であると考えられている[16]。

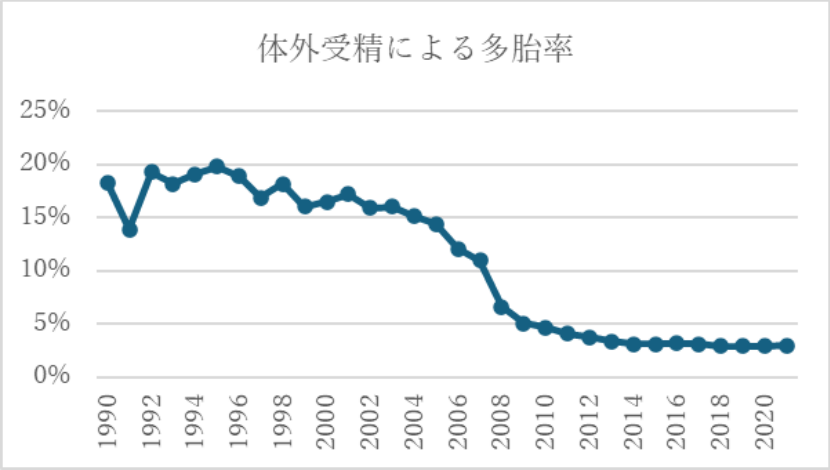

Figure 1　体外受精による多胎率（日本産科婦人科学会資料[20]より作成）

国内での経時的推移は以上のようであるが、世界の中での位置付けはどうなっているのだろうか。International Committee for Monitoring Assisted Reproductive Technologies（ICMART）の報告を分析した論文によれば、日本は 100 周期以上の新鮮胚移植を行っている国の中で双胎率が 4.2%で最低となっており、100 周期以上の新鮮胚移植を行っている国の中でも 4.2%で最低となっている[17]。

以上のように、現在日本は世界的に見ても低い多胎率を誇っており、全体的には日産婦の見解に沿って SET の利用が進んでいると考えられるが、現状に全く問題がないというわけではない。2022 年 10 月から同年 12 月、全国の体外受精実施施設 122 件から全国体外受精実施施設ガイドに寄せられたアンケートの集計結果は、個々の施設で見た際の問題点を示している[18]。まず、移植胚数に関して、DET を行う場合、「治療歴に応じて」「年齢に応じて」といった、日産婦の見解に沿った理由のほかに、「治療歴に応じて」の約半数のケースにおいて「夫婦の希望で」という理由が挙げられている。また、患者夫婦の双子希望に関して、「たまにある」との回答が 56 件あり、そのうち 11 件で希望に応じて実際に DET を行うと回答している。そして、多胎妊娠のリスクに関する説明では、特に行っていないとの回答が 3 件見られた。すなわち、医学的な適応を外れた DET や、十分なリスクの理解を得ないままの DET が行われている現状がある。なお、アンケートへの回答は任意であるため、上記のような不適切な DET の実施は少なく見積もられている可能性がある。

考察

「子どもが『早く』欲しい」と思うことも、双子の妊娠の効率が良いと思うことも、親側の希望に他ならない。もちろん、親側の幸福追求の増大だけでなく、それを加速させている社会の問題もあるが、DET による多胎妊娠のリスクを負うのは、生まれてくる子どもも親と同様であるのに、その希望は全く反映されていないという点を見逃してはならない。子宮内に戻す胚の数を決めるという人工的な操作で、多胎妊娠の確率をむやみにあげることは、胎児のリスクを無視した行為である。

一方で、胎児のリスクや希望を正当に評価することも難しい。そのため、体外受精による多胎妊娠と自然な多胎妊娠との間でリスクが変わらないとする評価もあることを踏まえて、まずは、体外受精による多胎妊娠率を、多胎妊娠が自然に生じる割合にまで下げることを目標として設定するべきであると考える。多胎妊娠が自然に生じる割合については、体外受精技術が導入される以前の厚生労働省の統計を参考にして求めることとする。1977 年には、単胎の出生数が約 175 万人、双子の出生数が約 2 万人となっており、十分に少数である三つ子以上の出生数を無視すれば、多胎分娩率は約 1.1%となる[19]。2021 年の体外受精による多胎率は 3.0%であり[20]、さらに減少させる余地はあると考える。

第 2 部

第 2 部では、多胎分娩率を自然の水準にまで低下させるためにどういったアプローチが考えられるかということを、いくつかの国の歩みと比較して考察していく。

〈1〉ベルギーの事例（金銭的援助を伴う法制化）

ベルギーは、2002 年時点で新鮮周期の約 85%において DET 以上の移植を行っていた[21]。2003 年、「生殖補助医療の規制のあり方」において、生殖補助医療を受けることのできる年齢の上限を 42 歳に定めるとともに、以下の移植数を守る場合は、最大 6 周期まで国が費用を全額負担するとした（**Table 1**）[22]。

	1st cycle	2nd cycle	3rd-6th cycle
36 歳未満	1	1（胚の質により 2）	2
36 歳以上 39 歳以下	2	2	3
40 歳以上 42 歳以下	制限なし	制限なし	制限なし

Table 1 ベルギーにおいて，国の全額負担が認められる移植胚数

問題は、この移植数が守られているかどうかの監視体制である。ベルギーには Belgian Register for Assisted Procreation(BELRAP)というベルギー国内の生殖補助医療を報告するために設立された公的な非営利団体が存在する。1999 年の「生殖医療センターの承認基準に関する勅令」においては、ART の実施基準が定められているが、その基準のひとつがオンライン登録の義務となっている。また、同年の「ケアプログラム'MAR(medically assisted reproduction)'のための医師会メンバーの任命に関する省令」においては、政府によって任命された医師が MAR における治療の質の監視に責任を負うということが記載されている。このように、2003 年以前に報告・監視体制も法制化されていた、ということは特筆すべきである[23]。

本法律施行後、DET は減少を続け 2021 年には約 20%まで低下した。また、2003 年から 2010 年の間に、1 周期あたりの妊娠率は維持したまま、多胎妊娠率が 27%から 11%に減少した。2021 年には多胎分娩率は 5%を切っている[21]。

〈2〉スウェーデンの事例（指令から政令）

スウェーデンでは、1993 年ごろまで TET が主流であり、多胎分娩率も約 30%あった[24]。1998 年、社会庁は勧告の形で「体外受精に使用される受精卵の数は原則 1 個、医学的適応のある際でも 2 個

まで」という指令を出したが、必ずしも守られなかった。1998 年のデータでは、SET が 1328 周期で行われているのに対し、DET は 403 周期で行われており、TET も 5 周期で行われていた[25]。こうした事態を受けて、2003 年に施行された改正体外受精法では、第 11 条に「政府または政府の指定する行政機関は、体外受精を受ける者または体外受精に使用される精子または卵子の提供を行う者の生命、身体及び安全を保護するため、体外受精の実施に必要な規則を定めることができる」ということが追加され、社会庁はその決定事項に強制力を持たせられるようになった[26]。SET 率は、2001 年には約 16%、体外受精法の改正手続き中の 2002 年には約 30%、改正体外受精法施行後の 2003 年には約 54%と、劇的に増加した。2004 年には、SET 率はほぼ 70%に達し、多胎分娩率は 6%を切るようになった[24]。

小括

以上の 2 ヶ国の例を鑑みると、法的な強制力は、もとの SET 率が低い場合に強力な効果を発揮すると考えられる。日本は日産婦の見解によってすでにそれなりに高い SET 率を有しているため、同様の法制化を行っても、さらなる SET 率の向上は見込めないだろう。日本の保険制度はベルギーの金銭的援助と似ており、治療開始時に 40 歳未満の女性については子ども 1 人あたり 6 周期まで、40 歳以上 43 歳未満の女性については子ども 1 人あたり 3 周期まで、体外受精が保険適応となる。算定要件に「治療に当たっては、関連学会から示されているガイドライン等を踏まえ、治療方針について適切に検討し、当該患者の同意を得た上で実施すること。」とは記されているものの、移植胚数との関連は明確にされていない[27]という点はベルギーと異なっている。保険制度の中で、不適切な DET が行われた場合は算定しないなど、SET が有利になるような構造を作ることは、多胎率減少に向けた動きの 1 つの方向性と言える。

また、この 2 ヶ国よりも厳しい法制化を行う、すなわち全例において SET を義務付ける、などの方向性も考えられる。日産婦の見解に従う遵法精神をもってすれば、この方法によっても多胎率減少が見込めるだろうが、問題点もあるということを、次のイタリアの例を通して述べることとする。

〈3〉イタリアの事例（民意と乖離した法制化）

イタリアは、1994 年に 62 歳の女性が卵子提供により出産、2002 年にクローン技術を用いた代理出産が成功するなど[28]、生殖補助医療の技術に関しては進んでいる国であったが、法制化の面では遅れをとっていた。補助生殖医療法案（以降 40 号法とする）が下院で可決、成立したのは、2004 年のことであった。40 号法は、カトリック教会の影響を強く受けており、イタリア独自の厳格性としては、

① 「胚の権利」の尊重（第 1 条）
② 第三者からの提供配偶子の利用禁止（第 4 条）
③ 胚の実験利用および廃棄の禁止（第 13 条）
④ 胚の凍結禁止、胚の生成は上限 3 個、作成した胚はすべて女性の子宮に戻すこと（第 14 条）

の 4 点が挙げられていた[29]。第 14 条について、胚の凍結が不可能だと、施術のたびに採卵しなければならず、母体に大きな負担がかかる。そして、採卵回数を減らすためには、成功率を上げる必要があり、患者が 1 回に戻す胚の数を最大にしようと考えることは自然である。これによって、特に若い世代において多胎妊娠が増加し、2005 年には全体の 16%から 21%に増加し、品胎妊娠は 1.8%か

ら 4.3%に増加した[30]。また、中絶は法的には禁じられてこそいないものの、教会が強い忌避感を示しており、事実 40 号法の「胚の権利」明記についても、中絶法廃止への足がかりにするつもりがあったようである[29]。こうして、多胎分娩が増加し母子の負担が増大したことを受けて、より少ない数の胚移植や凍結胚移植、あるいは第三者からの精子・卵子の提供、着床前診断など、イタリアでは受けられない施術を求めて国外のクリニックにかかりにいく生殖ツーリズムが増加していった。2005 年には、40 号法の改正を求める国民投票が行われたが、教会のプロモーションによる棄権票多数のため無効となった[29]。同年、イタリアの民間不妊治療クリニックの協会である Cecos によって、生殖ツーリズム記録所（Italian Fertility Tourism Observatory）が設立された。その観測結果から、国外で治療を希望するイタリア人の数は 2003 年の 1066 組から 2005 年には 4173 組に増加し、その中でもスペインが最も人気があることが明らかになった。さらに、スペインの 7 つのクリニックのデータによると、彼らが治療したイタリア人カップルの数は 60 組から 1365 組に急増し、患者の 10-50%を占めたという[30]。

第 14 条は、事実上着床前診断ができない、できてもどのみち全胚戻すのであるから意味がない、ということを意味しており、地中海性貧血などの病気の遺伝素因を持つ子どもが生まれたり、そうした遺伝素因を持つ胎児によって母親が流産を繰り返したりしていた。この問題の当事者であるカップルたちが、2004 年以降訴訟を各地で起こし、この問題点が広く知られるようになっていった。憲法裁判所は、2009 年 5 月に、女性および胚の健康という意味で第 14 条は違憲である、と宣言した。引き続いて、2014 年には第三者からの提供配偶子の利用禁止が違憲であるとの判決が下り、2015 年には胚の選択を禁じる第 13 条の一部も廃止するとの判決が下った[29]。着床前診断を求める動きが大きかったからであるとはいえ、多胎妊娠を促進していた第 14 条に最も早く違憲判決が下ったことは特筆すべき事項であると考える。現場の技術に関わらず、キリスト教の教義に沿った現実的でない立案を、教会と中道右派が行ったことが原因であろう。

小括

厳しすぎる法制化がもたらすのは、国内での改革の動きと、零れ落ちた需要による国外への流出である。イタリアの第 14 条については、違憲判決までの 5 年の年月を要しており、国内での改革は時間を要することが分かる。女性の妊娠可能年齢に対して 5 年は十分に長い期間であり、国外への流出はより短絡的な解決方法として選択されるだろう。胎児のリスクを無視した DET を批判する本稿の文脈において、DET が行われる場所が国外であれば良いということにはならない。そのため、全例において SET を義務付けるという方向性は、国内の統計に限っては効果があるかもしれないが、問題の全体像を踏まえた上では有害であると考える。

〈4〉オーストラリアの事例（ガイドライン）

オーストラリアは、1981 年に世界初の体外受精による双子誕生（1981 年）、3 つ子誕生（1983 年）、4 つ子誕生（1984 年）といったように、体外受精による多胎妊娠、分娩を世界に先駆けて成功させた国で、生殖補助医療技術の進んでいる国である[28]。

生殖補助医療に関する法律は州ごとに制定されているが、母体に戻す胚の数を決めた法律はなく、ガイドラインでは、「35 歳未満の初回新鮮胚移植

周期では SET が推奨される。40 歳以下には移植する胚数は 2 つ以下にすることが推奨される。」とされている。実際に、(ニュージーランドと合わせたデータではあるが、) 40 歳以上でこそ DET 率が 10%を超えており、双胎分娩率も 10%を超える結果となっているものの、全体で見れば、DET 率 6.4%、多胎分娩率は 3.0%と非常に低くなっていて、日本と同様に、ガイドラインがソフトローとしての役割を果たしていると言える[31]。

日本と異なるのは、オーストラリアでは代理出産も認められているという点である。倫理ガイドラインでは、代理母に対しては必ず SET を行うこととされている[32]。実際に、DET 数は 0 件であり[31]、生殖補助医療に関わる他の問題の議論を通して、多胎妊娠、分娩における母体の負担が重く捉えられている様子が窺える。

また、倫理ガイドラインには「個人またはカップルの選択が、現在の臨床的エビデンスや実践と相反する場合、生まれてくる人に悪影響を及ぼす可能性が高い場合、または社会的に明らかな悪影響を及ぼす場合(一度に複数の胚を移植する場合など)には、その処置に関する意思決定において、これらの要因が考慮されることが適切である。臨床医が治療を延期したり、個人やカップルの治療を拒否したりすることが妥当な状況もある。」とも記されている[32]。胎児に対する影響を鑑みるべきであるということや、自律尊重原則はあれども、過度な要求に対しては拒否が妥当であることもあるということが明確に記載されている点は注目に値するだろう。

小括

法ではなくガイドラインによる管理で一定の効果が得られているという点で、オーストラリアは日本と類似しているが、より進んでいる点としては、母体のリスクも胎児のリスクも同様に明示していること、そして、患者の希望は際限なく叶えなければならないものではないと明示していることが挙げられる。希望を叶えてもらえなかった患者が、希望を叶えてくれる他の施設を受診するということが生じると、国内の多胎率の減少には繋がらない。また、このように患者が自由に施設を選択できることは、不適切な治療を行う施設が利益を得て、治療を断る施設が損をすることにも繋がるため、慎重な DET 実施の方向に各施設を向かわせる力を弱めてしまう可能性がある。そこで、正当な治療を行う体外受精実施施設の判断を支持し守ることで、足並みを揃えさせるための文言として、「治療の拒否は妥当」といった記載を日本でも取り入れるべきであると考える。

考察

体外受精による多胎の問題は、親側に第三者が介在せず、代理母などに比べればセンセーショナルに取り上げられない傾向にある。そのため、自らの希望を叶えるために胚移植を国外で行うなどという考えもあまり浸透していない状態であると考えられる。換言すれば、現在、胚移植を求める患者は、ほとんどの場合でまずは国内施設に支援を求めることになる、ということである。そこで、今の段階で、国内施設において適切な説明、対応を行っていくことで、国内および国外での多胎の母体や児へのリスクを考慮していない軽率な DET 実施を防ぐことができると考える。国内施設の意識の向上のためには、IVF 実施施設において、単にこの職種がこの人数だけいれば良いということだけでなく、各人の適切な説明を行う能力まで評価するなどして、その認定基準を強化することなども必要だと考えられる。

結論

患者である親の「自律尊重の原則」がひたすら謳われる一方で、児は移植する胚の数を決定する段階ではまだ実体として存在せず、そのためか児の負うリスクは軽視されがちであると考える。現在の日本の多胎妊娠、多胎分娩率は世界の中で低いとはいえ、児に対する責任を考えるのならば、体外受精による多胎妊娠率は、多胎妊娠が自然に生じる割合と同等になるまで下げることを目標とすべきであろう。そのためには、医学的な適応のない DET を受けようとする患者や、行おうとする国内施設を減らす必要がある。国外で胚移植を受けるという発想が浸透しておらず、国内施設がほぼ確実に患者にアプローチできる今、一部国内施設の意識改善が必要である。それは、認定基準の強化や、過度な「自律尊重」に対して施設が拒否を示すことの妥当性をガイドラインで保証することによって達成されうる。また、保険の算定条件において現在曖昧にされている移植胚数の項目を明確にすることも有効であろう。

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Journal information

《目的と領域 -Aims and Scope-》

CBEL Report は日本における生命倫理・医療倫理研究のますますの発展に資するために創刊された学術雑誌である。当該分野の、新たな研究成果の開かれた発表の場として、また国際的な学問交流の場として、オープンアクセスの形で出版される。アカデミアの専門的研究の活発な知的交流の場を作り出すこと、およびそれに基づき全ての学問分野の研究者・学生ら、医療従事者、各種倫理委員会の委員、政策担当者、等に対して優れた知見を提供することをその使命とする。

《投稿規定 -Instructions for Authors-》

上述の目的のため、CBEL Report は、ここに広く研究成果を募集するものである。

1. 【投稿形式】投稿形式は以下のように定める：
   (ア) 字数に応じて以下のように投稿枠を区分する
      ① 短報（letter）：邦語 1,000 字以内、英語 500words 以内
      ② 総説（review）：邦語 20,000 字以内、英語 10,000words 以内
      ③ 論文（article）：邦語 20,000 字以内、英語 10,000words 以内
      ※ いずれも抄録、注、文献リストを除いての数字とする
   (イ) 上記のうち特に論文については、以下の 2 つの形式を定める
      ① 研究論文（regular article）：新規投稿の論文。他の雑誌との重複投稿は認めない。ただし他学会での学会報告を新たに論文化したものはこの限りではない。
      ② 翻訳論文（translated article）：他の媒体にすでに投稿した論文を翻訳したもの。英語への翻訳および日本語への翻訳を受け入れる（元の言語については限定を付さない）。投稿にあたっては著作権の許諾を証明する書類を添えること。

2. 【書式】投稿原稿は以下の書式を満たすものでなければならない。
   (ア) 和文あるいは英文とする。
   (イ) 投稿形式ごと、上記１条（ア）に示された分量を超えないものとする。
   (ウ) 提出原稿は、Microsoft Word によって作成した電子ファイルとする。
   (エ) 原稿の１ページ目に以下の情報を記入することとする：論文タイトル、投稿区分、著者名、所属、連絡先となる電子メールアドレス。
   (オ) 論文の場合には、冒頭に抄録（邦語 450 字以内・英語 200words 以内）およびキーワード（邦

語・英語ともに 3〜5 語）を添えること。

(カ) 注は各ページ下部に記載すること（論文末尾にまとめる形ではなく）。

(キ) 参照文献リストを論文末尾にまとめて記載すること。参照文献の記載形式は特に定めないが、以下の情報が全て含まれているものとする。

① 著作：著者名、発行年、書名、出版社

② 論文：著者名、発行年、論文タイトル、媒体、掲載頁数

③ 新聞記事：新聞名、掲載年、記事タイトル、日付（朝刊・夕刊の別）

④ ウェブサイト記事：サイト名、掲載年、ページアドレス、閲覧日

※ その他参照に関して疑問がある場合には投稿に際して編集部に問い合わせのこと

(ク) 図・表ともに本文に埋め込むこと（字数にはカウントしない）。カラーでも可。

(ケ) 研究資金について所属機関以外の組織・個人から支援を受けている場合には、その旨を論文末尾に必ず記載すること。

3. 【査読】上記の条件を満たした投稿原稿に対して、編集委員会あるいは編集委員会が依頼した査読者による査読を行い、採用、条件付き採用、不採用のいずれかの結果を著者に通知する。

4. 【投稿方法】投稿は電子メールにて受け付ける。上記の条件を満たした投稿原稿の電子データを、添付ファイルの形で編集委員会まで送ること（cbelreport-admin@umin.ac.jp）。投稿は随時受け付ける。

5. 【費用】審査料・掲載料は無料とする。

6. 【著作権】掲載論文の著作権は執筆者個人に帰属し、その編集著作権は東京大学大学院医学系研究科・医療倫理学分野に帰属する。その上で当分野は、当分野の指定する者が運営する電子図書館又はデータベースに対し、以下のことを依頼できる。（1）当分野の指定する者が運営する電子図書館又はデータベースが、本誌掲載論文等を掲載すること。（2）当分野の指定する者が運営する電子図書館又はデータベースが、本誌掲載論文等を利用者に提供すること、とりわけ、利用者が当該著作物を参照し、印刷できるようにすること。

2018 年 8 月 30 日　編集委員会決定

2020 年 3 月 30 日　編集委員会改定

2021 年 11 月 1 日　編集委員会改定

インデックス：Google Scholar, 医中誌、J-STAGE、Medical*Online、CiNii（申請中を含む）

《編集委員会 -Editorial Board-》

Journal information

Aims and Scope

CBEL Report is an academic journal launched for the further development of bioethics and medical ethics in Japan. The open-access journal offers a public outlet for presenting new research results, creating an international network for academic exchange within the field of bioethics and medical ethics. The mission of CBEL Report is to lead an active intellectual discussion for specialized research to provide useful knowledge to researchers and students in all disciplines, health professionals, members of ethics committees and policymakers etc.

Instructions for Authors

To fulfill the above objectives, CBEL Report calls all authors to share their research results by submitting their manuscripts.

[Types of manuscripts] All manuscripts must be supplied in the following style.

(a) Submitted manuscripts are categorized according to the word count as follows.

(1) Letters: Up to 500 words in English or up to 1,000 characters in Japanese

(2) Reviews: Up to 10,000 words in English or up to 20,000 characters in Japanese

(3) Articles: Up to 10,000 words in English or up to 20,000 characters in Japanese

*the word count without abstract, notes and reference lists

(b) "Articles" are categorized into the following two types.

(1) Regular articles: Newly published works. We do not accept articles that have been submitted simultaneously to other journals. However, this does not apply to works that have been previously presented at an academic conference and turned into papers.

(2) Translated articles: Articles translated into English or Japanese that have been published in other publications. (There are no restrictions for the original language.) Articles must accompany paperwork granting the copyright.

[Formatting] Submitted manuscripts must adhere to the following format.

(a) Must be in either English or Japanese.

(b) The word count must not exceed the limit stipulated in Section 1 (a) according to the type of manuscript.

(c) The manuscript must be presented in an electronic file prepared using Microsoft Word.

(d) The title, manuscript type, name(s) of author(s), name of institution/department and contact information such as e-mail address must be entered in the first page.

(e) Articles must include the abstract (up to 200 words in English or 450 characters in Japanese) and keywords (3 to 5 words for either English or Japanese) in the beginning.

(f) Notes should be provided at the bottom of the page as footnotes (instead of placing them at the end of the article).

(g) Reference list should be included at the end of the article. There are no requirements on reference styles but all the following information must be included.

(1) Books: Name(s) of author(s), year of publication, title, name of publisher

(2) Journal articles: Name(s) of author(s), year published, article title, medium, page(s)

(3) Newspaper articles: Name of newspaper, year published, article title, date (morning or evening paper)

(4) Website articles: Website name, year published, site address, date visited

* If you have any other questions regarding the reference list, please contact the editorial board.

(h) Figures and tables should be inserted to the text. They don't have to be counted in word count. Colored materials are available.

(i) Acknowledgement of financial support from organizations or individuals other than the affiliated institution, if any, should be included at the end of the article.

3. [Peer review] On the condition that the above requirements are met, manuscripts will be accepted for review by members of the editorial board or any other professionals assigned by the editorial board. The authors will be notified whether their manuscripts are accepted, accepted with conditions or not accepted for publication.

4. [Submission method] Manuscripts must be submitted via email. Make sure the manuscripts are in compliance with the above requirements. Send the electronic data to the editorial committee as an attachment (cbelreport-admin@umin.ac.jp). Submissions are accepted throughout the year.

5. [Fee] There are no fees for the review or publication.

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(Revised November 1, 2021)

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CBEL

The University of Tokyo Center for Biomedical Ethics and Law

CBEL Report
Volume 7, Issue 1

発行日　2024年10月21日

発行者　東京大学生命倫理連携研究機構
https://bicro.u-tokyo.ac.jp/
http://cbel.jp/

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