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We outlined five studies regarding the quality of the review by committees based on the Act on the Safety of Regenerative Medicine. The findings raise serious concerns about the independence, integrity, and quality of reviews of therapeutic plans by these committees with inappropriately close relationships to medical institutions and companies.

Introduction

The Act on the Safety of Regenerative Medicine (ASRM) was enacted in 2013 as part of a series of reforms targeting the regulations of advanced biotherapies in Japan. The act was designed to create an oversight system for both research and delivery of cell-based medical procedures by medical institutions. Two key features of the law were the implementation of a risk-based classification system for cell-based interventions and provisions for a review of research and therapeutic plans for regenerative medical procedures by authorized committees.

In 2019, the Ministry of Health, Labour and Welfare (MHLW) commissioned a series of studies to evaluate the review of research and therapeutic plans by certified committees and certified special committees for regenerative medicine (CCRMs and CSCRMs, respectively) in response to concerns about the quality of the reviews. The review by a CCRM, which has less stringent membership and expertise requirements, is required for class III research and therapeutic plans, whereas the review by the more stringently defined CSCRM is required for the nominally riskier classes II and I (see Figure S1). Under the general study commissioned by the MHLW, our group focused specifically on class II therapeutic plans, as the potential risks of such interventions are putatively greater. The full results of these reviews were published (in Japanese) on the MHLW website (MHLW, 2021a).

In the present forum, we summarize the findings presented in the MHLW report and highlight their implications and ongoing concerns with respect to regulatory oversights of the provision of stem and other cell-based interventions.

ASRM and mechanisms for enforcement

Detailed reviews of the ASRM and associated issues have been published (Konomi et al., 2015; Lysaght and Sugii, 2016). The law creates a single legal framework for regulating regenerative medicine (RM) research and therapy. Such interventions are categorized by assumed risk level, ranging from the highest risk (class I), which includes genetically modified, pluripotent, and/or xenogeneic cells, to the putatively lowest risk (class III), which comprises minimally manipulated somatic cells. The medium-risk category (class II) primarily encompasses cultured or otherwise manipulated stem cell-based research and therapeutic interventions (see Figure S2). Physicians seeking to conduct research or provide therapies involving class II biomaterials must undergo a review from a CSCRM. Notably, the overwhelming majority (~97%) of class II–III plans submitted for review as of 2022 has been for interventions of therapeutic, not research, intent. The number of committees (CCRM and CSCRM) established following the enactment of the ASRM is also significantly greater than the ministry's initial expectations (see Table 1) (Health Science Council, 2013).

Since 2014, the MHLW has issued emergency or improvement orders against non-compliant RM providers (MHLW, 2018). In two extreme cases, doctors who administered cord blood and adipose stem cells to patients in violation of ASRM procedures were arrested (Fujita et al., 2022). For plans submitted to MHLW, MHLW publishes the name of the plan, the

Table 1. Latest ASRM enforcement

Number of RM plans in practice (until February 28, 2022)[a]		
	Research	**Therapy**
Class I RM	20	6
Class II RM	45	1,040
Class III RM	52	3,534
Number of active CPCs (until February 28, 2022)[a]		
Active CPC with survey and approval by the MHLW		71
Active CPC with only a submission to the MHLW		3,141
CPC outside Japan		9 (6 in South Korea, 1 in China, and 2 in Taiwan)
Number of active review committees (until February 28, 2022)[a]		
CSCRM		66
CCRM		93
Total number of subjects or patients and cell administration identified using routine reports from April 1, 2020 to March 31, 2021[b]		
	Subjects or patients	Cell administration
Research	997	3,851
Therapy	57,962	84,087

The abovementioned information is based on the publication by the Ministry of Health, Labour and Welfare (https://www.mhlw.go.jp/content/000536605.pdf, https://www.mhlw.go.jp/content/10808000/000837360.pdf). ASRM, Act on the Safety of Regenerative Medicine; CCRM, certified committee for regenerative medicine; CPC, cell processing center; CSCRM, certified special committee for regenerative medicine; RM, regenerative medicine.
[a]These case numbers do not include the number of plans that have already ended or the number of CPCs and committees that were established but later closed.
[b]Institutions providing RM must submit an annual report for each RM plan within 90 days of the completion of the relevant period.

practitioner of the RM, the reviewing committee, and so on, along with the informed consent form. However, following the initial rollout of this oversight framework, concerns were raised by the Health Science Council (HSC), an advisory body to the MHLW, regarding research and therapeutic plans and their implementation and submitting institutions and review committees (Health Science Council, 2019). The MHLW decided to conduct a commissioned study to investigate the current situation and solutions to the problems that the HSC are concerned.

Evaluation of materials supporting submitted plans and scope of practice

The study initially focused on whether the materials submitted to support a given class II therapeutic plan fulfilled documentary standards consistent with the demands of the review process and whether the medical indication(s) targeted by a given plan were within the scope of practice of the providing physicians.

In its published criteria for the provision of RM interventions (MHLW, 2021b), the MHLW requires that physician-providers and review committees evaluate the safety, scientific validity, and ethical acceptability of therapeutic plans based on submitted materials, such as references to the scientific literature. An analysis of scientific articles referenced in 351 class II therapeutic plans revealed that 20 (5.7%) plans made no reference to published work. An additional 15 (4.3%) plans cited work from non-peer-reviewed media and/or unconfirmable sources (due to a lack of bibliographic information, such as title, URL, publication, ID, and author names). Another 8 (2.3%) plans cited articles from so-called predatory journals, which are characterized by a lack of or insufficient peer review. Moreover, 45 (12.8%) plans cited no clinical studies to demonstrate sufficient safety for therapeutic use. Thus, over 25% of the submitted plans did not provide information sufficient to make a determination of the "safety" of the proposed therapeutic intervention (see Text S1 for our rationale on the use of Cabell's list to identify predatory journals).

An accompanying analysis of 391 class II therapeutic plans examined whether target indications described in plans were broadly consistent with the scope of medical expertise of providing physicians, as indicated in their curriculum vitae. A qualitative evaluation by physicians and

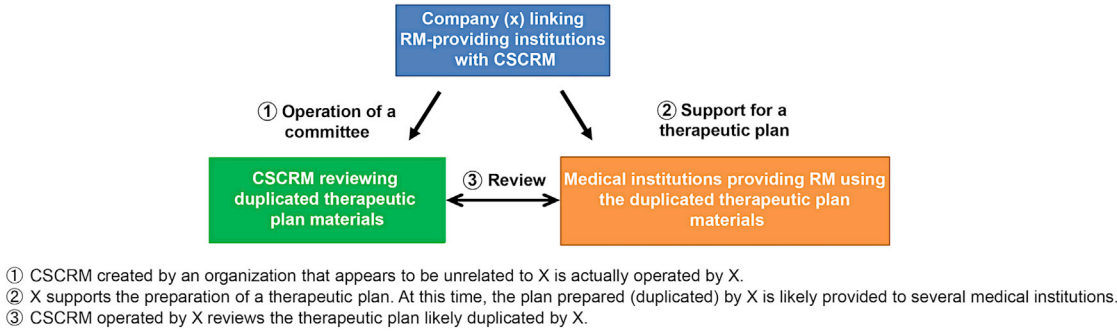

Figure 1. Inappropriate three-way relationships for the independence and integrity of CSCRM reviews

bioethicists in the study group found clear inconsistencies between the target indication and provider scope of practice in 55 (14.1%) plans. In the additional 62 (15.9%) plans, the scope of practice for a given condition was sufficiently unclear, or the relevant professional experience of providing physicians could not be determined. Thus, in 30% of all submitted therapeutic plans, potential inconsistencies were found between the target indication and the provider professional experience and acumen (methodological details and case examples are provided in Text S2).

The high fraction of therapeutic plans for which the evidence of safety and/or appropriate scope of medical practice were disputable raised questions regarding the quality of reviews conducted by individual CSCRMs, prompting the analyses described below.

Duplication of informed consent documents and integrity of review process

An analysis of materials associated with therapeutic plans revealed several causes for concern about the quality and stringency of the review process. Of the 371 therapeutic plan names identified on the MHLW website, we checked all of the informed consent materials with the same name and found that 241 (65%) plans were submitted for CSCRM review under titles identical to those of other plans. The great majority of the plans submitted under identical titles included the materials that were essentially identical, except for minor modifications (such as the name of the submitting institution), suggesting the duplicate use of materials required under the ASRM by multiple institutions. What is particularly concerning is that most duplicated materials were submitted to a subset of all active CSCRMs. In a smaller number of cases, an examination of the file properties of informed consent documents (.doc or .pdf) associated with multiple therapeutic plans had been prepared by a person or persons under the same username (indicating that they were likely prepared by a single individual).

The above-mentioned findings suggest possible three-way relationships between prospective providers of class II RM therapeutic interventions, a subset of CSCRMs, and third-party service providers that, for example, prepare duplicate-use materials as described above. A subsequent analysis of findings enabled by Internet searches for relevant keywords and names of participant organizations revealed the structure of such triads (Figure 1) involved in the preparation and submission of documents for CSCRM review. Four specific cases highlight relationships that indicate a potential need for heightened scrutiny of the independence of CSCRMs before the MHLW certifies them. In the first case, a single CSCRM reviewed multiple therapeutic plans prepared by a single consulting firm and filed identical (verbatim) review reports. In a second case, a cell processing company that prepared a plan used by multiple medical institutions was found to share its address and fax number with the CSCRM office performing the reviews. An employee of the cell processor also held a high-level position within a group of medical institutions that submitted to the plan and sat on the CSCRM that performed the review. Similarly, in the third case, a cell processing company and a CSCRM shared the same address; the committee performed reviews of therapeutic plans involving the use of the firm's cells, and an employee of the firm served as the committee's secretariat. Lastly, a fourth CSCRM was found to convene its review meetings within the physical offices of a company that provides cell processing services to RM medical institutions. The website for the same CSCRM advertises that it offers support for the preparation of documents in a clear fiduciary conflict with its duties as an independent review body. The prevalence and closeness of such relationships between providers, CSCRMs, and intermediary parties raise serious questions about the integrity and independence of the review process, which is a critical functional component underlying the stated objective of the ASRM: to

ensure the safety of regenerative medical interventions offered by medical institutions in Japan.

Use of proscribed promotional language by RM providers

The Medical Care Act, a comprehensive national law in Japan, prohibits the use of promotional language by medical institutions outside a strictly limited set of descriptions of neutral features. These descriptions include staff composition, hours of operation, contact information and location, the absence or presence of in-patient facilities, and brief introductions of clinical staff considered useful to informed decision-making by prospective patients. The advertisement of information outside these limits, such as language describing compliance with legally required activities in ways that suggest such compliance is an extraordinary accomplishment, is not permitted. That prohibition notwithstanding, an analysis of websites maintained by 254 medical institutions offering class II RM therapeutic interventions uncovered such promotional language on 132 sites (51.9%). Such language very frequently included statements to the effect that the provider was in "strict adherence to ASRM procedures," "approved by the MHLW," or "reviewed by a nationally certified committee." Given the range of serious issues identified in the analyses described in preceding sections, which cast doubt on the objectivity and independence of a substantial fraction of CSCRM reviews, the representation of an institution's participation in the review process as a mark of quality or credibility has potential problematic consequences for patient decision-making.

Conclusions

The results of the analyses described above raise serious concerns about the independence, integrity, and quality of reviews of class II RM therapeutic plans performed by CSCRMs with inappropriately close relationships to medical institutions and third-party cell providers. Despite these shortcomings, such interventions are often advertised as being in compliance with the ASRM, which may give false assurance to prospective patients.

Previous studies on direct-to-consumer marketing of stem cell interventions have examined physician expertise (Fu et al., 2019) and the placement of online advertisements by medical institutions (Murdoch et al., 2018). Differences in research focus and country-specific medical law preclude direct comparisons, but the issues raised by the present analyses of scope of practice and online promotion are broadly consistent with those highlighted in previous reports. The ASRM requirement for the citation of scientific studies to support therapeutic plans may be unique to Japan's regulatory environment; comparable studies may thus be difficult in other countries.

As the ISSCR mentions in the context of medical innovations, there is some value in emphasizing the delivery of novel RM therapies to patients with unmet medical needs. However, such attempts must be guided with great care (ISSCR, 2021) because patients should be protected from injuries, financial losses, and misleading information that skews informed decision-making. Despite those important caveats, the delivery of RM procedures under the ASRM has been haphazard. The highly variable quality of review committees operating under this law is an important contributing factor. At the time of its enactment, the ASRM represented an attempt to rationalize the oversight of RM research and therapeutics that was unique in the world. Other countries, such as Taiwan, have since introduced similar systems modeled on, but not exactly mirroring, Japan's ASRM. Notably, the Taiwanese system takes a more precautionary approach to the review and approval of RM technologies, which can only be performed by a national body established by the regulatory authority (Abolarinwa et al., 2021; Tsai et al., 2020). Just as Taiwan learned from Japan's experiment, it may now be time for Japan to learn from Taiwan.

Revisiting the provisions and implementation of the ASRM is crucial, specifically the conduct of research and therapeutic plan reviews by CCRMs and CSCRMs. The concerns are not merely academic. Poor-quality reviews of the use of new advanced biotechnologies in human subjects and patients can have real-world consequences, similar to the well-known Mediator incident that occurred in France (Mullard, 2011; Mckee, 2013).The findings of the MHLW commission on issues of scientific reliability, duplication of review materials, and conflicts of interest show that a similar disaster could occur in Japan.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.stemcr.2023.01.013.

AUTHOR CONTRIBUTIONS

T.I., T.H., and M.F. were responsible for conceptualization, methodology, and investigation. K.K. and S.S. were responsible for the validation of the investigation. T.I. wrote the original draft. All authors discussed and contributed to the final manuscript.

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CONFLICT OF INTERESTS

We conducted the studies commissioned by the MHLW. This paper is based on a

part of the report published as outcomes of the commissioned projects.

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