Stem Cell Reports
Perspective
ISSCR
OPEN ACCESS

Reflection on the enactment and impact of safety laws for regenerative medicine in Japan

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https://doi.org/10.1016/j.stemcr.2021.04.017

Japan's Act on the Safety of Regenerative Medicine (ASRM) created an innovative regulatory framework intended to safely promote the clinical development of stem cell-based interventions (SCBIs) while subjecting commercialized unproven SCBIs to greater scrutiny and accountability. This article reviews ASRM's origins, explains its unprecedented scope, and assesses how it envisions the regulation of SCBIs. This analysis is used to highlight three key insights that are pertinent to the current revision of the ASRM: clarifying how the concept of safety should be defined and assessed in research and clinical care settings; revisiting risk criteria for review of SCBIs; and taking stronger measures to support the transition from unproven interventions to evidence-based therapies. Finally, the article reflects on lessons drawn from Japanese experiences in dealing with unproven SCBIs for international endeavors to regulate SCBIs.

Introduction

Governments worldwide face the challenge of accelerating responsible clinical translation of stem cell-based interventions (SCBIs), including regenerative medicine, while protecting vulnerable patients from harmful unapproved or unproven interventions (Lindvall and Hyun, 2009; Sipp et al., 2017). In this article, "unapproved" refers to treatments that have not been approved to enter the market and/or are not covered by national health insurance, while "unproven" therapies refer to those for which scientific and therapeutic evidence is not fully demonstrated. Advocates of legitimate SCBIs fear that reckless use of unproven therapies will not only fail to help patients but will also expose them to undue financial burdens (Lomax et al., 2020; Lysaght et al., 2017). The International Society for Stem Cell Research (ISSCR) has produced guidelines for responsible translation, encouraging the establishment and enforcement of regulations by both government and professional associations (International Society for Stem Cell Research, 2016). In practice, however, national strategies related to the regulation of SCBIs vary widely (Sleeboom-Faulkner et al., 2016). In Europe, countries initially opted to regulate cell-based products on a case-by-case basis (Kent et al., 2006). The European Union (EU), recognizing that such regulatory diversity impeded its aim of a coherent internal market for SCBI products, created a new centralized regulatory classification of "advanced therapy medicinal products" (ATMPs) in 2007, which adapted the pharmaceutical regulatory model for SCBIs (Faulkner, 2012). This is one example of what Faulkner (2009) termed "governation," in which scientific innovation is accompanied by parallel innovations in regulation and governance.

In Japan, there is another noteworthy example of the exploratory governance of SCBIs: the Act on the Safety of Regenerative Medicine (ASRM) (Government of Japan, 2013). The ASRM, enacted in 2013 and enforced in 2014, has unique features worth consideration. Its provisions apply to both medical research and treatment and include the regulation of SCBI-related cell-processing facilities and quality standards (Azuma, 2015). It also excludes SCBIs from entry into or being developed for the pharmaceutical market. This distinguishes it from the major regulatory pathways for advanced therapies used in Western jurisdictions, such as the ATMP classification in the EU or any human cells, tissues, and cellular and tissue-based products (HCT/Ps) regarded as biological products in the US. In Japan, research and development of SCBI products seeking authorization and approval for marketing are covered by a separate law: the Pharmaceuticals and Medical Devices (PMD) Act (Government of Japan, 1960). This act was revised from the existing Pharmaceutical Affairs Law in 2013 (enforced in 2014) to include new regulatory classifications and pathways for industrial SCBI products in clinical trials (Azuma, 2015). Japanese oversight of SCBIs thus distinguishes clinical trials for pharmaceutical marketing authorization and approval from all other clinical research (e.g., academic research) and unapproved therapies: the former are covered by the PMD Act and the latter, including SCBI provision by healthcare professionals, hospitals, and private clinics, by the ASRM. Although superficial similarities in regulations covering medical treatment purposes exist between the ASRM and compassionate use and "hospital exemption" provisions in other countries, the unprecedented scope and aims of the ASRM mean it has no direct equivalent.

This article traces the ASRM's history, especially preceding discussions and regulatory measures, to elucidate what it was intended to achieve in its current form and how these aims were operationalized within the Japanese regulatory system. This analysis draws on a historical examination of the ASRM and the reports and minutes of

meetings that preceded its enactment. Based on this analysis, the paper then presents a set of recommendations to strengthen the act's capacity to safely promote the clinical development of SCBIs outside the regulatory framework for industrial products in Japan and to support the translation of unproven therapies into evidence-based therapies. In so doing, this paper supplements and extends accounts explicating (Konomi et al., 2015; Tobita et al., 2016) and critiquing (Cyranoski, 2019; Lysaght, 2017; Lysaght and Sugii, 2016) the ASRM.

ASRM: Background and establishment

Intensive state support for regenerative medicine in Japan began in 2000 with the Genome Project research funding stream (Kurata and Choi, 2012; Mikami, 2015), which provided financial support for translational life sciences research. Among a series of ethical regulations established for various biomedical fields (Minari et al., 2014), a designated governmental committee set up by the Ministry of Health, Labour and Welfare (MHLW) was directed to discuss appropriate regulation of clinical stem cell research. The deliberations of this committee eventually led to the 2006 *Guidelines on Clinical Research Using Human Stem Cells* (Ministry of Health, Labour and Welfare, 2006), which introduced a duplicate review system for clinical stem cell research to ensure consistent institutional review board (IRB) performance (Science and Technology Subcommittee of Health Science Council, 2005). This duplicate review system required the Japanese National Review Committee and the IRBs at all the institutions involved in the research to approve a research plan before initiating any trial with human participants. This dual review system was intended to ensure adequate assessment of SCBIs. These guidelines constituted the oversight of SCBIs in a research context until the enforcement of the ASRM.

Combined with the increasing popularity of autologous SCBIs, the 2007 discovery and related developments in human induced pluripotent stem cells (iPSCs) (Takahashi et al., 2007) provided an impetus for the government to review the existing regulatory frameworks for clinical practice in Japan. As a result, the Governmental Committee for Institutional Frameworks of Regenerative Medicine was formed in 2009 to devise a governance regime covering unapproved autologous stem cell treatments in clinical practice. Its first report included standards for providing cell products being made in hospital settings for patients. The report also argued that unapproved autologous cell therapies used in clinical settings should be subject to oversight similar to that in clinical research (Governmental Committee for Institutional Frameworks of Regenerative Medicine, 2010). The report was released through a Director Notification from the MHLW (Ministry of Health, Labour and Welfare, 2010), indicating ministry support for the report's recommendations but not granting it legislative force. The 2006 guidelines (for research) and 2010 notification (for clinical practice) each influenced the ASRM in different ways, as is described in subsequent sections.

While consideration of the regulation of SCBI promotion was progressing (Azuma, 2015), the MHLW established the Governmental Committee for Promoting and Ensuring Safety of Regenerative Medicine in 2012 (hereafter, 2012 committee). This committee, which included medical professionals, lawyers, and lay participants, met ten times between 2012 and 2014. One of the main reasons for the establishment of the 2012 committee was that a patient from a South Korean firm died of a pulmonary embolism in 2010 after receiving autologous stem cell treatment through a private clinic in Japan (Cyranoski, 2010). Given this tragic event and the growing concern that private clinics were often providing unreliable, unproven SCBIs (Fujita et al., 2016), the 2012 committee saw an opportunity to create a more effective and practical regulatory framework for unproven SCBIs. As the 2006 guidelines and 2010 notification did not constitute formal legislation, the main legal basis for the oversight of SCBIs fell under two conventional Japanese laws (Konomi et al., 2015). One is the Medical Care Act (1948), which provides the legislative basis for assessing the appropriateness of medical facilities and systems, mandates the provision of medical care, and ensures good quality of care (Government of Japan, 1948a). The other is the Medical Practitioners' Act (1948), which sets out terms for the licensing, training, and practice of physicians to promote public health and support healthy lives (Government of Japan, 1948b). In combination, these acts permit broad discretion in medical practice by individual physicians and medical institutions, ranging from "off-label" uses of approved drugs and devices to use of unapproved medical products, and as such they were associated with the legal acceptance of unproven SCBIs.

Given these conventional regulatory frameworks, the 2012 committee released a summary report with six key elements that laid the direct groundwork for the future ASRM: (1) the necessity and purpose of a regulatory framework for ensuring the safety of SCBIs, (2) the regulation's scope and definition, (3) a framework for ensuring safety in accordance with risk, (4) standards for cell culturing and processing, (5) ensuring ethicality, and (6) provision of information to the public (Governmental Committee for Promoting and Ensuring Safety of Regenerative Medicine, 2013). The characteristics of the 2013 report are shown in Table 1, with a comparison with those of the 2010 report.

Identifying the ASRM's scope and shaping terminology

The major debates of the 2012 committee focused on how to effectively regulate unproven SCBIs. Similar challenges

Table 1. Comparison between the 2010 and 2013 reports

Committee	Governmental Committee for Institutional Framework of Regenerative Medicine (2009)	Governmental Committee for Promoting and Ensuring Safety of Regenerative Medicine (2012)
Ministry	Ministry of Health, Labour and Welfare (MHLW)	MHLW
Major reports	2010 report and Director Notification	2013 report[a]
Aim	to promote appropriate use of unapproved and experimental autologous stem cell-based interventions (SCBIs) in clinical treatment through multiple medical institutions	to appropriately use unproven SCBIs in both clinical research and clinical treatment while ensuring safety under unified robust regulations
Focus (scope)	- soft (non-statutory) regulations for unapproved and experimental practice of SCBIs (excluding clinical trials for market approval) - autologous stem cell processing - minimum institutional requirements for single and multiple medical centers - good manufacturing practice (GMP)-type facilities/equipment and quality control requirements for collaborative medical facilities	- the need for a regulatory framework (possibly statutory) for unproven SCBIs (excluding clinical trials for marketing approval) - autologous and allogenic cell processing - a unified set of regulations for medical centers, research institutions, private clinics, and industries - GMP-type facilities/equipment (currently called Good Gene, Cellular, and Tissue-based Products Manufacturing Practice [GCTP]) and quality control requirements for all public and private cell-processing facilities (including industries) - registration and licensing cell-processing facilities
Concepts (philosophy)	- unapproved and experimental treatment should be initiated as research, with specific reference to the 2006 *Guidelines on Clinical Research Using Human Stem Cells* - implementation of research toward developing an evidence base for routine (standard) treatment - the need for consistency across multiple medical sites	- draw on both the 2010 report on SCBIs in clinical treatment and the 2006 guidelines for clinical research with SCBIs - risk management, including risk classification of cell culturing and processing, irrespective of the research or treatment setting - consideration of standardized cell-processing facilities criteria and procedures for medical research institutions, hospitals, private clinics, and industries
Key elements	- responsible and collaborative institutional preparation (e.g., as a specific requirement of the institutional review committee) - sampling procedure, cell-processing facilities management, and transplantation/administration - evaluation of safety and efficacy	- the necessity and purpose of a regulatory framework ensuring the safety of SCBIs - the regulation's scope and definition - a framework for ensuring safety in accordance with risk (e.g., three-tier risk classifications) - standards for cell culturing and processing - ensuring ethicality - provision of information to the public
Secondary considerations	- proper operation of cosmetic and private practices - the need to promote collaboration within the representative academic societies	- the need to promote acceleration of legitimate SCBIs - increasing public expectations of SCBIs - inadequate regulations of unapproved SCBIs - the sense that Japan was becoming a destination for medical tourism

[a]This report mainly reflected on the draft text of the ASRM.

have been faced in other jurisdictions. For example, European regulators developed the ATMP classification into such categories as gene therapies, cell therapies, tissue engineered medicines, and combination therapies to capture the diversity of actual and potential SCBI products. However, unlike the ATMP classification, the 2012 committee had to consider the oversight of the SCBIs, both for research other than the development of products covered by the

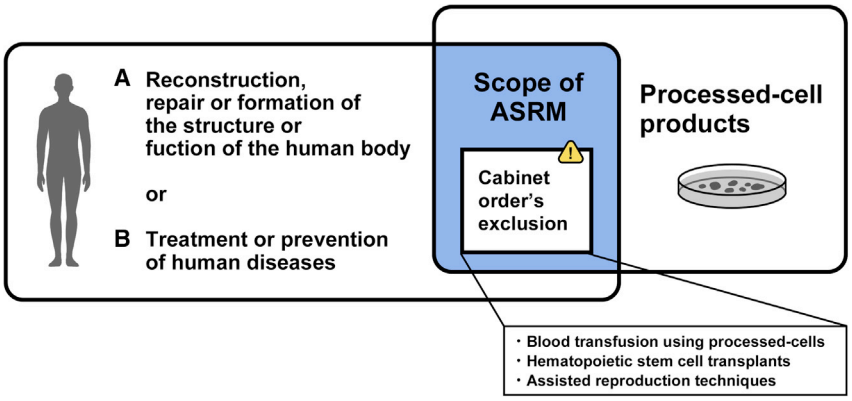

Figure 1. Diagram of the legal scope of the Act on the Safety of Regenerative Medicine and its exclusions
The scope of the act is highlighted in blue.

PMD Act and for discretionary unproven therapies in private practice.

To this end, the committee's discussions attended to the shaping of the proper scope of the regulation and defining what, precisely, it would regulate. According to committee minutes (Ministry of Health, Labour and Welfare, 2012–2014), a key debate was whether to select the term "regenerative medicine," as commonly used, or "cell therapy" to best describe this scope. Regenerative medicine could be defined either in terms of the *purpose* of a given medical treatment or the *outcome* of that intervention. If it were defined solely in terms of the aim of intervention, the concept could apply to interventions with little or no efficacy in achieving regenerative functions (the regeneration of biological functions and of bodily organs and tissues). In this case, there was concern that non-evidence-based interventions could easily fall within the official definition of regenerative medicine. If the term were defined from the perspective of therapeutic outcomes, however, it would exclude from the act all regenerative therapies in development, including innovative clinical research and practices that have not yet demonstrated sufficient efficacy in achieving the regeneration of bodily tissues and organs. This dilemma, discussed by the committee, reflects the inherently emergent and developmental state of most SCBIs.

A related discussion involved whether cell therapy, rather than regenerative medicine, should be adopted for the scope of the regulation. While regenerative medicine refers to a purpose and function or outcome of medical treatment, cell therapy refers to a specific modality of medical treatment. The latter term was considered to present a clearer image of the methods of SCBIs to the public than regenerative medicine. Using the term cell therapy instead of regenerative medicine for the scope would emphasize the incorporation of a variety of cell therapies but might undervalue the concept of regeneration and mislead patients or the public to think that it includes non-regenerative cell and tissue transplants. This discussion clearly illustrates the committee's mandate to manage the practical implications of enacting the legislation, which involved noting the considerable public awareness of regenerative medicine in Japan (Shineha et al., 2010). Ultimately, the 2012 committee's summary report presented "(unproven) medical practice using cells" as an appropriate scope for the ASRM, suggesting the use of the term "regenerative medicine and cell therapies."

When the ASRM was enacted, however, legislators adopted the term "regenerative medicine et cetera" for consistency with other legal instruments dealing with SCBIs, which Article 2 of the ASRM explains as follows (Government of Japan, 2013): "Regenerative medicine et cetera" indicates medical intervention using processed-cell products under these two purposes, specified by a Cabinet order: (1) reconstruction, repair, or formation of the structure or function of the human body or (2) treatment or prevention of human diseases. This article indicates a tripartite structure, including a "method"—medical intervention using processed-cell products—and two "aims." It reflects the 2012 committee's desire that new regulation should be comprehensive, incorporating both regenerative medicine and cell therapy and clarifying the precise scope of the act (Figure 1). The final definition of "medical intervention using processed-cell products" excludes organ transplantation as well as interventions with small-molecule drugs or biological agents, such as cytokines (which do not use cells). This definition also excludes *in vivo* gene therapy and *in vivo* gene editing, which are transfected directly into the human body. The term "et cetera" is often overlooked in non-Japanese-language discussions regarding the ASRM, but it is significant as it gives the act the flexibility to capture future, yet-to-be developed cell-based technologies, and covers unapproved non-regenerative modalities, such as *ex vivo* gene-edited cell therapies (e.g., unapproved chimeric antigen receptor T cell [CAR T] therapy). A further refinement of the act's scope by Cabinet order specifically excludes three areas of medical technology that might otherwise fall under the act, including blood

transfusion using processed cells. Even here there are exceptions to this exemption so that, for example, gene-transferred or iPSC-derived blood cell components are still covered by the ASRM.

Regulatory framework for unproven medical interventions

The analysis now turns to an explanation of how the current ASRM came to cover both research and therapy with unproven SCBIs. Foundational texts of medical research governance present at least three aspects of the assessment of unproven therapies. The first is directed at considering the distinction between research and treatment, the difficulty of which the Belmont Report describes as follows: "The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called 'experimental' when the terms 'experimental' and 'research' are not carefully defined" (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Second, relatedly, although it is sometimes difficult to distinguish between research and clinical care, interventions, including a research element, should be reviewed within their research framework, particularly following the principle of protecting human subjects. Third, an unproven intervention may be allowed for a very small number of patients, but it should be followed subsequently by formal clinical research, as stated by the 2016 ISSCR guidelines (International Society for Stem Cell Research, 2016), with similar perspectives shared in the Declaration of Helsinki of the World Medical Association (General Assembly of the World Medical Association, 2014). These perspectives contribute to providing basic and general directions; however, each nation should design country-specific regulations based on both local and international contexts.

The 2012 committee's work toward enacting the ASRM sheds light on how to manage the unresolved features of unproven SCBIs in the Japanese context. As mentioned earlier, the focus of the 2012 committee arose in part from a 2010 case of death in a private clinic. However, there was potential tension regarding this regulation: while the safe provision of SCBIs needed to be managed by additional regulations, both academic freedom in research contexts and the broad discretion of medical professionals in the context of clinical care had to be carefully ensured under the Japanese Constitution (Government of Japan, 1946) and other specific laws, such as the Medical Practitioners' Act. The Japanese Constitution stakes out a broad commitment to individual rights and freedoms, including access to healthcare, in Article 13, and it protects freedom of occupation (associated with physicians' discretion) and academic freedom in Articles 22 and 23, respectively (Governmental Committee for Promoting and Ensuring Safety of Regenerative Medicine, 2013). In this regard, the committee eventually advocated that it is acceptable for these freedoms and discretions to be limited in the interest of prioritizing the protection of human life and health: this helped to justify additional regulation of medical practice.

In formulating the 2013 report, which set out recommendations for a more robust regulatory framework, the 2012 committee was able to draw on and extend the prior recommendations of the 2010 notification. Regarding cell-processing facilities, the 2013 report argued that quality assurance measures for cell culturing and processing should apply not only to medical institutions, but also to commercial enterprises that offer private (i.e., outsourced) manufacturing of cell products. In this regard, the report aimed to promote efficient development of SCBIs, reduce the load on medical institutions, and assure the quality of cell-processing facilities. The resultant ASRM incorporated the extension of cell-processing regulation from medical institutions to commercial enterprises in establishing the registration and licensing system of cell-processing facilities (Maeda et al., 2015).

The 2010 notification's other major recommendation that experimental treatments using unproven SCBIs be subject to the same ethical oversight measures as clinical research led to the 2012 committee presenting a pre-review procedure for both research and care (including private practice). The implication of this recommendation was associated with a perspective described in the 2010 notification, which advised that unapproved SCBI should be initiated as research, with specific reference to the 2006 guidelines. The 2012 committee prescribed a three-tiered risk classification, depending on cell and cell-processing type. Based on this suggestion, the ASRM has adopted a three-class system. Class 1 (e.g., those using novel cells, such as iPSCs, embryonic stem cells to which genes have been introduced, and xenogeneic/allogenic cells) is the high-risk category; class 2 (e.g., cell therapies using somatic stem cells or cultured cells) is the medium-risk category; and class 3 (e.g., cell therapies using somatic cells and non-cultured cells) is the low-risk category. The SCBIs in class 1 are reviewed by duplicated local and national review committee systems (similar to the duplicate review framework in the 2006 guidelines). Some similarities can be detected in risk-based classifications used in other jurisdictions, for example, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), which distinguish between cell-based therapies on the basis of homologous or non-homologous use and on the degree of manipulation of the cells. However, the EMA and FDA regulations are for products in clinical trials for market

authorization, whereas the ASRM explicitly excludes this activity.

Reflections on the ASRM's impact and lessons for the future

The ASRM has been in force for several years. Its impact can be felt in terms of the two overarching aims behind its development: the safe promotion of SCBIs in Japan utilizing evidence-based procedures, and the reining in of the provision of unreliable, unproven SCBIs. Japan has achieved several of the world's "first in human" trials of human iPSC-derived therapies (Takashima et al., 2018; Yamanaka, 2020). As for the more robust regulatory framework, since the act was launched, some private clinics have been subject to emergency measures to temporarily suspend SCBI provision (under Article 22 of the act) and an order for improvements ensuring safety, among other aspects. (Article 23). The offending clinics were also publicly listed on the MHLW website, which can contribute to the development of a resource to help patients and their families select better treatment providers. In 2017, six arrests were made of parties supplying umbilical cord blood without proper regulatory authorization (Sipp and Okano, 2018). While these events possibly testify to the utility of the ASRM, three major insights have been gleaned from the above historical analysis shaping the ASRM for its further development.

First, the comprehensive scope of the ASRM, which covers research, care, and even cosmetic enhancement procedures, appears not to clarify the concept of "ensuring safety" over these different contexts. While the ASRM ensures the safety of SCBIs, especially through quality standards for cell culturing and processing, applicants (e.g., physicians) have the discretion to decide whether their application will be reviewed as research or as medical treatment. Although there are several differences in application procedures between research and treatment (the former is more demanding than the latter), there can still be an opportunity to revisit how "ensuring safety" is defined and assessed in the different contexts. For example, the WHO describes patient safety as "a framework of organized activities that creates cultures, processes, procedures, behaviors, technologies, and environments in health care that consistently and sustainably lower risks, reduce the occurrence of avoidable harm, make error less likely and reduce its impact when it does occur" (World Health Organization, n.d.). In particular, regarding unproven therapy, although ensuring safety can be somewhat more complex because of the need to judge whether there is sufficient scientific plausibility to support the intervention, allowing identified risks to be managed within particular clinical settings (Taylor, 2010), future iterations of the ASRM would benefit from greater clarification of appropriate concepts for ensuring safety in the respective contexts of research and unproven treatment.

Second, the present risk-based classification could usefully include a broader range of factors. Current risk classification under the ASRM mainly depends on cell type and degree of manipulation but does not include other risk factors. Indeed, the ASRM does not truly reflect the 2013 report, which recommended assessing the risks of the intervention method and the (anatomical) administration site, as well as the cell source and cell processing. In general, standardizing and evaluating intervention methods, such as surgical procedures involved in clinical practices, have always presented daunting challenges (Ergina et al., 2009), as their procedures and techniques remain governed predominantly by professional standards (Angelos, 2013). To address this challenge, under the ASRM, regenerative medicine review committees have several roles in evaluating the application, including the review not only of the appropriateness of applicant investigators but also of an evaluation report from an expert(s) in the target disease area. However, given the increasing necessity of properly evaluating risk factors of SCBIs beyond cell and cell-processing type, as shown in a representative article on two stem cell therapies for patients with age-related macular diseases (Daley, 2017), a broad range of academic and professional societies should be more closely integrated into the practical process of reviewing disease-specific aspects of proposed SCBIs. More specifically, the novelty and uncertainty of surgical or other interventional procedures could be incorporated into existing risk assessment procedures when SCBIs are stratified under the ASRM into classes that determine the stringency of regulatory oversight. Relatedly, the specialization of regenerative medicine review committees, which means that each committee has an expert area (e.g., digestive disease and cardiovascular disease), should be considered in the ASRM. Professional expertise could also be supplemented by drawing on existing guidance on how to identify when a surgical practice is considered innovative (Hutchison et al., 2015; McCulloch et al., 2013).

Third, clear and detailed pathways for transforming unproven SCBIs into more evidence-based SCBIs are still lacking. After the release of the 2013 report, the 2012 committee continued to meet and have discussions that focused increasingly on the issue of the efficacy and effectiveness of unproven SCBIs. Specifically, the committee was concerned that harmless but ineffective "unproven treatments" might continue to be provided to patients. A key question here was how scientific evidence to confirm the efficacy of unproven SCBIs should be managed and verified when medical professions aim to provide therapeutic benefits to specific patients. To address this question, the current ASRM requests applicants to clarify the scientific

validity of unproven SCBIs in their application form and their periodic report to review committees. This approach can be effective, but managing ineffective SCBIs warrants further consideration. Specific considerations for the future development of the ASRM should include (1) requiring review committees to assess follow-up plans for the clinical development of unproven SCBIs, (2) measures to ensure consistency of assessments of scientific validity of unproven SCBIs between different committees, and (3) support for small private clinics to properly evaluate their own treatment provision. More specifically, to strengthen the impartiality and quality of the relevant review committees' roles and responsibilities, measures such as introducing a quality management system of review committees and fully independent review committees, should be considered in the act. Furthermore, to encourage the robust clinical practice of unproven SCBIs, especially for small medical institutions and private clinics, systematic educational, administrative, and financial support regarding the conducting of formal clinical studies should be implemented in a sustainable manner.

In addition, so-called real-world evidence (Franklin and Schneeweiss, 2017; Schneeweiss et al., 2016) could potentially provide a preliminary evaluation of the safety and efficacy of unproven therapies. In a hospital setting, for instance, this can draw on existing systems for quality management and comparative effectiveness of clinical care, which are expected to support continuous institutional learning and improvement of standard treatment, at least in theory. Such support could integrate novel, unproven SCBIs into a "learning healthcare system" (Faden et al., 2013). Earl (2019) endorsed this type of approach to clinical innovation with SCBIs in the US context, while a 2016 report coordinated by the Wellcome Trust recommended a comparable form of ongoing evaluation of clinical practice data to accelerate access to innovative treatments and services in the UK's National Health Service (UK Department of Health, 2016). This again implies opportunities for mutual learning across jurisdictions, particularly where lessons can be learned from existing or planned registries and similar tools for longitudinal evidence collection (Abou-El-Enein et al., 2018; Jørgensen et al., 2019; Okada et al., 2018). However, there may be concerns about the adequacy and accuracy of data collected through real-world practice. Detailed and robust data collection can be an additional burden for clinical staff members. Given that the frequency of cosmetic and other so-called enhancement SCBIs is increasing (Erikainen et al., 2019), there is an especially urgent need for the standardization of the scientific evaluation of outcomes, utilizing real-world evidence.

Finally, careful consideration should be given to clarifying the variety of different activities that can constitute "providing unproven therapies" and to incorporating this understanding in future discussion of the relevant regulations. "Unproven" treatments exist at various levels, from interventions never previously attempted in patients to those applied multiple times but not yet approved, and scientific evidence also exists at various levels. In the academic literature and policy documents, terms, such as "unproven," "innovative," and "experimental," have often been imprecisely or interchangeably utilized, which may make it difficult to build appropriate regulatory frameworks around these categories. As a representative example, unproven is basically used to describe treatments whose safety and/or efficacy are uncertain or unknown. On the one hand, this term has especially negative connotations in the SCBI field, primarily in relation to problems with so-called direct-to-consumer marketing and global stem cell tourism (Berger et al., 2016; Sipp et al., 2017; Turner and Knoepfler, 2016). On the other hand, in a broader sense, it is sometimes used to describe yet-to-be established but potentially promising treatments. The latter case can be similar to the term "innovative," which is associated with novel therapies, different from standard treatment, and not yet validated (Holzer and Mastroleo, 2019; Taylor, 2010). Clarifying the term experimental is more complex, given the nature of its use in both research and therapy, as stated in the Belmont Report.

Against this backdrop, a newly suggested three-category framework derived from the 2010 notification and 2013 report could be useful for stratifying/determining the status of unproven SCBIs. This categorization focuses on three main streams of unproven SCBIs: "exploratory intervention," "experimental and therapeutic intervention," and "commercialised intervention." The exploratory intervention category covers legitimate clinical research, including innovative or frontier research and pilot clinical intervention, which is undertaken to accumulate scientific knowledge and achieve novel and promising future treatments. The experimental and therapeutic intervention category consists mostly of healthcare professional-directed treatments, such as the use of extreme measures for patients who have exhausted their treatment options, off-label use of approved treatments, and the use of treatments that are professionally accepted but unevaluated through formal clinical trials. The commercialised intervention category includes interventions provided in for-profit contexts and treatments for enhancement purposes (e.g., cosmetic surgery) mainly in private clinics, which cover unevaluated treatment. These categories are preliminary classifications derived from the Japanese experience of regulations, but they could be valuable for future regulatory considerations of broader types of unproven therapies and for theoretical debates about classifications of emerging medical technologies.

Conclusions

The 2014 ASRM has been a challenging experiment within Japan's overall regulatory strategy for the clinical translation of stem cells and other regenerative therapies. The act's unprecedented scope makes sense in light of the highly heterogeneous landscape of the activities which it was intended to regulate; the use of unproven SCBIs in research, treatment, and enhancements. Following the previous guidelines and notification about SCBIs, the act has embedded two key ways to manage unproven SCBIs: (1) standardization and authorization for cell processing and (2) risk classification and oversight over research and unproven therapies. However, at least three challenges remain: reconsidering safety concepts for research and unproven therapies, revisiting the range of risk factors used to determine review classifications, and clarifying the pathway for unproven therapies to transition to evidence-based interventions. As a further step, public engagement must be encouraged to protect patients' rights, empower patients, and promote trustworthy SCBIs, as discussed by the 2012 committee.

Reflections and suggestions regarding these ASRM issues and subsequent revisions are timely, opportune, and warranted. In 2019, the MHLW released an interim report (Ministry of Health, Labour and Welfare, 2020) setting out the anticipated direction for major revisions of the ASRM. The revision agenda encompasses (1) a response to advancing medical technology regarding SCBIs and *in vivo* gene therapies; (2) further measures to ensure the safety and scientific validity of regenerative medicine, such as quality assurance of physicians, institutions, and review committees; and (3) promotion of research in SCBIs. One of the latest partial revisions of the act, in June 2020, was related to genome-editing technology, where gene-edited cells, in addition to gene-transferred cells, were incorporated into class 1 of the risk categorization. A similar response has been suggested as part of a planned review of the ATMP Regulation in Europe (Mourby and Morrison, 2020). The current focus of the ongoing ASRM revisions, conducted by two specific working groups, is on (1) the regulatory framework for *in vivo* gene therapy and (2) the risk classifications and the scope of the exemptions within the ASRM.

Finally, the ASRM's scope already anticipates new, originally unplanned cell therapy modalities through the use of "regenerative medicine et cetera" in its formal title. In its current form, the ASRM is a notable piece of innovative and developing governance that has taken significant steps toward extending regulatory oversight to SCBIs in unproven therapies and clinical research. From this perspective, the act is relevant not only to Japan but also to other jurisdictions struggling with the regulatory challenges of unproven SCBIs (cf. Stewart et al., 2020). Regulatory innovation, including in the biomedical field, is a practical learning process whereby mutual information sharing about implementation, outcomes, and concerns can promote better practice at the international level.

AUTHOR CONTRIBUTIONS

K.T. and J.M. conceived the idea and wrote the first draft. K.T. analyzed the related meeting minutes. M.M. contributed to international context and drafting and revising the manuscript. All authors discussed and contributed to the final manuscript.

ACKNOWLEDGMENTS

The authors thank Andrew Webster and Tamra Lysaght for their valuable and fruitful comments. The authors also appreciate Misaki Ouchida for providing a clear figure. K.T.'s work was supported by AMED under grant no. JP20bk0104080. M.M.'s work was supported by the Leverhulme Trust through grant no. RPG-2017-330. J.M.'s work was partly supported by the JSPS Grant-in-Aid for Challenging Research (Exploratory), no. 19K21566. J.M. and K.T. are partly supported by the SECOM Science and Technology Foundation.

CONFLICTS OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as conflicts of interest.

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