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# Amendments to ASRM: Can we move away from a "Therapeutic Haven"?

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## SUMMARY

The key amendment to the Act on the Safety of Regenerative Medicine in June 2024 is regarding on-site inspections and the criteria for disqualifying the Certified Special Committees for Regenerative Medicine and Certified Committees for Regenerative Medicine. Appropriate regulations are needed after the legal amendment to stop the widespread use of unproven interventions and move away from the concept of a "Therapeutic Haven."

The Act on the Safety of Regenerative Medicine (ASRM), enacted in Japan in November 2013, was amended on June 7, 2024. The ASRM was designed to establish an oversight system for research and therapy involving cell-based medical procedures. Two key features of the Act were the implementation of a risk-based classification system for cell-based interventions and provisions for reviewing research and therapeutic plans for regenerative medical procedures by government-authorized committees. The two main points of this amendment to the ASRM are as follows (MHLW, 2024).

### Issues requiring ASRM amendment

The first point of the ASRM amendment is to include *in vivo* genetic medicine within its regulatory scope. The problem was that unproven *in vivo* genetic medicine, which was performed in private clinics, was not regulated in Japan. Problems had been reported by families of patients with cancer regarding private clinics that offered expensive gene therapy that had not been proven safe or effective (Hara, 2017). The ASRM previously regulated *ex vivo* gene medicine by classifying it as Class I regenerative medicine (RM), which is considered a high-risk procedure involving genetically modified, pluripotent, and/or xenogeneic cells. Class I RM cannot be allowed without review by the National Health Science Council (NHSC). Therefore, *in vivo* genetic medicine is expected to be considered similarly. It is difficult to say if the ASRM effectively regulates Class II and Class III RM therapies, which are considered lower risk procedures and do not require NHSC review. Class II RM generally involves stem cell-based interventions that have undergone some form of manipulation or culture, whereas Class III RM typically involves minimally manipulated somatic cells. Based on the ASRM, a risk classification tree for RM was proposed, categorizing it into three classes (from I to III), each with a corresponding review system (Ikka et al., 2023a).

Second, the Ministry of Health, Labour, and Welfare (MHLW) will be authorized to conduct on-site inspections of the Certified Special Committees for Regenerative Medicine (CSCRMs) and Certified Committees for Regenerative Medicine (CCRMs), which are the cornerstone of the ASRM system, and clarify the grounds for disqualification from the CSCRM/CCRM so that reviews are conducted properly. We have reported several relationships between CSCRMs and reviewed RM providers that cannot be expected to be fair and independent as per the ASRM requirements. Moreover, at least 25%–30% of Class II RM therapeutic plans reviewed by the CSCRMs have questions about the scientific basis of therapeutic safety and physician expertise (Ikka et al., 2023a). We also reported on the current situation in which RM-related adverse events are not properly reported to CSCRMs/CCRMs, i.e., the CSCRMs/CCRMs do not note their occurrence, despite the law's objective of "ensuring safety" (Ikka et al., 2023b). Our studies were mentioned and discussed in the House of Representatives (https://kokkai.ndl.go.jp/#/detail?minId=121304260X01920240515&current=8), which debated the revision of the law and raised serious concern about these issues. Revising the ASRM means that the government will begin to address the quality of CSCRM/CCRM reviews and RM practiced at private clinics.

### Continuing CSCRMs/CCRMs problems and the importance of the legislative changes

After we have published papers and identified problems with the ASRM and CSCRMs/CCRMs, serious problems have been identified for several committees. According to the information available on the MHLW's website (https://saiseiiryo.mhlw.go.jp/disclosed_committee/preview/12C2312004; https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000186471.

**Table 1. Trends in the number of regenerative medicine plans**

| | | 2016/10/31 | 2020/5/31 | 2023/12/31 |
|---|---|---|---|---|
| Class I regenerative medicine | Therapy | 0 | 0 | 7 |
| | Research | 17 | 14 | 16 |
| Class II regenerative medicine | Therapy | 75 | 575 | 1,571 |
| | Research | 37 | 55 | 43 |
| Class III regenerative medicine | Therapy | 3,264 | 3,287 | 3,898 |
| | Research | 50 | 54 | 42 |

html), we found that a CCRM with only five dentists, a cosmetic medicine clinic physician, and a pharmacist as medical experts had reviewed at least 32 RM cancer therapeutic plans as of May 31, 2024. A CCRM reviewed 45 plans in 1 h on September 9, 2021, and 258 plans in one meeting on October 8, 2015, raising doubts about whether proper reviews were conducted or a review fee business was established by processing multiple reviews in a short time (Iwasawa, 2022).

On June 1, 2024, it was reported that at least three patients at the same private clinic who received intravenous infusions of adipose-derived mesenchymal stem cells for menopausal symptoms and ovarian dysfunction developed primary visual impairment (Kyodo, 2024a). After receiving the adverse event report, the CSCRM conducted a review to determine the cause of the adverse event and determined that it was not the stem cells but the organic solvent used to preserve the cells, dimethyl sulfoxide. It then approved a change to the plan to ensure that the concentration of the organic solvent was not biased during administration (Kyodo, 2024b). No matter how carefully implemented, the occurrence of adverse events may be unavoidable and reporting their occurrence to the CSCRM was appropriate. However, the committee meeting minutes (https://x.gd/oLtyH) revealed that the committee did not order the clinic to stop this therapy plan until the cause was identified. The committee had initially accepted the plan to administer mesenchymal stem cells for menopause and ovarian function improvement as appropriate. Can it be said that this committee conducted an appropriate review? In fact, a company that sells medical devices serves as the secretariat for the CSCRM. The company is also in the business of preparing RM plans and assisting in dealing with ASRM procedures for RM-providing institutions. Therefore, it is presumed that a conflict of interest exists (https://www.cuore-inc.co.jp/business). It should be noted that, according to information available as of 6 August 2024 (https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000186471.html), the committee has reviewed the largest number of therapy plans (318) for Class II RM underway in Japan.

The second point of the ASRM amendment is important for the current situation where such committees exist. The MHLW will be able to conduct on-site inspections and withdraw accreditation for CSCRMs/CCRMs that raise doubts about whether they are carrying out proper reviews, where therapy plans that are generally condemnable cannot be modified or banned in advance. The specific method for conducting on-site inspections of the CSCRM/CCRM is still unclear; the content of the ASRM's enforcement regulations to be prepared by the MHLW will be crucial. For example, in cases where the Department of Health and Human Services has revoked a review board's status on the basis of conflicts of interest between reviewers and the research under review (several members assisted in the preparation of research protocols and informed consent documents, consulted with researchers, and reviewed and approved those research plans), sloppy reviews, lack of minutes of review meetings, and initiatives such as the Food and Drug Administration regulations on which the revocation was based should be of interest to the MHLW (Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, 2016).

## Moving away from therapeutic haven

Approximately 98% of the regulated interventions are not research but therapeutic interventions at private clinics which self-designate as "advanced medicine." As Table 1 presents, there has been an explosion of Class II RM therapies since the ASRM came into effect. Moreover, saying that the ASRM and CSCRMs have allowed this increase is fair. Many of these likely include those condemned by the ISSCR "the administration of unproven stem cell-based interventions outside of the context of clinical research or medical innovation" (ISSCR, 2021). In the past, the Japanese Society for Regenerative Medicine expressed concern, stating, "There are countries in the world used as 'Tax Havens,' but we are deeply worried that Japan might be (and is already becoming) used as a 'Therapeutic Haven' in the field of stem cell interventions by other countries" (JSRM, 2011). However, if the situation continues as it is, there is a possibility that it could worsen further.

We hope that the MHLW measures (such as drafting of ASRM enforcement regulations and guidelines) following the revision of the ASRM will be effective. Unless we can ensure the expertise of physicians performing

RM, certify only committees conducting appropriate reviews under independent and fair relationships with RM providers, and establish a system to create truly safe and effective RM by collecting, recording, and verifying not only the occurrence of adverse events but also the results of therapies, we will not be able to avoid the provision of non-evidence-based therapies or move away from the concept of a "Therapeutic Haven."


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## AUTHOR CONTRIBUTIONS

T.I. prepared the first draft. All authors discussed, revised, and approved the final draft.

## DECLARATION OF INTERESTS

We conducted the studies for improving the quality of the CSCRMs/CCRMs commissioned by the MHLW in FY 2019–2020.

## DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During manuscript preparation, the authors used DeepL for translation and editing. After using this tool/service, the authors reviewed and edited the content as needed. The authors take full responsibility for the content of the publication.

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