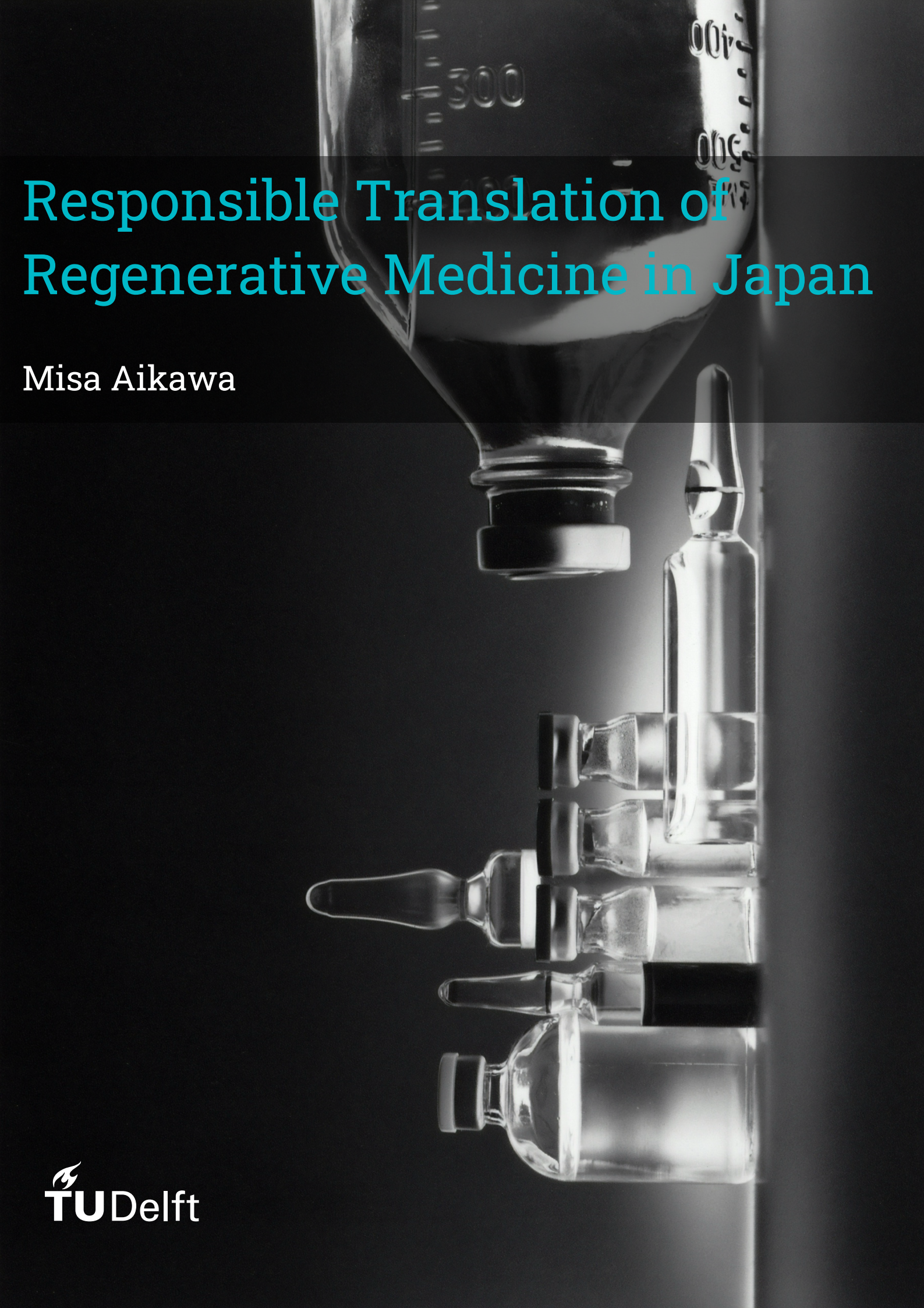


Responsible Translation of Regenerative Medicine in Japan

Misa Aikawa

TU Delft

Responsible Translation of Regenerative Medicine in Japan

By

Misa Aikawa

in partial fulfilment of the requirements for the degree of

Master of Science
in Engineering and Policy Analysis
at the Delft University of Technology,
to be defended publicly on Thursday 8th August, 2024 at 8:00

Thesis committee:	Dr. Samantha Copeland,	TU Delft, First Supervisor
	Dr. Saba Hinrichs-Krapels,	TU Delft, Second Supervisor, Chair
	Dr. Irene Grossmann,	TU Delft, Advisor

Cover: Chemotherapy vials by the National Cancer Institute

An electronic version of this thesis is available at https://repository.tudelft.nl

TU Delft

Executive Summary

Background issues

Healthcare is an essential part of both individuals and society. However, people have problems with their health, such as diseases and age-related matters, and society faces challenges in the healthcare system, including financial burden and fair distribution of services. Regenerative medicine would offer promising solutions to these issues. Regenerative medicine involves techniques to replace or regenerate human cells, tissues, or organs to restore normal function. However, it faces numerous challenges in the translation of this technology from "bench to bedside." This is because it shares the characteristics of emerging technologies, i.e., uncertainties, risks, and impacts. Therefore, changes in society, including political, regulatory, and public acceptance, are required for the translation of regenerative medicine.

Regenerative medicine in Japan

Japan has a heavy burden on the healthcare system due to the growing ageing generation in addition to challenges related to all generations, such as difficult diseases and scarcity of donors. To address these healthcare issues, Japan has promoted the translation of regenerative medicine by unique regulations for about 10 years. Their main feature is that hospitals or clinics that intend to provide patients with regenerative medicine can conduct such treatment without rigorous scientific assessments by having the provision plan reviewed and submitted by the certified committees and the Ministry of Health, Labour and Welfare (MHLW). Moreover, in terms of selling regenerative medicine products by pharmaceutical companies, there is an accelerated path for regenerative medicine, which enables them to market the products before collecting full scientific evidence, namely conditional approval. These regulations aim to promote prompt development and provision of regenerative medicine with minimum safety, enabling people to access it and making the industry thrive. Progress has been made, but problems have also been observed in Japan. For example, the possibility of providing not enough safe regenerative medicine and a lack of a standardised process of translation of regenerative medicine. Issues involved in the governance of new technologies should be approached by taking ethical considerations into account. However, there are few analyses of the translation of regenerative medicine as a system with an ethical perspective in Japan.

Research question

Hence, this research explores the Japanese framework for the translation of regenerative medicine, incorporating ethical considerations, as a case study for managing the translation of emerging technologies. The main research question was identified as "*How can ethical considerations be incorporated into the translation of regenerative medicine in Japan?*" This research employed an interdisciplinary approach, using mixed qualitative analysis, such as literature review, Actor analysis, Thematic analysis, Conceptual synthesis, and conducting an online questionnaire with a supplementary interview.

Results and Conclusion

First, the key processes to intervene and actors who could influence the situation in the translation of regenerative medicine in Japan were identified. The key processes were identified as those from the clinical research phase to the start of marketing. In this process, there is no solid ethical anchor to be followed by practitioners. Through the Actor analysis, it was found that the system of the translation of regenerative medicine in Japan is complicated and involves many actors who interact with each other. As the results of the analysis, MHLW and the Ministry of Education, Culture, Sports, Science and Technology (MEXT), as regulators, and large hospitals owned by universities and universities/national research institutions who own their hospitals, as practitioners, are determined as the key actors.

Next, current and possible ethical issues and possible approaches to the issues were identified from combined sources from the literature review and online questionnaire. The issues are broad, from scientific

limitations due to the novelty of the technology to the burden on the healthcare system or anxiety of people by technological development in the future. While they could be categorised by phases of the translation based on the original studies' focusing points, some of them overlap and connect to each other. The possible approaches were also identified through the comparison with other countries' policies.

Then, those results were synthesised to develop a set of steps which Japan should take to incorporate ethical considerations into the translation of regenerative medicine by the procedure as follows: Within the key process, ethical issues were explored deeply to understand their relations (i.e., cause and result) for finding the leverage points. Next, the feasible ways for Japan to address those points were elaborated based on identified possible approaches. Then, responsibilities for each approach were determined to make them more practical. The results are presented in Figure A.

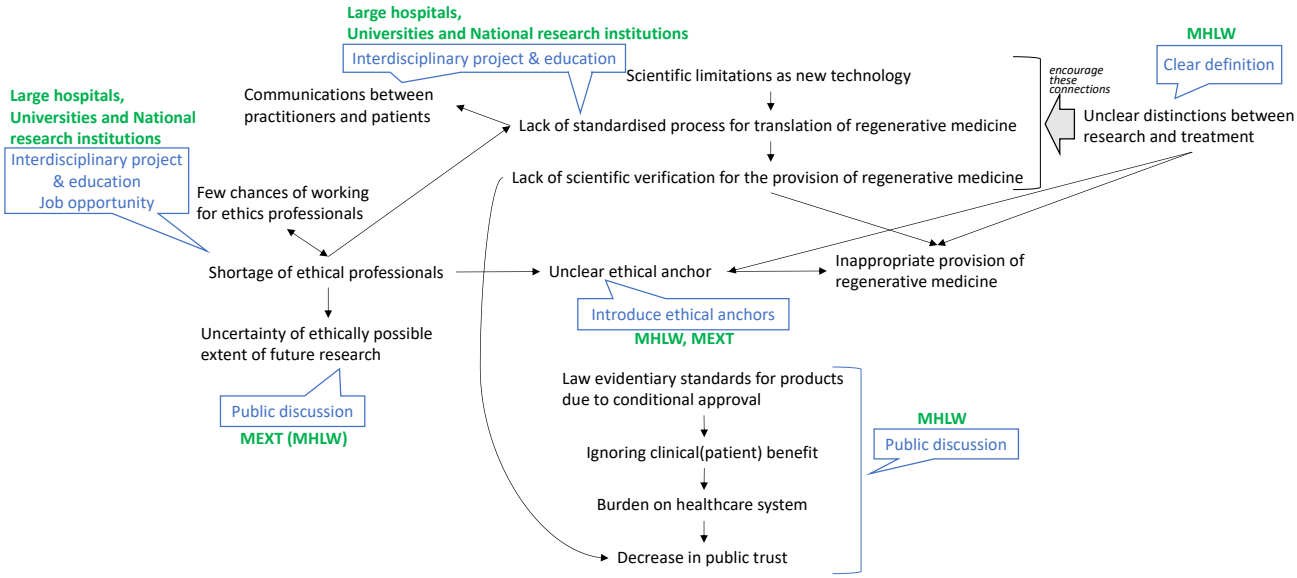


Figure A. Relations among issues and possible approaches with responsible actors. Black letters represent ethical issues regarding regenerative medicine in Japan, black arrows mean the relations between those issues (i.e., causes and results), blue rectangular callouts mean the possible approaches to the issues, and green letters represent actors who are responsible for approaches.

Finally, those steps were translated into a conceptual framework as recommendations for actors with expected actions to realise the desired system between clinical research and pre-marketing, as follows.

- First of all, MHLW should clearly define and distinguish the terms in the current regulations, such as "unproven," "innovative," "research," and "treatment."
- Hospitals should aggregate experiences in practice and reflections on guidelines to enable MHLW and MEXT to review guidelines if necessary. Also, hospitals should elaborate their provision plans, including communication with patients, and research projects related to regenerative medicine, which usually work together with universities or national research institutions where hospitals connect, by learning from the model cases of interdisciplinary research projects that the ministries have presented.
- MHLW and MEXT should collect opinions from practitioners by sometimes cooperating with a governmental agency or researchers' communities and utilise such information to introduce or review ethical guidelines.
- Other than the key actors, doctors and researchers are expected to work with the government's policy and their institutions by presenting reflections on guidelines from practical experiences and incorporating the lessons from interdisciplinary model cases when promoting regenerative medicine.
- Public discussion is recommended as a further step. Translating regenerative medicine is connected to societal challenges, and it is difficult to proceed without public acceptance. Not only patients but also the public should be aware of this and join the discussion for better approaches to ethical consideration

in Japan. Ministries also need to incorporate such discussions to make policy from the bottom-up perspective.

The results of this research would help Japan to incorporate ethical considerations into the translation of regenerative medicine. Especially the government, MHLW and MEXT could utilise this framework to refine the policies of regenerative medicine incorporating hospitals and universities/national research institutions. This research shed light on the system of Japan from an ethical perspective. It also reviewed the system of the translation of regenerative medicine in Japan, incorporated a practical perspective. This attitude led to generating feasible ways to improve the system in Japan, which mainly differs from the results of existing studies. Furthermore, the approach of this research could contribute to further research in the translations of emerging technologies in Japan and other countries.

Table of Contents

1. Introduction

This chapter provides the introduction to this research, including research questions. The context and broad direction of this research are presented step by step in Section 1.1. Then, the knowledge gaps are identified based on the preliminary literature review in Section 1.2. Section 1.3 provides the main research question, and Section 1.4 explains this research's relevance to the master's course and academic context. Finally, the structure of this report is described in Section 1.5.

1.1. Context

Innovation for Healthcare: Regenerative Medicine

Healthcare is the base of people's lives, and the healthcare field is the most critical and essential part of society. However, people have health-related issues due to multiple elements, such as age, environment, disease, or by nature. Also, many countries have difficulties in the healthcare system, such as financial burdens and distribution of healthcare services. Scientific and technological innovation in healthcare and medicine could benefit individuals and society. For example, it can contribute to lengthening people's healthy life spans by preventing critical diseases and establishing effective cures for complex diseases. From the societal perspective, this leads to mitigating the shrinking workforce population and reducing social security expenditures while lengthening individuals' life spans.

Regenerative medicine is one example of such innovation. Regenerative medicine can be explained as a group of techniques for replacing or regenerating human cells, tissues, or organs to restore or establish normal function (Science and Technology Committee of UK Parliament, 2013). This means it can potentially heal or replace tissues and organs damaged by age, disease, trauma, or congenital problems, overcoming the current therapies' hurdles, such as limited donor and immune problems (Mao & Mooney, 2015). Chen et al. (2012) say the progress of regenerative medicine technology may reduce the burden on the world's healthcare systems in the long term. While regenerative medicine was coined in 1999 by William Haseltine, the field itself started in the late 1970s in the form of tissue engineering in the U.S. In the 1990s, stem cells got attention and, after that, combined with tissue engineering to create regenerative medicine. At that time, many private companies tried to use regenerative medicine as a business in the U.S. However, most of them failed due to technical and financial challenges. After 2000, regenerative medicine also started to thrive in other countries, such as the U.K. and Japan. Regenerative medicine has shown promise globally, and governments and private sectors in such countries have invested in and promoted the translation of regenerative medicine until today. On the other hand, the translation of regenerative medicine has a lot of challenges in each phase and is ultimately unachieved (Jacques & Suuronen, 2020).

Need for Societal Adaptation and Ethical Considerations

That is, such a new and novel technology includes uncertainties. Since it is new and no one knows its full characteristics, there may be scientifically unknown aspects when using the technology. Especially, emerging biotechnologies are often perceived as having uncertainty, ambiguity, and transformative potential (Gardner et al., 2015). Also, especially in the medical field, there is little data or examples of patients' reactions to the treatment that employs the new technology due to the newness. So, there are also statistical uncertainties about the new technology.

Generally, new technologies have societal impacts and risks caused by those uncertainties, including both positive and negative ones. If the technology is in the medical field, the risks are identified as the possibility of the inequity of receiving the test, i.e., the unbalanced distribution of the benefits or values from

the technology, and people's decisions about behaviour after knowing the result (Baldus, 2023; O'Shaughnessy et al., 2023). The uncertain impacts of technology are large risks that influence social acceptance (Van Dijke et al., 2022; O'Shaughnessy et al., 2023). The usage of the technologies, namely dual-use, is also considered a risk, such as using the technology for new weapons (Buzdugan et al., 2022; O'Shaughnessy et al., 2023). Also, technologies would affect existing values; for example, regenerative medicine presents the human body as malleable or machine-like. This raises the question of whether the human body or life is something to be engineered or not and makes the boundaries blur between corporal and technical, and natural and engineered (De Kanter et al., 2023).

Therefore, considering these uncertainties, risks, and impacts, changes in society, including political, regulatory, and public acceptance, are required to deal with them ethically when society introduces and implements regenerative medicine as one of the new and novel technologies. However, how should it be achieved? Many countries where research and development of regenerative medicine are thriving or are expected to thrive have already tried to establish regulations and cultivate social acceptance.

One such country is Japan. Japan has been a precedent example of an ageing population for other countries due to its low fertility rate, long life expectancy, and low immigration flow (Hee Hong & Schneider, 2020). It has the highest elderly population and the highest old-age dependency ratio in the OECD (OECD, 2023-a; OECD, 2023-b). Hence, in addition to challenges related to all generations, such as difficult diseases and scarcity of donors, Japan has a heavy burden on the healthcare system. To address the problems around the healthcare system in Japan, the Japanese government is trying to promote innovative research, including regenerative medicine (Sawaji, 2021). Also, regenerative medicine is focused on as an innovative technology for healthcare in Japan by the national healthcare strategy, the Healthcare Policy (Cabinet, 2021).

For about 10 years, to achieve a healthy and long-lived society, Japan has tried unprecedented regulations that aim to promote translational research in regenerative medicine and smooth product/treatment provision to patients with unmet medical needs. Other countries, such as Taiwan, South Korea, and India, have introduced similar systems modelled on Japan (Ikka et al., 2023; Cyranoski, 2019). However, some literature mentions scientific and ethical problems which have been observed under the new regulations of Japan (This is further elaborated in Chapter 4).

Therefore, this research will explore the Japanese framework for the translation of regenerative medicine as a case study for managing translations of emerging technologies.

1.2. Research Gaps

Ethical Approach around the World and in Japan

Consideration and implementation of ethical, legal, and social aspects are required to promote innovation effectively and facilitate its development in a more favourable way that is in line with the ideal social vision and values (Center for Research and Development Strategy, Japan Science and Technology Agency, 2022; Kanama et al., 2019). Also, Kanama et al. (2019) say that an ethical approach could help society benefit from new technologies without suffering from the problems of technology governance that usually occur.

To understand existing studies related to the translations of emerging technologies while taking ethical aspects into account, a brief literature review was conducted. Scopus, an aggregating database containing journals of applied social sciences (Falagas et al., 2007), which fits the aim of this brief literature review, was used to find literature. The search terms were determined by four key focused aspects for this research: 1) emerging technology: "emerging technology" OR "new technology" OR "cutting-edge technology", 2) process of implementation: "implement" OR "implementation", 3) national-scale policy: "public policy" OR "national policy" OR "government", 4) taking perspectives of ethic/responsible innovation into account: "responsible" OR "responsibility" OR "ethic*". The searched literature was limited to articles, conference papers, and reviews whose publication stages were "final" and were written in English. In

addition, to focus on the current trend, the publishing year was set as the last 10 years (2013-2023). After checking abstracts of the found literature in terms of relevance to this research, the number of related articles became 12. The overview of the reviewed literature is shown in Appendix 4. Also, academic and grey literature related to Japan was reviewed to understand approaches to ethical considerations in the translation of emerging technologies so far in Japan. Literature was searched by using Scopus for the academic literature and Google Scholar for including grey literature with "emerging technology" AND "implementation" AND "Japan" as search terms.

Regarding the geographical scope, the studies of translation of emerging technologies with ethical aspects mainly targeted Europe and North America, though some studies mentioned guidelines published by Japanese public organisations. As van Dijke et al. (2022) mentioned, it is also important to understand the contexts of innovation by unravelling the culture. For example, healthcare systems differ by country and the balance of numbers of public medical services and commercial ones (van Dijke et al., 2022). Also, especially related to healthcare, sociocultural aspects have some influences on public acceptance. For instance, the study by Delatycki et al. (2019) provides an insight into the enormous variability in how reproductive carrier screening is offered across the globe, which largely relates to geographical variation in local health care and financial, cultural, and religious factors. Considering this, it can be assumed that the situation in Japan, especially in the healthcare field, would be different from that in Western countries, where many studies have been conducted.

Based on the literature related to Japan, awareness of the ethical aspects of new technologies was evoked around 2000, especially in the fields of information technology and biotechnology, following the trends in the EU and the U.S. (Center for Research and Development Strategy, Japan Science and Technology Agency, 2022). When looking at how to deal practically with such ethical perspectives in science and technology policy in Japan, governmental budgets were infrequently allocated for ethical considerations for emerging technologies' research projects over a long time (Kishimoto, 2021). After Japan became aware of the ethical aspects of new technologies around 2000, the government began establishing regulations, including non-legally binding guidelines. For example, the Genome Guidelines were established in 2001, and they have largely contributed to regulating genome research in Japan (Minari et al., 2021). Also, in 2004, a working group considering ethical aspects was established for the first time within a large research project led by the government in Japan (Center for Research and Development Strategy, Japan Science and Technology Agency, 2022). After that, opportunities for arguing ethical aspects, such as working groups and committees, have been set for research projects in a wide range of technology fields (Center for Research and Development Strategy, Japan Science and Technology Agency, 2022). Currently, there is a program which promotes the development of practical collaborative models for identifying ELSI (Ethical, Legal, and Social Issues (In the EU, this term is often called "ELSA," which stands for ethical, legal, and social aspects.)) of emerging technologies and advancing RRI (Responsible Research and Innovation) to realise a society where technologies can continuously provide new societal values while achieving harmony between technologies and society (Japan Science and Technology Agency, n.d.).

Knowledge Gaps

To put the current situation simply, Japan has promoted a unique system for the translation of regenerative medicine as a national policy for achieving a healthy and long-lived society for people. At the same time, some problems/arguments under the regulations have arisen gradually in the decade since the regulations were implemented, such as the possibility of allowing inappropriate clinics and an uncertain ethical anchor which the practitioner should follow in the translation of regenerative medicine. To improve this situation, ethical approaches should be incorporated into the system of translation in Japan.

Based on the brief literature review in the previous section, studies on implementing emerging technologies that take ethical aspects into account have been conducted mainly in Europe and North America, and there are few cases examined in Asia. Literature related to Japan mainly focuses on the concept of approaches incorporating an ethical perspective involved in developing emerging technologies,

namely how it would be important for Japan to develop new technologies with an ethical perspective to create a desired society. However, as done in Europe and North America, studies that analyse the social system of translations of emerging technologies and explore processes of the translations with perspectives of ethics and responsibilities for making science and technology policies which aim to realise an ideal society have not been conducted so far in Japan. Van De Poel and Robaey (2017) also suggest that a solution is not to be sought to put all responsibility to the technology users but rather in a model.

Therefore, there is a gap between the required analysis and existing studies regarding the system in Japan, and there is also a knowledge gap about how to manage the translation of regenerative medicine incorporating an ethical perspective based on the current situation in Japan.

1.3. Research Question

In light of the identified research gaps outlined in the preceding section, and in pursuit of achieving the ideal society to address the challenges of healthcare in Japan through the translation of regenerative medicine—an objective underscored by Japan's national policy—it is imperative to find a better way to address challenges related to the translation of regenerative medicine with an ethical perspective. Therefore, this research's main question (MQ) is identified as follows:

How can ethical considerations be incorporated into the translation of regenerative medicine in Japan?

The final deliverable of this research will be a framework for incorporating ethical considerations in the translation of regenerative medicine in Japan. This framework will enable Japan to promote regenerative medicine while also covering ethical aspects.

1.4. Relevance

This research is conducted as a master's thesis research in the master's programme, Engineering and Policy Analysis (EPA). EPA's central focus is on addressing the complex problems that involve many parties with conflicting interests, i.e., societal grand challenges. The starting point of this research's interest, the healthcare problem, is an obvious grand challenge, and the process of translating emerging technologies in a responsible way is also recognised as a concern throughout the world (European Commission, Directorate-General for Research and Innovation, 2012).

In addition, when focusing on the translation of regenerative medicine in the Japanese healthcare field, multiple actors, including government organisations, namely several ministries, researchers/research institutions, doctors and hospitals/clinics, patients, and the general public are identified roughly. Also, issues that arise in the translation of regenerative medicine would be broad, from scientific content to societal aspects. These futures mean that this research needs to employ an interdisciplinary approach and qualitative analysis (the details of methods are presented in Chapter 2), such as a literature review and interview with thematic analysis and actor analysis, which are approaches linked to the EPA programme.

In the context of science and technology innovation policy, the importance of ethical aspects of new technologies when introducing them to society started to be recognised relatively recently in Japan compared to Europe (Center for Research and Development Strategy, Japan Science and Technology Agency, 2022). Therefore, in terms of academic relevance, this research could stimulate research in the social science area mainly and also in the biotechnology or healthcare technology area in Japan. Also, the results could be utilised for further research related to other countries that employ now or will employ a similar system of the translation of regenerative medicine in Japan.

1.5. Structure of This Report

The structure of the remainder of this report is as follows. Chapter 2 presents the research design, the four sub-research questions and research methods. The findings about the key processes and actors in this research field, which is the answer to the first sub-question, are described in Chapter 3. Ethical issues which would arise and possible approaches to the issues are identified in Chapter 4, as answers to the second and third sub-questions. Chapter 5 shows the results of the online questionnaire and supplementary interview. Then, these results are synthesised to answer the fourth sub-question in Chapter 6. Also in Chapter 6, based on all results, a conceptual framework is generated as the answer to the main research question. Chapter 7 summarises this research process and results. It also includes the limitations of this research and prospects for future research.

2. Research Methods

This chapter describes the research design and methods. In Section 2.1, the research design was determined. Then, sub-research questions were identified in Section 2.2, and Section 2.3 describes detailed research methods for each sub-research question and the main research question.

2.1. Research Design

In designing this research, the research philosophy and approaches were decided first. This was considered referring to the research onion developed by Saunders et al. (2019) (Figure 2-1). The research can be designed by defining the philosophy and paradigms from the outer layer of the onion to the centre.

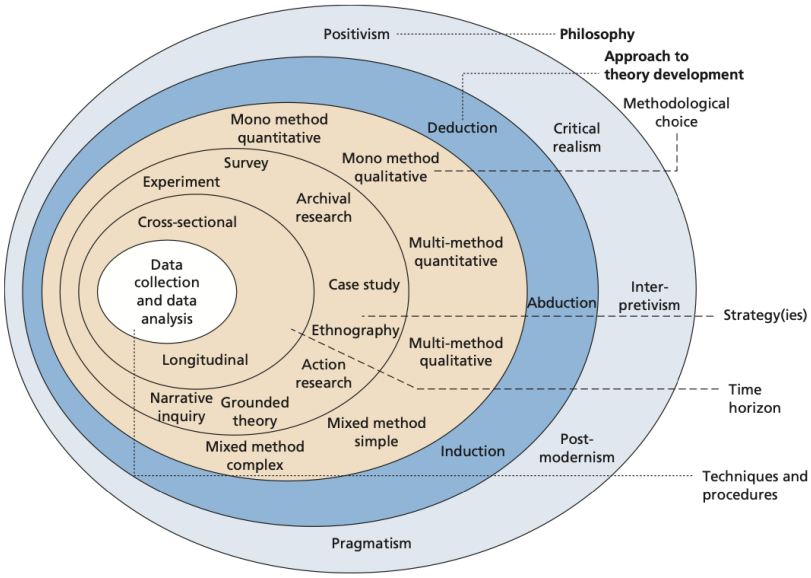


Figure 2-1. The research "onion": Research needs to explain the outer layers to reach the actual techniques and procedures in the central point. *Note.* From *Research Methods for Business Students* (8th ed., p. 124), by M. Saunders, P. Lewis, A. Thornhill, and A. Bristow, 2019, Pearson Education. Copyright 2015 by Mark Saunders, Philip Lewis and Adrian Thornhill.

Research Philosophy

The aim of this research is to develop a framework for better approaches to ethical considerations in the translation of regenerative medicine. This framework is expected to be utilised to promote the translation of regenerative medicine while addressing ethical concerns in Japan. Considering these research's features, pragmatism can be utilised as this research philosophy.

Pragmatism incorporates both objectivism and subjectivism, facts and values, accurate and rigorous knowledge and different contextualised experiences. It aims to contribute practical solutions that inform future practice by starting with a problem (Saunders et al., 2019). Also, this research explores the translation of regenerative medicine in Japan as a system, not one actor's activities or viewpoint. This attitude aligns with pragmatism, which thinks there are many different ways of interpreting the world and undertaking research, no single point of view can ever give the entire picture, and there may be multiple realities (Saunders et al., 2019).

Research Approach

In terms of research approach, through the brief literature review in Section 1.2, it was found that each study related to the translations of emerging technologies while considering ethical aspects starts by reviewing and organising the existing official policy and information published mainly by governments and related public organisations. This research also employs a similar direction since there is no uniform theory for this research's objective in Japan based on the brief literature review, and it is necessary to understand the current situation deeply first. This research approach can be categorised as induction, in which the research starts by collecting data to explore a phenomenon and generate or build a theory or a conceptual framework.

Taking a step further, this research can utilise the interdisciplinary approach, since it requires points of view from multiple disciplines, such as healthcare itself, the ethical view as this research's main focus, the legal view, and the political view. According to Klein and Newell (1997) (as cited in Post et al., 2016), interdisciplinarity is defined as a process of answering a question, solving a problem, or addressing a topic that is too broad or complex to be dealt with adequately by a single discipline or profession. Also, it draws on disciplinary perspectives and integrates their insights through the construction of a more comprehensive perspective. There are studies which report the utility of an interdisciplinary approach for related fields of studies; Van Noorden (2015) finds that studies of social sciences and healthcare tend to be interdisciplinary since they incorporate broad fields, and Smye and Frangi (2021) state that complex problems in healthcare cannot be addressed successfully by a single discipline. Therefore, interdisciplinarity approach can be utilised in this research.

Post et al. (2016) develop a model process for interdisciplinary research: In the Orientation phase, 1) identify the problem or topic, 2) formulate the preliminary research question; in the Preparation phase, 3) develop the theoretical framework through literature research and giving an overview of the "state of the art", 4) finalise the research question, 5) identify sub-questions, 6) determine research methods and design; in the Data phase, 7) collect and analyse the data; and in the Finalization phase, 8) interpret the results, draw conclusions, and write the discussion. As the process of this research so far aligns with this model process (from 1 to 4), it continues to follow the model process by starting with step 5 in the next section.

2.2. Sub-Research Questions

The process of acquiring the answer to the main question can be divided into some steps conceptually, based on the model process mentioned in the previous section. For each step, sub-questions (SQ) are identified to proceed the research to the main goal.

SQ1: What are the key processes and actors involved in the translation of regenerative medicine in Japan?

SQ2: What ethical issues could arise in the translation of regenerative medicine?

SQ3: How could ethical issues that would arise in the translation of regenerative medicine in Japan be addressed?

SQ4: What steps could be taken to improve the approach to ethical considerations for the translation of regenerative medicine in Japan?

SQ1, SQ2, and SQ3 are related to step 7 of a model process for interdisciplinary research, and SQ4 corresponds to step 8. Figure 2-2 shows the overall process of this research.

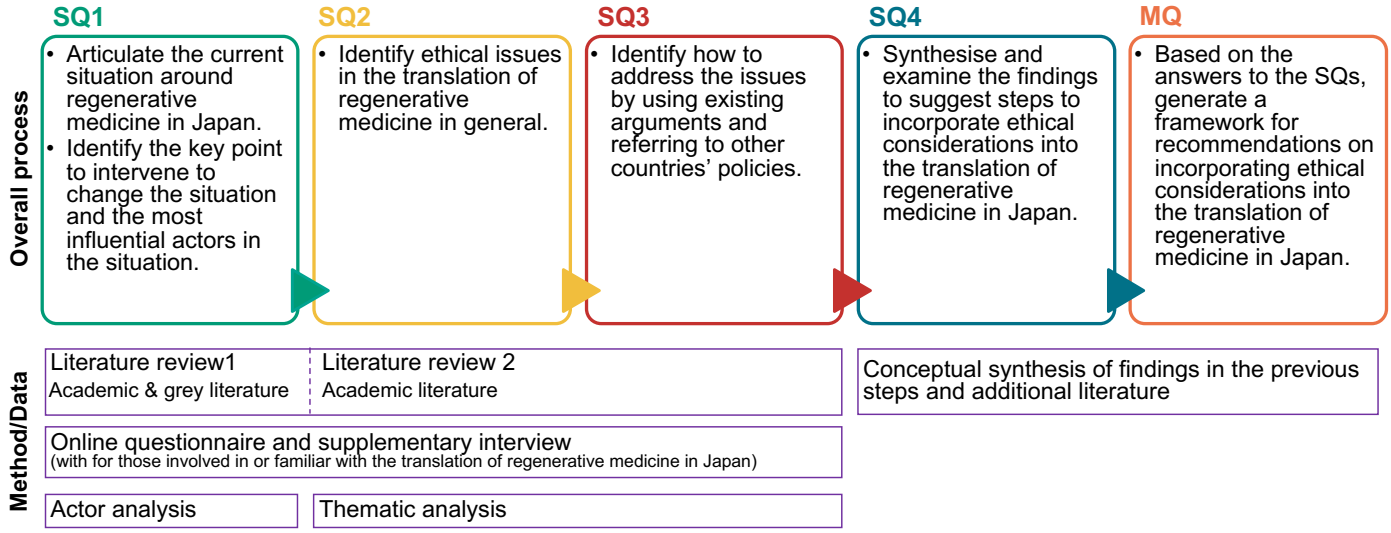


Figure 2-2. Research process and methods

2.3. Research Methods

This research employed multi-method qualitative for methodological choice. Qualitative research has the potential to reveal larger societal, structural, and organisational barriers to change, to shed light on the complexity of human experience within systems, and to disclose the challenges that are not evident in quantitative research (Broom & Broom, 2024). This research's scope incorporates societal aspects and the complexity of multiple actors' viewpoints; hence, qualitative research can be appropriate. This can be justified by the state that researchers using an inductive approach are more likely to work with qualitative data and use various methods to collect these data to establish different views of phenomena (Saunders et al., 2019) and that one characteristic of interdisciplinary research is the qualitative mode of research (Aboelela et al., 2006).

The detailed methods for each SQ are as follows.

SQ1 - Literature review 1, Actor analysis

The first step is to deeply understand the current situation around regenerative medicine in Japan by answering SQ1. It started with an overview of the healthcare system in Japan compared to other countries, Japanese policies for regenerative medicine, and current related regulations and guidelines in Japan. Then, the current process of translating regenerative medicine in Japan was clarified based on the literature review, and the actors involved in the process were identified based on the literature and considered through the Actor analysis. By reviewing the clarified process and results of Actor analysis, the key processes to intervene and actors who could influence the situation in the translation of regenerative medicine were identified.

Literature review 1

A brief literature review was conducted to understand the current situation around regenerative medicine in Japan. Aggregating databases were used to find related literature broadly. Since this research incorporates healthcare and social science aspects, Pubmed, which indexes mainly journals relevant to health and medicine, and Scopus, which covers a wide range of journals, including applied social sciences (Falagas et al., 2007), were selected. The search terms were "regenerative medicine" AND "ethics" AND "japan." Abstracts of the found literature were briefly reviewed, and unrelated literature was eliminated based on the following criteria. Finally, 24 pieces of literature were picked up.

Excluded literature

- Literature not related to regenerative medicine.
- Literature about the process or improvement of practical and specific technology, such as successful surgery cases or hypothetical treatments for unmet medical needs using regenerative medicine.
- Literature which focuses only on bioethics related to the use of embryo cells or cell banking.
- Literature about specific countries other than Japan.

Also, grey literature, such as government reports and information on government and related organisation websites, was reviewed to understand policies, regulations, and guidelines. Based on the author's experiences of working as a staff in the Ministry of Education, Culture, Sports, and Science and Technology in Japan (MEXT), the websites of the Headquarters of Healthcare Policy, Ministry of Health, Labour and Welfare (MHLW), MEXT, Japan Agency for Medical Research and Development (AMED), and Pharmaceuticals and Medical Devices Agency (PMDA) were mainly reviewed. This is included in documents and webpages written in only Japanese, and the author has translated them.

The information obtained from this literature review was synthesised by categorising it as the background of Japanese policies for regenerative medicine, processes of translating regenerative medicine in Japan, and the actors involved in that. The first two are presented in Section 3.1 and 3.2, respectively, and the latter was used for Actor analysis in Section 3.3.

Actor analysis

Actor analysis was conducted to identify the important actors in the translation of regenerative medicine in Japan. The analysis followed the steps introduced by Enserink et al. (2022) as follows.

1) Formulation of a problem and associated decision arena as a point of departure: This was addressed as the problem formulation of this research in Chapters 1 and 2. Therefore, the analysis started from step 2.
2) Identification of the actors involved: This means making an inventory of the actors involved. In this research, an extensive list of possible actors was generated based on information obtained from the literature review 1 and exploring actors' websites and reports.
3) Mapping the formal institutional playing field: Based on the information from the literature review 1, the listed actors in step 2 were mapped by their formal positions and relations as a Formal chart.
4) Identifying actor characteristics: The main players in the Formal chart were explored deeply by clarifying their interests, objectives, perceptions, and resources. This was presented as a table, and information from literature review 1 and each actor's websites and reports were utilised. Also, actors' resource dependencies were explored to determine critical actors in terms of the translation of regenerative medicine in Japan.
5) Summarising the interdependencies between actors: The interdependencies between actors are visualised as a Power-interest matrix. In this research, two types of matrices were drawn to observe the situation from different points of view.
6) Determining the consequences of these findings with regard to the problem formulation: Finally, to partly answer SQ1, key actors in the translation of regenerative medicine in Japan were identified.

The results of steps 1 to 5 are in Section 3.2, and the result of step 6 is in Section 3.4.

SQ2, SQ3 - Literature review 2, Thematic analysis

As the second step, ethical issues in the translation of regenerative medicine were identified by the literature review to understand what Japan needs to address from an ethical perspective. There is a possibility that other ethical issues that are not recognised in Japan but arise in other countries or under other systems. These issues should also be considered, since they may occur now or will occur in Japan. Consequently, this step tries to identify ethical issues that would arise when translating regenerative medicine generally.

The same literature review also identified possible approaches to addressing those ethical issues in the translation of regenerative medicine to answer SQ3.

Literature review 2

Some literature found in the process of literature review 1 for SQ1 mentioned ethical issues related to translating regenerative medicine in Japan. Since the previous literature review aimed to understand the situation around regenerative medicine in Japan, at this time, additional literature was searched, and literature which was found by the literature review 1 and found this time was reviewed together to identify issues that would arise in the translation of regenerative medicine not only in Japan but also in other systems. In addition, since solutions or suggestions are sometimes presented in the same literature as those argue issues, they were also reviewed in parallel.

Pubmed and Scopus were used again. The search terms were “regenerative medicine” AND “ethics” AND “translation” AND “issue.” Abstracts of the found literature were briefly reviewed, and unrelated literature was eliminated based on the following criteria. Finally, 16 pieces of literature were picked up.

Excluded literature

- Literature not related to regenerative medicine.
- Literature about the process or improvement of practical and specific technology, such as successful surgery cases or hypothetical treatment for unmet medical needs using regenerative medicine.
- Literature that focuses on only bioethics related to the use of embryo cells or cell banking.
- Literature about specific developing countries. This is because Japan is categorised as a developed country, and the issues which would arise in Japan should be observed in the system of developed countries.
- Literature that indicates only abstract or broad issues, such as just saying, “There are ethical issues.”
- Literature that discusses based on outdated information, such as previous regulations or technologies which are not currently used.

Additionally, to identify solutions/suggestions, other countries’ policies were also reviewed. To this end, the literature found through the literature review 2 was reviewed, apart from the aim of identifying issues. Namely, literature that mentions other countries' policies was focused on this time when filtering literature. As a result, two additional articles were picked up.

The information obtained from this literature review was processed by the Thematic analysis and additionally explained in Chapter 4.

Thematic analysis

The issues and suggestions found in the literature review 2 were organised according to the process of the Thematic analysis. Thematic analysis is a method for analysing qualitative data to identify, analyse and interpret meaning through systematically generating codes that lead to developing themes (Braun et al., 2016). The analysis was conducted using the six-phase model described by Braun et al. (2016).

Phase 1-2: Reading data items (literature in this research) and tagging with a code relevant to SQ2 and SQ3. The phases of translating regenerative medicine, from preclinical research to treatment or manufacturing products, and the focus point of issues themselves were defined as codes for the analysis.

Phase 3 : Organising codes and coded data into candidate themes by clustering codes to identify higher-level patterns. In this step, relevant issues coded in the previous step were clustered.

Phase 4-6: Refining, finalising candidate themes to answer SQ2 and SQ3, and writing up. As a result, the extensive list of ethical issues arising in the translation of regenerative medicine and possible approaches to those issues was constructed.

The results are presented in Section 4.1.

SQ4, MQ - Conceptual synthesis

As the next step, all the results so far were synthesised to identify the practical steps Japan should take to incorporate ethical considerations into the translation of regenerative medicine and construct a conceptual framework as the final deliverable of this research.

The findings were synthesised based on the approach of the Conceptual synthesis. Conceptual synthesis is a method used to identify concepts (the Japanese system of the translation of regenerative medicine accompanied ethical issues in this research). It focuses on identifying concepts' defining attributes and can be used to develop a synthesis model (Tricco et al., 2016). The results of concept synthesis give a basic understanding of the underlying attributes of the concepts which help to define the leverage points clearly. As Tricco et al. (2016) mention, this method has no firm rules, so this research took the following procedure: Within the key process determined in the first step as the answer to SQ1, ethical issues identified in the previous step as the answer to SQ2 were deeply explored to understand the relationships among them and find the leverage points. Then, based on the answer to SQ3, i.e., possible approaches to ethical issues, the feasible ways for Japan to address these leverage points were determined. Next, by using the findings through the Actor analysis in the first step of this research, responsibilities for each approach were considered for the practical use of this research, considering the critical actors determined in the process for SQ1. Finally, the results so far were elaborated as a set of steps to incorporate ethical considerations into the translation of regenerative medicine in Japan. These steps answer SQ4, and the procedure and results are presented in Section 6.1.

The answer to SQ4 was translated into a conceptual framework as recommendations for Japan by defining the desirable system to carry out the steps. This translation involves reviewing the activities and responsible actors of each step of the answer to SQ4 and clarifying the interactions between activities and actors. This is the answer to the main research question, shown in Section 6.2.

Online questionnaire and Supplementary interview

The online questionnaire was conducted to collect additional information from more practical sources to supplement the findings from the literature survey. It was hosted on an online questionnaire tool, Qualtrics. It was aimed at those involved with regenerative medicine in Japan, such as researchers, doctors, promoters, or regulators related to regenerative medicine, patients, and other people familiar with regenerative medicine in Japan. It comprised a combination of Likert scales and open-ended questions. The questions were about issues the participants have experienced or recognised, ideas for addressing them, perceptions of the current Japanese situation, and perceptions of each actor's level of influence to change the situation. It was done in English and Japanese, and the answers in Japanese were translated to English by the author. The details of the questionnaire are in Appendix 1. The questionnaire was distributed via the contact points of researchers and doctors' communities in Japan, which was aimed at researchers, doctors, and promotors/regulators, and the author's SNS account, which was aimed at the general public who have some knowledge of regenerative medicine in Japan. While the questionnaire asked only the category of the participants and was conducted anonymously, those who agreed to be interviewees for deeper analysis of the questionnaire's answers also joined in the online supplementary interview. The questionnaire was open for responses for four weeks, from May 30th to June 25th, 2024. During this period, five responses were collected.

An online supplementary interview was conducted with one participant in the questionnaire. The interview was designed as a semi-structured interview to better understand the ideas and backgrounds of the interviewees' answers in the online questionnaire. The details of the interview are in Appendix 2.

The results are briefly shown in Chapter 5 and reflected on the results in Section 4.1 (list of ethical issues and possible approach). The summary of the results of each question, including the interview, is presented in Appendix 3.

3. Result I: Key Processes and Actors

This chapter provides the results of the literature review 1and the Actor analysis to answer sub-question 1. Section 3.1 introduces an overview of the healthcare system and policies and related current regulations in Japan. Section 3.2 describes the current processes of the translation of regenerative medicine in Japan. The process and results of the Actor analysis are provided in Section 3.3. Finally, the key processes and actors, namely the answer to sub-question 1, are identified in Section 3.4.

3.1. Regenerative Medicine in Japan

An Overview of the Healthcare Systems

Before delving into the situation around regenerative medicine in Japan, the overall healthcare system of Japan was briefly reviewed in comparison with that of the Netherlands, the U.K., and the U.S.

Table 3-1 shows an overview of each country's healthcare system. Japan employs universal health insurance. By law, all residents in Japan must be enrolled in a health insurance programme. While practical insurance services are operated by municipal governments or communities of employers, the central government, MHLW, sets related regulations and the uniform fee schedule for insurance reimbursement. Basically, 30% of the cost of medical expenses is paid by patients directly, and the remainder is covered by health insurance and tax (Sakamoto et al., 2018). In Japan, as in other countries, there are medical care services that are unapproved by MHLW and uncovered by social insurance (The Japanese Society for Regenerative Medicine, n.d.-b). When patients receive these uncovered medical services, they pay the full prices determined by the hospitals or clinics. New medicine, which uses emerging technologies, cosmetic surgery, and so on, are included in such uncovered medical services.

Table 3-1. Overview of the healthcare systems of Japan, the Netherlands, the U.K., and the U.S.

	Japan	the Netherlands	the U.K.	the U.S.	References
Healthcare system	Universal health insurance for all residents	Health insurance for all residents *Focusing on the short-term health care system	National Healthcare Service (NHS) for all residents	Public: Medicare (for seniors and some of the disabled), Medicaid (for some of the poor and near-poor) Private: Health insurance for others	(Sakamoto et al., 2018; Kroneman et al., 2016; Anderson et al., 2022; Rice et al., 2020; Ministry of Health, Labour and Welfare, 2019)
Operator of health insurance	Municipalities or Communities of employers	Private insurers	The U.K. government	Public: the U.S. government Private: private insurers	(Sakamoto et al., 2018; Kroneman et al., 2016; Anderson et al., 2022; Rice et al., 2020)
Resource	Insurance Tax	Insurance National subsidies	Tax	Social insurance	(Sakamoto et al., 2018; Health and Global Policy Institute, 2012; Anderson et al., 2022; Rice et al., 2020)

First access point of healthcare provision	Patient can choose	GPs	GPs	Patient can choose	(Sakamoto et al., 2018; Kroneman et al., 2016; Union of Kansai Governments, n.d.)
Payment by patients	Basically 30 % of the cost	Basically free	Free	Depends on the type of insurances	(Sakamoto et al., 2018; Health and Global Policy Institute, 2012; Ministry of Health, Labour and Welfare, 2019)

Background of Policies for Regenerative Medicine in Japan

Since the beginning of the 21st century, the government has considered technologies related to regenerative medicine as one of the critical pillars of a national strategy for research and development. On the other hand, there have been criticisms that those research results only have poor clinical and economic impacts (Mikami, 2014). The success of establishing induced pluripotent stem cells (iPS cells) in 2006 by a Japanese scientist stimulated national policy, and the Ministry of Education, Culture, Sports, Science and Technology (MEXT) launched a project to implement regenerative medicine technologies with a large budget. Simultaneously, the guidelines for conducting regenerative medicine research, which MEXT had established, were amended and organised to simplify the ethical assessment processes for using human cells in research (Mikami, 2011).[1]

In 2011, to realise regenerative medicine products/treatment as soon as possible, a long-term project was launched in collaboration with MEXT, the Ministry of Health, Labour and Welfare (MHLW), and the Ministry of Economy, Trade and Industry (METI) to provide continuous support and bridge research and development to the realisation (establishing products and marketing) (Japan Science and Technology Agency, n.d.-b). In addition, new laws were enacted and enforced, and related laws were amended in 2013 to promote regenerative medicine (Shineha, 2020) (Law 2, 3, and 4 in Table 3-2). Moreover, in 2014, a new governance system, including a new law (Law 1 in Table 3-2), a new national strategy (the Healthcare Policy), and a new funding and management organisation (Japan Agency for Medical Research and Development (AMED)), was constructed to strongly promote research and development in the healthcare field, including regenerative medicine as one of the largest pillars (Cabinet Office, 2015).

These laws and systems are still the foundation of regenerative medicine in Japan. In the next section, the contents of laws and systems are reviewed from an ethical perspective.

Related Current Regulations

Related laws

Four laws strongly relate to this research's focused stage in regenerative medicine, and Table 3-2 provides an overview of them.

Table 3-2. Overview of the four laws related to the translation of regenerative medicine in Japan

	Law	Overview	Mention of ethics (Summary)
Law 1	Act on the Promotion of Healthcare and Medicine Policy (Act No.48 of 2014)	Identify essential initiatives to be taken by the government and the system for the management to promote advanced research and development and the creation of	The government is to undertake the necessary initiatives to ensure the fair and proper operation of research and development in the medicine

[1] While the technique to create iPS cells was introduced as a potential solution for the issue of the use of human embryonic stem cells (Takahashi & Yamanaka, 2006, as cited in Mikami, 2014), which had been the main big hurdle from an ethical perspective, there are still ethical concerns related to regenerative medicine (Shineha, 2020), for example, safety and efficacy and equity, and fairness, as mentioned by European Academies' Science Advisory Council & Federation of European Academies of Medicine (2020).

		new industries in healthcare and medicine field.	field, so that related actors comply with laws, regulations and guidelines and give consideration to bioethics and proper management of personal information. *Set as one of the essential initiatives
Law 2	Act on the Comprehensive Promotion of Enabling Citizens to Receive Regenerative Medicine Promptly and Safely (Act No.13 of 2013)	Clarify the government's responsibility of prompt and safe development, provision and dissemination of regenerative medicine to enable citizens to receive regenerative medicine.	Bioethical considerations based on the characteristics of regenerative medicine must be taken into account when promoting regenerative medicine.
Law 3	Act on Securing Safety of Regenerative Medicine (Act No.85 of 2013)	For clinical research and uncovered medical care, clarify the measures to be taken by the agents who provide regenerative medicine for the prompt and safe provision of regenerative medicine.	Bioethical considerations based on the characteristics of regenerative medicine must be taken into account and necessary initiatives must be conducted when providing regenerative medicine.
Law 4	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices *Focusing on contents related to regenerative medicine (Act No.145 of 1960)	For producing and selling regenerative medicine products (including imported products), enable regenerative medicine products to be approved earlier than other products under the limitation.	-

Law 1 aims to promote medical research and development, including regenerative medicine. Following this law, the government constructed the Healthcare Policy, which set regenerative medicine as one of the key fields to be promoted as a nation (Cabinet Office, 2015).

While both Law 1 and the Healthcare Policy mention that the government is to undertake initiatives to ensure the fair and proper operation of research and development (Cabinet, 2021), there is no additional information (such as the definition of “fair and proper” and details of the initiatives) or monitoring system. Therefore, these terms can be interpreted broadly and are left up to the individual research.

Law 2 prescribes the government’s responsibility regarding the development, provision and dissemination of regenerative medicine. In response to Law 2’s concept, Law 3 and Law 4 prescribe the process for the “prompt and safe” promotion of regenerative medicine (Ministry of Health, Labour and Welfare, n.d.-b).

Law 3 focuses on clinical research and uncovered medical care, which means they are unapproved by MHLW and uncovered by insurance. It prescribes the process to be taken by agents who intend to provide regenerative medicine. Before the enforcement of this law, researchers in regenerative medicine only had a set of guidelines to follow for conducting clinical research (Tobita et al., 2016), and any agents could provide regenerative medicine as uncovered medical care without notifying any authorities. This situation caused regenerative medicine tourism, in which foreigners visited Japan to receive treatments that were not allowed in their home countries, while those treatments were suspicious of safety and efficacy (Nakazawa et al., 2016). Hence, to ensure the safety of the provision of regenerative medicine, this law classifies the level of risks of regenerative medicine (for example, using iPS cells is High-risk since they have not been applied to humans so far) and determines the processes of informing or assessing regenerative medicine by the level before the provision.

The overall process is the following: 1) the provider builds the provision plan, 2) the certified committee and the certified special committees for regenerative medicine, which are usually established in the institution of the provider and certified by MHLW, assess the plans of Low-risk and Medium- and High- risk

plan respectively, 3) the plan is submitted to the minister of MHLW, 4) if it is classified as High-risk, the minister can order to change it based on opinions of the Council for Health Science, which is an advisory council of MHLW (Ministry of Health, Labour and Welfare, n.d.-b).

In addition, this law requires the agents to publish the explanatory and consent documents for patients beforehand. This can help patients to make decisions and ensure the transparency of medicine (Fujita et al., 2022). This law also addresses criticisms such as the lack of appropriate review committees and governmental control in clinical studies, and it follows the World Medical Association Declaration of Helsinki (version 2013) (Tobita et al., 2016). Moreover, by allowing the outsourcing of the cell culture/processing to private contractors who MHLW certificates, the law enables doctors to focus specifically on treatment and research, potentially further promoting the use of regenerative medicine (Tobita et al., 2016).

Law 4 provides the control required to secure the quality, efficacy, and safety of regenerative medicine products and other pharmaceuticals and medical products. Considering Law 2, Law 4 was amended to promote regenerative medicine products by constructing an exclusive approval process for regenerative medicine products (Pharmaceuticals and Medical Devices Agency, 2015). In the process, companies intending to produce and sell products are assessed through documents and on-the-spot investigation from three aspects: governance of the company, efficacy and safety of the product based on clinical research, and governance of producing and managing the products. These assessments are conducted by the Pharmaceuticals and Medical Devices Agency (PMDA), owned by MHLW. Finally, the products are approved by the minister of MHLW. Since patients who need regenerative medicine are usually fewer than those who need medicine for popular diseases, it is more difficult to collect enough data. This situation hinders the prompt realisation of regenerative medicine products. Hence, Law 4 enables the assessment of efficacy and safety of regenerative medicine products to be conducted in shorter periods compared to other products. While the products are assessed again after being commercially available and need to be approved again, patients can access the products faster (Pharmaceuticals and Medical Devices Agency, n.d.; Pharmaceuticals and Medical Devices Agency, n.d.-b).

In contrast to Law 3, Law 4 requires scientific data and information and does not mention ethical aspects.

Related ethical guidelines

Based on these laws, ethical guidelines for the research related to regenerative medicine, "the Ethical Guidelines for Medical and Biological Research Involving Human Subjects," are set by the collaboration with MEXT, MHLW, and METI to ensure the scientific quality, reliability of results, and ethical validity of medical and biological research involving human subjects, while protecting the human rights, maintaining safety and improving the welfare of research subjects (Ministry of Education, Culture, Sports, Science and Technology et al., 2021). The guidelines identify the responsibilities of researchers, heads of research institutions, and ethics committees, which should be established in research institutions, when carrying out research (Table 3-3). The guidelines' eight main principles are as follows:

1) Conduct research that has social and academic value
2) Ensure scientific validity in accordance with the characteristics of the research field
3) Weigh up the benefits from the research against the burdens and other risks to the research subjects
4) Be reviewed by an independent and impartial ethics review committee
5) Provide sufficient explanation to the research subjects in advance and obtain their voluntary consent
6) Give special consideration to socially vulnerable persons
7) Appropriately manage personal and other information used in research
8) Ensure the quality and transparency of research

They correspond with the seven principles of the National Institutes of Health in the U.S., with the addition of protection of private information (7) and research integrity (8).

Table 3-3. Responsibilities of researchers, heads of research institutions, and ethics committees in the Ethical Guidelines for Medical and Biological Research Involving Human Subjects

Who	What

Researchers	• Respect lives, health, and rights of subjects. • Construct a research plan which ensure ethical and scientific validity, get an allowance from the ethics committee and the head of the institution, and conduct it appropriately. • Register the plan to the open database (e.g., database of MHLW). • Get informed consent from the participants beforehand and protect their information. • Respond appropriately and promptly to inquiries from subjects. • Protect the information obtained through the research. • Let participants know the research is related to the specific group's characteristics, if applicable. • Take education about necessary ethics, knowledge and technology related to the research.
Heads of research institutions	• Monitor and manage the research. • Protect the information obtained through the research. • Make the rules and environment to conduct the research appropriately. • Ensure necessary measures taken in the case of subjects having any health issue through the research. • Make sure to protect the human rights of participants and maintain the transparency in the research to participants. • Make the research results publicly available with protecting the rights and benefits of involved people with the research. • Evaluate if the research is following the guidelines by themselves and respond appropriately. • Cooperate with the review procedure conducted by the ethics committee. • Educate its researchers and themselves.
Ethics committees	• Consists of specialists in medical science, ethics and law, the persons who have the perspective of general people including the research participants. • Include outsiders of the institution as members. • Review the research plan independently from ethical and scientific perspectives and give necessary opinions including changes of the plan and discontinuation of the research. • Protect the information obtained through the review. • Make members take education to acquire the necessary knowledge to review.

3.2. Processes of Translating Regenerative Medicine in Japan

The process from basic research to post-marketing assessment is described in Figure 3-1 and Figure 3-2. Figure 3-1 is related to Law 3 and shows the process for providing regenerative medicine treatment, which is mainly involved with hospitals and clinics. It also contains the process for other medicines for reference. Figure 3-2 is related to Law 4 and shows the process for manufacturing and selling regenerative medicine products, which is usually conducted by pharmaceutical companies.

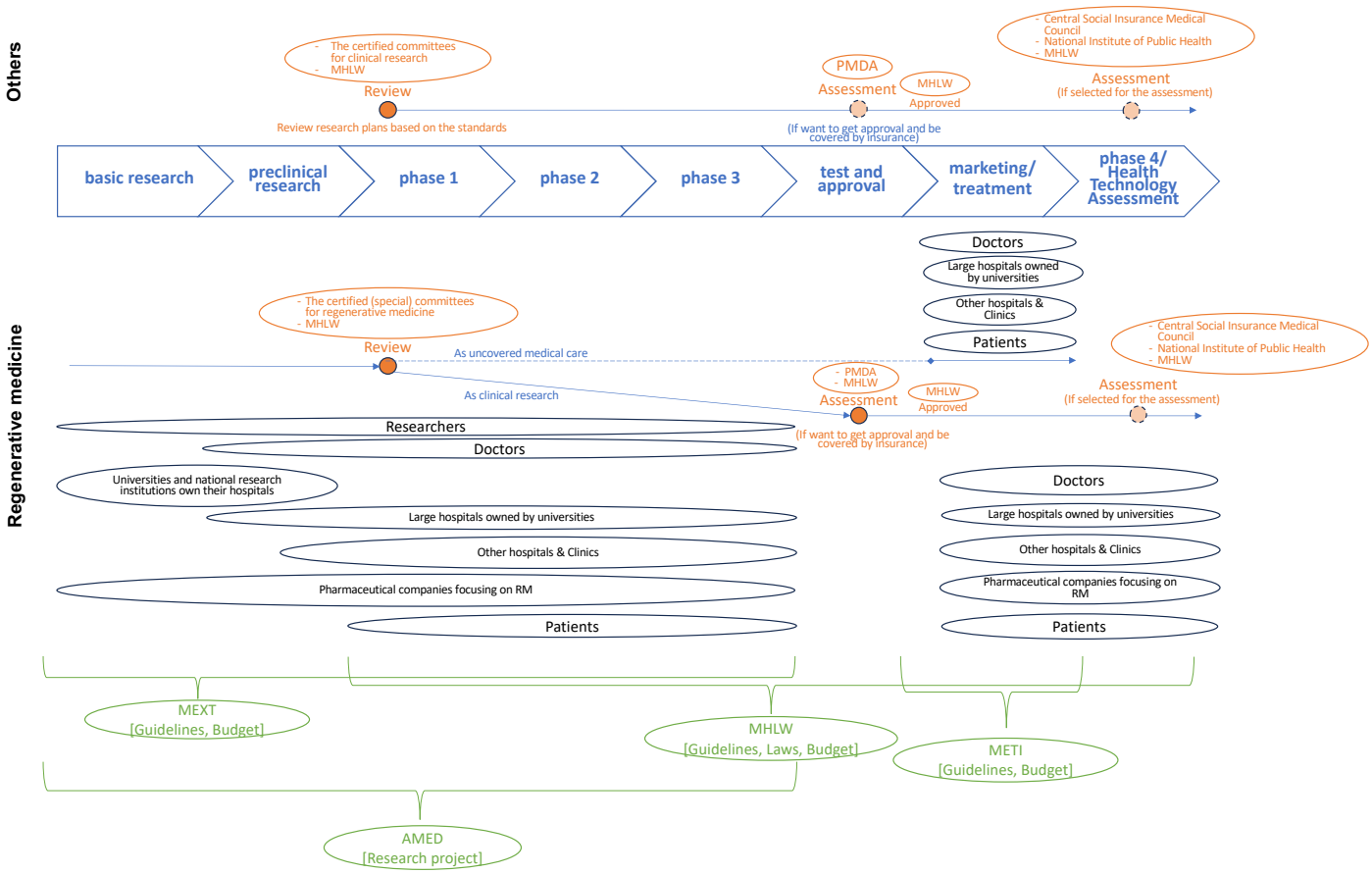


Figure 3-1. Overview of the process for implementing treatment in Japan. The lower part is about regenerative medicine, and the upper part is about others. Blue: processes, oval shapes: actors involved, dot lines: skipped/exempt processes, orange: intervention to the processes, green: regulatory matters.

Looking at research projects related to regenerative medicine, which are overseen by AMED (Japan Agency for Medical Research and Development, 2023), most medical and healthcare research in Japan is conducted in universities and national research institutions with their own hospitals, and they sometimes cooperate with pharmaceutical companies. Also, researchers belonging to such universities or institutions can play the role of doctors who conduct clinical research with participants (patients) and provide treatment at hospitals, since the hospitals are part of the universities or research institutions. When they complete preclinical research and want to start clinical research, which means the research's subjects are human, they need to let their research plan be reviewed by the certified committees and be submitted to MHLW. If it is a medicine other than regenerative medicine, they will conduct clinical research and take the assessment of PMDA for approval by MHLW to be covered by social insurance (Ministry of Health, Labour and Welfare, 2020) (see the upper part of Figure 3-1). On the other hand, regarding regenerative medicine, after the review and submission of the plan, which requires choosing whether the plan is as clinical research or treatment, doctors (researchers) at hospitals (or clinics) can conduct clinical research or provide regenerative medicine as a treatment to patients in response to the plan (see the lower part of Figure 3-1). If it is treatment, doctors at hospitals or clinics can start their medical businesses with regenerative medicine technology, though it is not covered by social insurance unless taking the assessment. Treatment without insurance coverage means patients are to pay the fees determined by the hospitals or clinics themselves. If it is clinical research, it will follow a similar process to other medicine except for the following process, which can be applied to regenerative medicine. Participants in clinical research basically do not need to pay the fees.

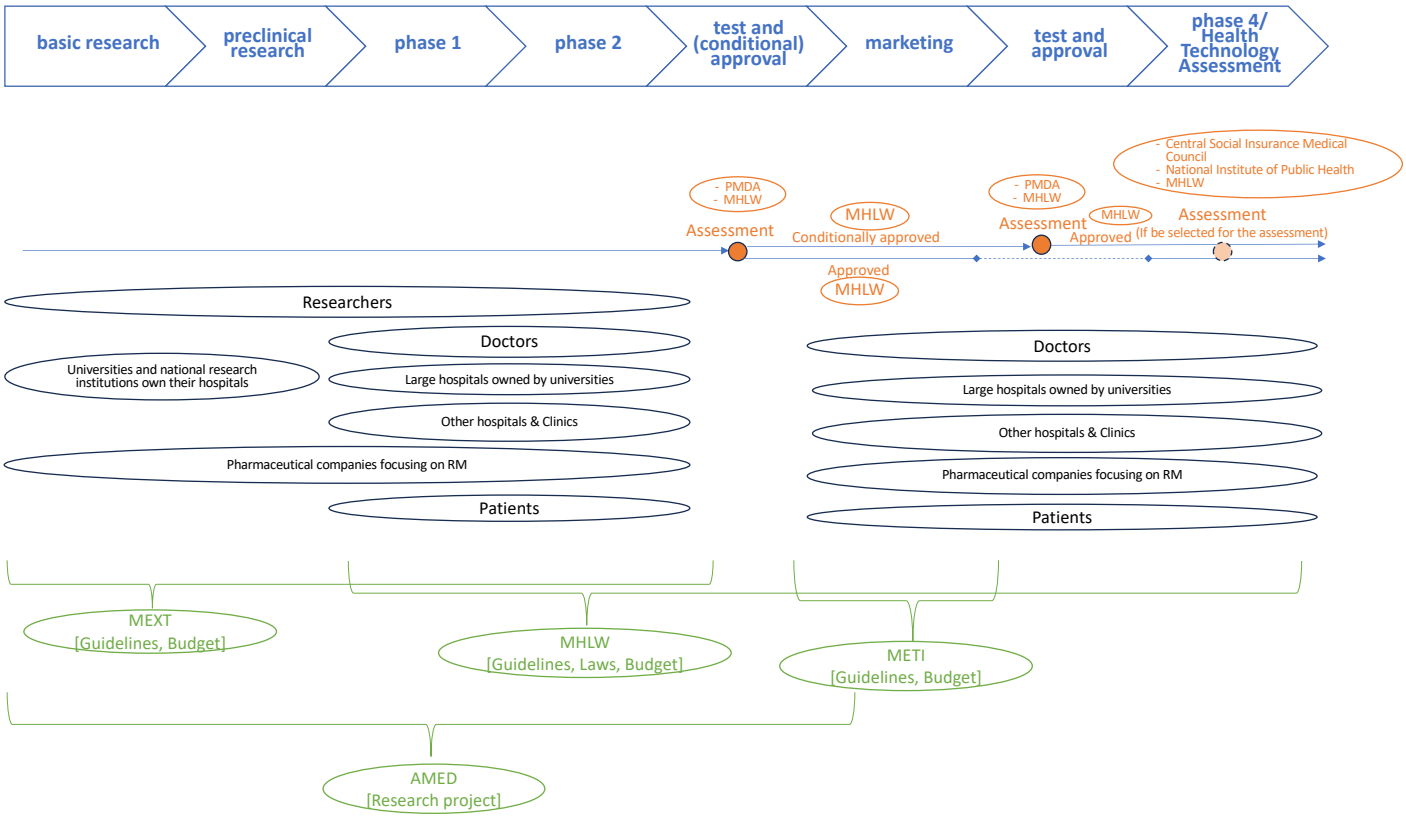


Figure 3-2. Overview of the process for selling regenerative medicine products in Japan. Blue: processes, oval shapes: actors involved, dot lines: skipped/exempt processes, orange: intervention to the processes, green: regulatory matters.

Regenerative medicine products have a fast track to marketing, as mentioned in the previous chapter regarding Law 4. They can be assessed by PMDA before collecting complete data, which are required in cases of other medicines, i.e., only data in phase 1 or 2 (Pharmaceuticals and Medical Devices Agency, 2015) (see Figure 3-2). Then, if they get approval, the regenerative medicine product can be distributed in the same way as other products with insurance coverage. This means patients need to pay only part of the cost and hospitals or clinics get reimbursement from the insurance, which partially consists of the national budget. Even if the approval is conditional, the product can be provided, while the data needs to continue to be collected for the next assessment at the latest after seven years. As of June 2023, 16 products have been approved and distributed in total, and two of them have been approved conditionally (National Institute of Health Sciences, 2023).

After the approval, a health technology assessment sometimes examines the overall cost related to mainly new products covered by social insurance, including patients' risks and benefits, and modifies the price of the products to use the national budget effectively if necessary (Ministry of Health, Labour and Welfare, 2021).

In the process, the assessments and approvals are stipulated in law and overseen by MHLW and its related governmental organisations. The research phase, including clinical research, is to be aligned with the Ethical Guidelines published by MEXT, MHLW, and METI. MEXT and MHLW also subsidise basic to clinical research projects and clinical research projects, respectively (Headquarters for Healthcare Policy, 2023-b).

3.3. Actors Involved in the Translation of Regenerative Medicine in Japan

This section provides the results of the Actor analysis regarding the translation of regenerative medicine in Japan.

Possible Actors

Firstly, an extensive list of possible actors was constructed, as shown in Table 3-4. Some actors can be categorised as outside this research's scope, and some are divided into multiple actors or combined with others.

Table 3-4. The extensive list of possible actors

Actors	Roles/Activities
Politicians who have interests in regenerative medicine	• Make and promote policies of regenerative medicine
Parliamentary group for regenerative medicine	• Currently, there is one group: Parliamentarians for the Promotion of Regenerative Medicine. • Make a movement from the political side to promote regenerative medicine. → This is very similar to "politicians." Hence, this actor will be regarded the same actor with "politicians."
Government	• In Japan, usually defined as the Cabinet and the ministries including the Cabinet Office, who work for administrative things based on law enacted by the diet which consists of politicians (Cabinet Secretariat, n.d.). Therefore, this research employs this definition, and the government does not include politicians. • Has responsibility for comprehensively and systematically formulating and implementing measures for advanced research and development and the creation of new industries in the health and medicine field (Law 1). • Has responsibility for comprehensively formulating and implementing measures to promote the prompt and safe research and development, provision and dissemination of regenerative medicine (Law 2). →The following actors are parts of this actor. Hence this research will not use "government," but each individual actor which identified below.
Cabinet Office	• Is in charge of basic policies for the comprehensive and systematic promotion of advanced research and development and the creation of new industries in health and medicine. • Is in charge of policies for allocating budgets, human resources, and other resources for research and development in the medical field and the development of its environment. (Act No. 89 of 2009)
Headquarters for Healthcare Policy	• Be under the Cabinet Office. • Make a draft of Healthcare Policy and promote the implementation of the policy planning and drafting of policies for the allocation of budgets, human resources and other resources, and overall coordination, in relation to research and development in the medical field and the development of its environment. • Plan, formulate and coordinate the important policies on advanced research and development and the creation of new industries in health and medicine. (Act No. 48 of 2014)
Ministry of Health, Labour and Welfare (MHLW)	• Oversees the following things: - Research and development, promotion, improvement and coordination of production, distribution and consumption of regenerative medicine products. - The development, improvement, and coordination of the industry for the production, distribution, sale, lending, and repair of regenerative medicine products. - Ensuring the quality, efficacy and safety of regenerative medicine products. - The prevention of the occurrence or spread of health and hygiene hazards due to the use of regenerative medicine products.

	- The development and dissemination of industrial standards for regenerative medicine products. - Technical guidance and supervision of regenerative medicine products. - Licensing of the manufacture of regenerative medical products. (Cabinet Order No. 252 of 2010) - Submission of the provision plan and supervision of the providers related to the Law 3. - Certification and supervision of the committee related to the Law 3. (MHLW Order No. 1 of 2011) • Has budgets for R&D in the medical field. (39% FY2023 (Headquarters for Healthcare Policy, 2023))
Ministry of Education, Culture, Sports, Science and Technology (MEXT)	• Oversees the following things: - Developing and promoting basic policies for research and development of life science, science and technology for the improvement of the quality of daily life and safety of human lives. - The evaluation of the impact of research and development in science and technology on the economy, society and the lives of the people, including safety assurance and bioethics in relation to research and development in the life sciences. (Cabinet Order No. 251 of 2010) - Developing and promoting basic policies for research and development related to regenerative medicine. (MEXT Order No. 1 of 2011) • Has budgets for R&D in the medical field. (38% FY2023 (Headquarters for Healthcare Policy, 2023))
Ministry of Economy, Trade and Industry (METI)	• Oversees the following things: - The planning and promotion of comprehensive policies on research and development of technologies related to health care within the jurisdiction of METI. (Cabinet Order No. 254 of 2010) • Has budgets for R&D in the medical field. (9% FY2023 (Headquarters for Healthcare Policy, 2023))
Prefectures and municipalities	• (Only prefectures) Approve for establishing hospitals and clinics. • Has a responsibility to formulate and implement voluntary measures that make use of the characteristics of its local area, regarding advanced research and development and the creation of new industries in the health and medicine field, with cooperating with the government (Law 1). → Since this actor does not have so much relevance to this research scope, analysis in this report wil not take this actor into account.
Pharmaceuticals and Medical Devices Agency (PMDA)	• Regulatory agency, working together with MHLW. • Incorporated administrative agency with non-civil service status. • Conducts scientific reviews of marketing authorization application of pharmaceuticals and medical devices, monitoring of their post-marketing safety. (Pharmaceuticals and Medical Devices Agency, n.d.-c)
National Institute of Health Sciences	• Is established under MHLW. • Is in charge of the development and evaluation of test methods to ensure the quality, safety and efficacy of products, as well as basic research related to regenerative medicine products. (National Institute of Health Sciences, n.d.)
Japan Agency for Medical Research and Development (AMED)	• Ministers in charge: Prime, MEXT, MHLW, METI. • Promotes integrated research and development in the field of medicine, from basic research to clinical trials (through funding and managing R&D in the medical field and the development of an environment for R&D). (Act No. 49 of 2014) • Budget comes from budgets of Cabinet Office, MEXT, MHLW, METI.
Hospitals/clinics	• Provide treatment for patients.

	• Approve their establishment by prefectures. • Need to try to cooperate with the government for the promotion of R&D in the medical field (Law 1). • High-risk (Class 1) regenerative medicine is provided as treatment by relatively large hospitals owned by universities. • Middle- and Low-risk (Class 2 and 3) regenerative medicine is provided as treatment by various hospitals and clinics. (Ministry of Health, Labour and Welfare, n.d.) • Hospital has over 20 beds; Clinic has under 20 beds or does not have any beds. → This actor can be divided into two groups; large hospitals owned by universities, and other hospitals and clinics.
Doctors (surgeons) who apply regenerative medicine	• See patients and consider providing regenerative medicine, carry out treatments for curing or easing the patients' diseases/problems. • Need to try to cooperate with the government for the promotion of regenerative medicine (Law 2).
Research institutions (including universities)	• Encourage their researchers to conduct research by offering environments for making results as institutions or following the governmental objectives. • Need to try to pursue research and development in the medical field, the dissemination of its results, and the development of human resources (Law 1). • Need to follow the Ethical Guidelines (only the head of the institution). • Most of the research institutions involved with national projects related to regenerative medicine are universities that have their own hospitals or national research institutes that have their own hospitals and are supervised by MHLW. (Japan Agency for Medical Research and Development, 2023) → This research focuses on the research institutions that research regenerative medicine with their own hospitals. Other research institutions (including universities) are outside the scope of this research.
Researchers/scientists of regenerative medicine	• Research regenerative medicine for realising new usage of regenerative medicine. • Need to try to cooperate with the government for the promotion of regenerative medicine (Law 2). • Need to follow the Ethical Guidelines.
Researchers' community	• For example; the Japanese Society for Regenerative Medicine. • Aim to advance, develop and foster regenerative medicine and to contribute to the promotion of human health and welfare. • Make a network of doctors/researchers related to regenerative medicine. • Certificate doctors/engineers/researchers related to specific technology related to regenerative medicine. • Offer technological support for researchers and institutions. • Communicate with other communities, not only domestic ones but also international ones. (The Japanese Society for Regenerative Medicine, n.d.)
Pharmaceutical companies	• Develop, produce and provide products for the patients or the providers as a business. • Need to follow the process stipulated in Law 4 when selling new products. • Need to try to cooperate with the government for the promotion of regenerative medicine (Law 2). • Need to try to pursue research and development in the medical field and cooperate with the government (Law 1). • 11 companies produce and sell regenerative medicine products as of June 2023. The five of the 11 companies are defined as medium-sized companies. Most of these medium-sized companies focus on only

	regenerative medicine products as their business, while other (large) companies work for other fields of medicine as well. (National Institute of Health Sciences, 2023). • 41 companies (incl. some of the 11 companies) have interests in developing products with research institutes that have seeds of regenerative medicine. (Japan Agency for Medical Research and Development, 2023-b). → Not only medium-sized companies but also large companies are interested in regenerative medicine products. However, few of them have products as part of their business, and medium-sized companies that focus on only regenerative medicine take the lead in disseminating new products. So, this actor can be divided into two groups: companies focusing on regenerative medicine including start-ups, and companies with interests in regenerative medicine. This research centres on only the former, who relate directly to the process of the translation of regenerative medicine.
Companies' community	• For example; Forum for Innovative Regenerative Medicine (FIRM) • Aim to establish systems to ensure that the community has safe and stable access to the benefits of research into regenerative medicine. • Give advice from the international standpoint on commercialisation strategies. • Indentify the standards/guidelines. (Forum for Innovative Regenerative Medicine, n.d.)
Patients involved with clinical research of regenerative medicine or taking regenerative medicine now	• Want to be cured without bad side effects or risks. • Want to get enough information to make a decision to participate in the research/test. • Want to get enough information about the medicine they are taking. • Patients' conceptions are varied by individuals (Kato & Sleeboom-Faulkner, 2017).
Patients waiting for regenerative medicine for their diseases	• Be assumed to hope that the proper medicine is invented and provided promptly and affordably. →These patients can be combined as one actor "Patients."
Public (including donors of cells, future patients; as a member of society, as a taxpayer)	• Be assumed to want society to be getting better and they can receive benefits as a society member/contributor. • Be assumed to want to get enough information related to regenerative medicine.

Relations among Actors

Based on the list, the Formal chart, which shows formal positions and relationships between actors, was created (Figure 3-3).

In light of the processes in Section 3.2 and actors' roles in Table 3-4, there can be roughly three groups of actors: the ministries' group, which consists of ministries and related organisations overseeing policies (regulations and budget) related to regenerative medicine; the practitioners' group, which carries out research, development, and treatment of regenerative medicine practically aligning with national policies or their interest; and the patients' group, which comprises patients and the public.

Japan employs a system of separation of powers: legislature, administration, and judiciary. The ministries handle administrative matters based on laws enacted by the diet, which is in charge of the legislature and consists of politicians. Therefore, politicians are not part of the ministries' group. Politicians can impact or pressure the ministries for the policies while being representatives of the public. Therefore, they are located on the border of the ministries.

In Japan, researchers in the medical field usually have doctor's licenses and can work as doctors (and vice versa) as long as seeing the research projects supported by AMED (Japan Agency for Medical Research and Development, 2023). Also, research facilities in the medical field, such as universities and national research institutions, have hospitals. As the process of translating regenerative medicine in Japan

shows (Figure 3-1), they work very closely and overlap. Hence, they can be categorised into the same group of practitioners, which means they work in regenerative medicine on the ground.

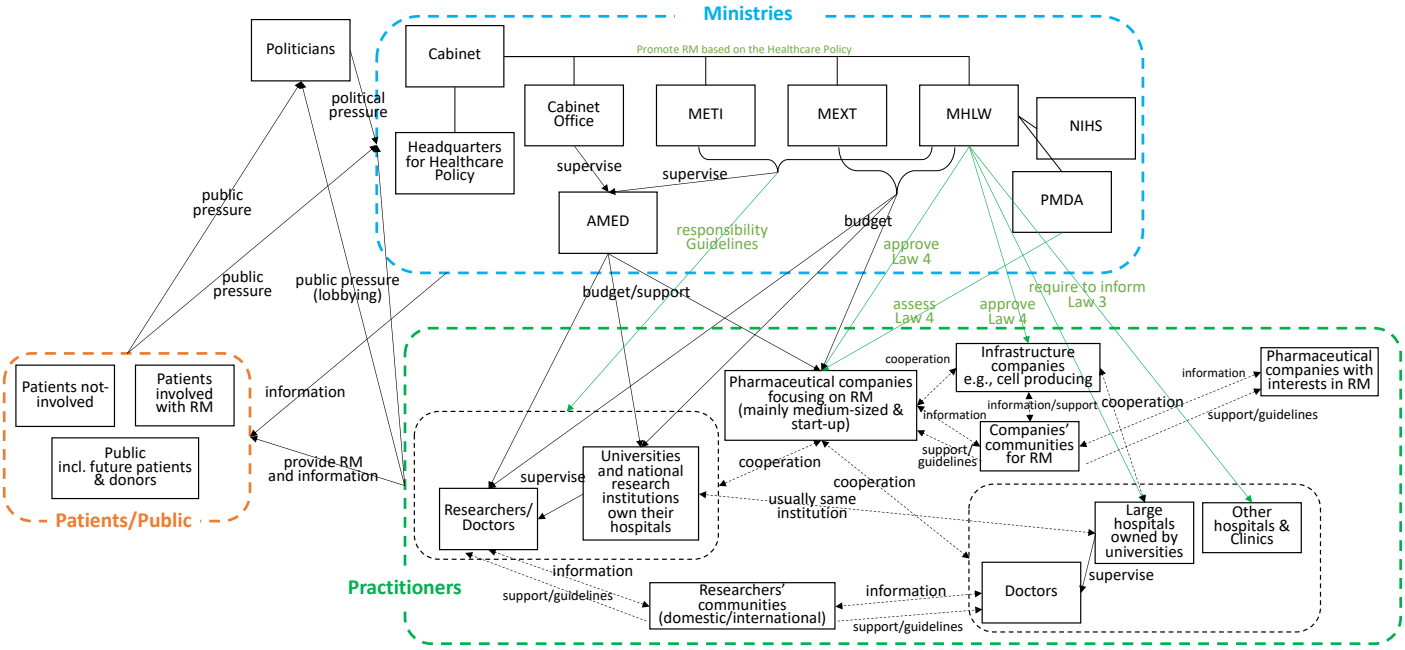


Figure 3-3. Formal chart; overview of relationships between actors. Black arrows: hierarchical relationships of resources, green arrows: hierarchical relationships stipulated in regulations, and dot arrows: conceptual relationships.

Overview of Main Actors

Actors' characteristics

The next step is to review the actors' detailed characteristics: their interests, objectives, perceptions, and resources. Based on the Formal chart, the focused actors are narrowed down, and some actors are categorised into one group. Table 3-5 shows the result, i.e., the overview of actors' characteristics.

Table 3-5. Overview table of actors' characteristics

Actors	Interests	Objectives/Responsibilities related to regenerative medicine (Desired situations)	Perceptions or Gaps between ideal and real situations	Possible actions/ Resources
Politicians	Whole society in Japan Public opinions	Thriving R&D and industries in health care and medicine field Prompt and safe development, provision and dissemination of regenerative medicine with people's trust for politics.	• Not enough promotion for R&D. • Unclear criteria and procedures. • Not attractive market for potential providers ("再生医療の産業化に向けリ・スタート 議員の会で提言まとめる [Re-starting the industrialisation of regenerative medicine - Parliamentary group summarises proposals]," 2024)	Political pressure Establish law (via the diet)
MHLW (Ministry of Health, Labour and Welfare)	Social welfare, social security and public health (Act No.97 of 2009) preclinical research, clinical research (Headquarters for Healthcare Policy, 2023-b)	Thriving R&D and industries in health care and medicine field (Act No. 48 of 2014). Prompt and safe development, provision and dissemination of regenerative medicine (Act No. 13 of 2013).	• Japan has created a system that gives the highest priority to patient safety, aligning with Declaration of Helsinki (Tobita et al., 2016) • Medicine which are not tested scientifically may be provided as free medical care. Some clinical studies are conducted without review of scientific evidence. (Fujita et al., 2022) • The committees may lack transparency and independence, integrity, and quality of reviews in several cases. (Fujita et al., 2022; Ikka et al., 2023)	Regulations (especially, be in charge of Law 3 & 4) Budget (for research) Approval of products
MEXT (Ministry of Education, Culture, Sports, Science and Technology)	Science and technology (Act No.96 of 2009) Basic and applied research, preclinical research, and partly clinical research (Headquarters for Healthcare Policy, 2023-b)	Thriving R&D and industries in health care and medicine field (Act No. 48 of 2014). Prompt and safe development, provision and dissemination of regenerative medicine (Act No. 13 of 2013).	• Some steps are required to provide patients with regenerative medicine such as clinical research with scientific evidence based on essential science. • Lack of researchers who has the enough knowledge of legislation, ethics, and patent to implement the results of research. (Ministry of Education, Culture, Sports, Science and Technology, 2022)	Regulations Budget (for research)
METI (Ministry of Economy, Trade and Industry)	Economic and industrial development (Act No.99 of 2009) basic technology and infrastructure for industrialisation	Thriving R&D and industries in health care and medicine field (Act No. 48 of 2014). Prompt and safe development, provision and dissemination of regenerative medicine (Act No. 13 of 2013).	• There are few successful examples (companies) so far, and the market is still immature (Igarashi & Sato, 2018).	Regulations Budget (subsidies for industrialisation)

	(Headquarters for Healthcare Policy, 2023-b)			
AMED (Japan Agency for Medical Research and Development)	R&D in the medicine field, from basic research to clinical trials (Act No.49 of 2014)	Thriving R&D and industries in health care and medicine field (Act No. 48 of 2014). Prompt and safe development, provision and dissemination of regenerative medicine (Act No. 13 of 2013).	• Same with the ministries' concerns since it works with the ministries.	Budget Advice on R&D Collect information from researchers
PMDA (Pharmaceuticals and Medical Devices Agency)	Pharmaceuticals and medical devices intended for marketing	Prompt and safe provision and dissemination of regenerative medicine (Act No. 13 of 2013).	• Ethical concerns about exclusive approval process for regenerative medicine.	Assessment of products
Pharmaceutical companies *Pharmaceutical companies focusing on especially regenerative medicine	Producing and marketing regenerative medicine	Earning money through regenerative medicine.	• Translational research in regenerative medicine has so far attracted relatively little interest from the pharmaceutical industry. The reasons are general uncertainties with regard to the therapeutic promise of cell-based regenerative medical/medicinal products, high production and quality control costs, and extreme logistical complexity related to the specific characteristics of these products, such as their generally short shelf life, relatively long-term investment commitment before any financial return, and the existence of different international regulatory environment. (Matsuyama, 2013) • The knowledge base for new developments in stem cell research generally resides in the academic research community, small- to medium- size biotechnology companies with substantial research capacity, and those well connected to academic research teams. (Matsuyama, 2013) • There are few successful examples (companies) so far and the market is still immature. A major challenge in establishing it as a business model is the cost of	Produce and sell products

			development and production. (Igarashi & Sato, 2018) • An analytical concern with medical innovations that are not amenable to the business model of Big Pharma (i.e. the development of scalable, mass-produced medicinal products that can be stored long-term and shipped across long distances) (Rosemann et al., 2018)	
Companies' communities	Market of regenerative medicine	Thriving market of regenerative medicine.	• Japan does not take the lead of market of regenerative medicine. • Regulations do not consider the variety of products. Various product values are not evaluated appropriately, as is the price, and it is difficult to conduct new investments due to the lack of enough benefits from previous products. Human resources who can work for regenerative medicine products are scarce. (Forum for Innovative Regenerative Medicine, 2023)	Advice Collect information from companies Present guidelines for the industry
Hospitals & clinics 1. Large hospitals owned by universities 2. Other hospitals and clinics	Provision of treatment for patients	Provision of scientific and proper treatment for patients Good management of the organisation (Medical Care Act, Act No. 205 of 1948).	• There are worries about the risks to study participants, the appropriate selection of study participants, setting relevant goal(s) for measuring outcome, and the need for evidence-based medicine and scientific integrity (worried about the hype of regenerative medicine) (Niemansburg et al., 2014) • Insufficient reimbursement for medical institutions that provide regenerative medicine products is a barrier to the dissemination of regenerative medicine to institutions. (Forum for Innovative Regenerative Medicine, 2023) • Scarce are the physicians, nurses, therapists or biomedical engineers that have been educated in the regenerative acumen. (Yamada et al., 2021)	Provide treatment
Research institutions	R&D in regenerative medicine	Development of regenerative medicine.	• The knowledge base for new developments in stem cell research generally resides in the academic research community, small- to	Manage research environment and research project

*Universities and national research institutions that own their hospitals		Good management of the organisation.	medium- size biotechnology companies with substantial research capacity, and those well connected to academic research teams. (Matsuyama, 2013) • Lack of researchers who has the enough knowledge of legislation, ethics, and patent to implement the results of research. (Ministry of Education, Culture, Sports, Science and Technology, 2022) • Few budget.	Conduct research
Doctors	Provision of treatment for patients	Provision of scientific and proper treatment for patients.	• There are worries about the risks to study participants, the appropriate selection of study participants, setting relevant goal(s) for measuring outcome, and the need for evidence-based medicine and scientific integrity (worried about the hype of regenerative medicine) (Niemansburg et al., 2014) • Scarce are the physicians, nurses, therapists or biomedical engineers that have been educated in the regenerative acumen. (Yamada et al., 2021)	Conduct treatment
Researchers *Usually have doctor's licenses	Research	Development of regenerative medicine.	• There are worries about the risks to study participants, the appropriate selection of study participants, setting relevant goal(s) for measuring outcome, and the need for evidence-based medicine and scientific integrity (worried about the hype of regenerative medicine) (Niemansburg et al., 2014) • A challenge for some scientists accustomed to conventional academic research is that entrepreneurial science also increases the expectations for impact measured in commercial or social terms. (Hogle, 2014) • The academic researchers are less familiar with the project and/or product management demands of the industry. (Matsuyama, 2013) • Lack of researchers who has the enough knowledge of legislation, ethics, and patent to	Conduct research

			implement the results of research. (Ministry of Education, Culture, Sports, Science and Technology, 2022)	
Researchers' communities	R&D of regenerative medicine	Share skill and knowledge for the development of regenerative medicine.	• The knowledge base for new developments in stem cell research generally resides in the academic research community, small- to medium- size biotechnology companies with substantial research capacity, and those well connected to academic research teams. (Matsuyama, 2013) • Researchers still have problems to implement their results of research into society (translation).	Collect information from researchers Present guidelines and support systems for researchers
Patients	Health of themselves	Recovery from disease without bad side effects or risks and extremely high cost.	• Some patients are longing for opportunities for clinical experiments at home even when risk is involved. Others, however, prioritise safety and wait until treatment is established. (Kato & Sleeboom-Faulkner, 2017) • Patients rely on information from their physicians who may have conflicting financial or professional interests in marketing the intervention or in the intellectual property, which leads to quality of informed consent and raises important public health concerns and questions of distributive justice (patient selection, early access vs burden) (Lysaght, 2017) • Few options of regenerative medicine. • High price.	Participate in research Public pressure
Public (including donors of cells and future patients)	Daily lives practical matters (costs, risks, and governance/operation system)	Better society without anxiety for their health. Benefits as a society member/contributor.	• Different image of the effect of regenerative medicine from researchers and doctors. • The public is more interested in the post-realization aspects of RM, such as cost of care, countermeasures for risks and accidents, and clarification of responsibility and liability, than in the scientific aspects in which scientists have more interests. So, there may be a gap between the expected information and the information offered by	Participate in research Public pressure

			researchers and doctors. (Shineha et al., 2018) • Negative perception against human-animal chimera research (Inoue et al., 2016) On the other hand, there is also possibility of relieving negative perception to some extent by enough information/ecplanation about the technology. (Sawai et al., 2017) • It is not surprising that public concern and mistrust of government technology policies would be on the rise in Japan: in the wake of the Fukushima nuclear disaster, there has been a persistent perception of lack of community involvement in decisions that affect citizens' health and lives. (Hogle, 2014) • Unfair benefit. • Inappropriate invest on research in diseases which influence few patients.	

Resource dependency

In this sub-step, the resource dependency of actors was explored to distinguish whether they are critical to this research theme. Enserink et al. (2022) describe that resource dependency can be assessed by Table 3-6. Therefore, using Table 3-6, actors' criticalities in the translation of regenerative medicine were determined, as shown in Table 3-7. This determination was considered not only from an ethical perspective but also in general.

Table 3-6. Resource dependency (Enserink et al., 2022)

	Limited Importance	**Great Importance**
Limited option to replace	Medium dependency	High dependency
Can easily be replaced	Limited dependency	Medium dependency

Table 3-7. Overview table for determining critical and non-critical actors

Actors	Possible actions/Resources	Replaceable?	Dependency	Critical actor?
Politicians	Political pressure Establish law (via the diet)	No	Medium	No
MHLW	Regulations (Law 3 & 4) Budget for research Approval of products	No	High	Yes
MEXT	Regulations Budget for research	No	High	Yes
METI	Regulations Budget for industrialisation	No	High	Yes
AMED	Budget Advice on R&D Collect information from researchers	Yes	Limited	No
PMDA	Assessment of products	No	High	Yes
Pharmaceutical companies focusing on especially regenerative medicine	Produce and sell products	No	High	Yes
Companies' communities	Advice Collect information from companies Present guidelines for the industry	Yes	Medium	No
Large hospitals owned by universities	Provide treatment	No	High	Yes
Other hospitals and clinics	Provide treatment	Yes	Medium	No
Universities and national research institutions that own their hospitals	Manage research environment and research project Conduct research	No	High	Yes
Doctors	Conduct treatment	No	High	Yes
Researchers	Conduct research	No	High	Yes
Researchers' communities	Collect information from researchers Present guidelines and support systems for researchers	Yes	Medium	No
Patients	Participate in research Public pressure	Yes	Limited	No
Public	Participate in research Public pressure	Yes	Limited	No

Positions of Main Actors

Considering the information in Figure 3-3, Table 3-5 and Table 3-7, the diagram (Figure 3-4) presents the actors' position in terms of their power to enforce regulations related to regenerative medicine and their interest in translating regenerative medicine under regulations in Japan. The details of the diagram (Figure 3-4) are as follows.

- Politicians (1) can establish law through the necessary procedures and discussions in the diet as representatives of citizens in Japan. Considering this, they have power to some extent. However, while some politicians have an interest in regenerative medicine and make the group, it is not a big movement at this moment. Therefore, the current power is medium in this matrix. If their level of interest becomes larger as a whole, their location would move to the top right.
- MHLW (2) oversees the main regulations when conducting regenerative medicine (even when it is clinical research) and has a budget for promoting research and development in medical fields. Hence, it is located at the highest point of power. Also, since the government is responsible for promoting R&D in regenerative medicine and the creation of new industries, and it is a part of the government, it should have a strong interest. Other governmental bodies are also located at high points of interest because of the same reason.
- Since MEXT (3) has a budget similar to MHLW's and took the initiative to establish the guidelines for the research whose subject is human, it is located second to MHLW in terms of power.
- METI (4) oversees the scaling-up stage of the regenerative medicine industry/business. In other words, it is not involved with the initial process of translating regenerative medicine technology. Hence, it is located next to MHLW and MEXT.
- PMDA (5) plays a key role when assessing regenerative medicine products for provision, so the level of power is relatively higher next to the ministries. However, it is not proactive in promoting regenerative medicine, so its level of interest is lower than that of other governmental organisations.
- AMED (6) is supervised by the three ministries and the Cabinet Office. Therefore, its location of power is under them.
- Usually, universities and national research institutions (7) that study regenerative medicine own their hospitals, and the hospitals (10) aim to provide regenerative medicine. Therefore, these two actors are located at the same point. Since they intend to translate regenerative medicine, their interest is relatively high, and they also have the power to conduct research aligning with the regulations practically. In addition, many research institutions receive some budget to conduct research aligned with national policies. Therefore, their level of interest is closer to that of governmental organisations than that of companies. On the other hand, other hospitals and clinics (11) that are not connected with universities or national institutions have a bit weaker power than large hospitals due to their resources, while they also have the same level of interest in providing regenerative medicine. Hence, they are located in a lower place than the group of large hospitals and national research institutions.
- Researchers (8) and doctors (12) also contribute to the promotion of regenerative medicine with a high level of interest. Yet, they belong to hospitals/clinics or research institutions, so they are located under them in terms of power.
- Researchers' and companies' communities (9) (14) are the communities that promote regenerative medicine. Hence, their interest should be stronger than those of individual researchers and companies. Also, their level of power is slightly higher than others since they sometimes offer additional guidelines or standards that help individuals follow the broad regulations and guidelines by the ministries and make the standards of quality in the industry better to promote the industry. They also have more power than individuals to make public statements and pressure politicians and ministries.
- Pharmaceutical companies (13) can practically provide regenerative medicine, which means they have the power to develop regenerative medicine products aligning with the regulations practically as well as universities, research institutions, and hospitals. Therefore, their level of power is close to that of universities, research institutions, and hospitals. They can decide whether to do so, referring to their

objectives, even though they focus on regenerative medicine. If they find the provision of regenerative medicine unattractive, they would not be involved with it (i.e., they would change their focus as a business). Hence, their level of interest is less than that of others as they can observe the situation.

- The interest level of patients (15) is obviously high. However, what they can do in translating regenerative medicine is make decisions about participating in clinical research or taking regenerative medicine and pressurise politicians, ministries, and practitioners, which is limited power in this context.
- The public (16) does not have a strong interest or power in regenerative medicine itself compared to other actors at this moment.

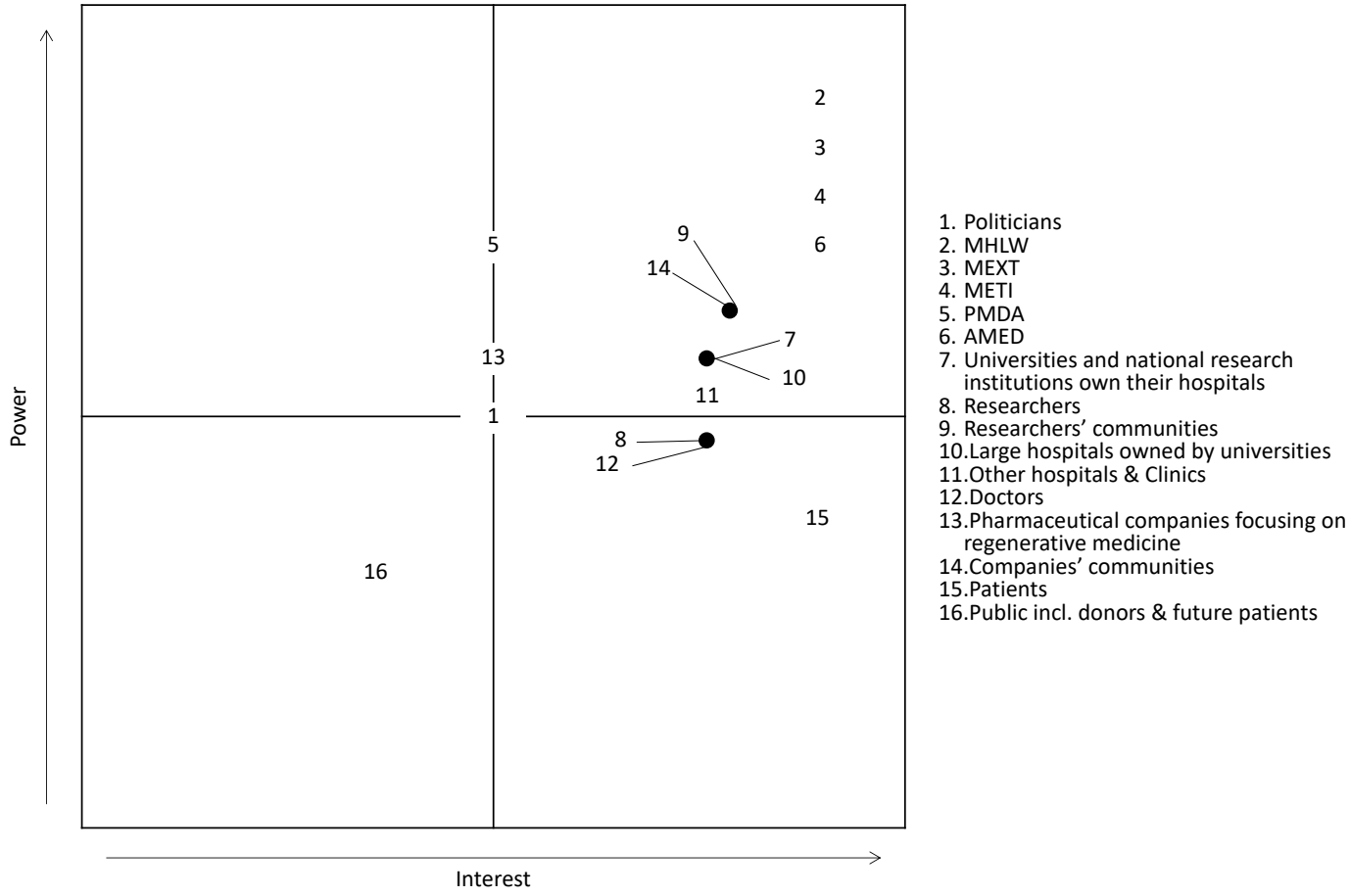


Figure 3-4. Actors' positions regarding the power to enforce regulations and the interest in translating regenerative medicine under the regulations in Japan.

In addition, to identify the key actors, comparing with the previous diagram (Figure 3-4), Figure 3-5 presents the actors' levels of power to initiate change in the current situation to take ethical considerations into account more and their interest in translating regenerative medicine with ethical considerations in Japan. The details of the diagram (Figure 3-5) are as follows.

- As mentioned above, the level of interest of politicians (1) is medium. However, they have the potential power to change the situation by establishing laws or working on the ministries to establish regulations or systems in response to their own awareness or lobbying by other sectors, such as patients and groups of doctors. Therefore, the level of power is as high as the ministries that oversee regulations.
- The three ministries are highly interested in translating regenerative medicine with ethical considerations, as Law 1 and Law 2 stipulate their responsibility. MHLW (2) can use laws, regulations, and budgets and collaborate with related agencies under its jurisdiction, such as PMDA. Hence, its level of power is high.

- MEXT (3) can also use regulations and budgets, which are critical for the research and development of novel regenerative medicine, especially basic research, which requires a lot of costs. Since, for example, it could initiate changes by designing the research project with budgets, the level of power is close to that of MHLW.
- The jurisdiction of METI (4) is industry, which is the goal of the translation. Therefore, its level of power to initiate changes is lower than the other two ministries, which are involved with a broader process of the translation of regenerative medicine.
- PMDA (5) is the assessment agency, so it does not have a proactive interest or power to influence the current system of translating regenerative medicine, though it is to follow the policies determined by the ministries, especially MHLW.
- AMED (6) oversees research projects within the governmental budget; however, it does not take action formally without the policies of the ministries that supervise it. Therefore, while its interest is located at the same level as that of ministries, its power is relatively lower.
- Universities and national research institutions that own their hospitals (7) and large hospitals owned by universities (10) are again considered to be in the same position. They are generally interested in the translation of regenerative medicine with ethical considerations, which is aligned with government policies, to gain honour as organisations for research and treatment. They could also construct a better practical approach to translating regenerative medicine with ethical considerations. This means they could initiate change from the bottom up. Hence, their level of power is as high as that of the ministries, which can change the system from the top down. On the other hand, other hospitals and clinics (11) are relatively small in scale and do not have as much power.
- Researchers (8) and doctors (12) also have the same level of interest as the organisations to which they belong. Since they are individuals, their power to initiate changes is slightly lower than that of research institutions or hospitals/clinics, while they still have an influence on the system as working on the ground.
- Researchers' and companies' communities (9) (14) more strongly aim to the translation of regenerative medicine with ethical considerations than individual researchers and companies to make the field thrive. Researchers' communities can lobby politicians and ministries to change the system based on the information from individual research institutions and hospitals and individual researchers and doctors. Therefore, their level of power is the same as that of them. Since the scope of companies' communities is industry, their level of power is lower than that of researchers' communities, similar to METI.
- Pharmaceutical companies (13) have slightly weaker power to initiate changes than companies' communities since they do not have as much influence as the aggregated impact of companies' communities. Also, they can choose if they use regenerative medicine for their business, which means they are neutral position to promote the translation of regenerative medicine. Hence, the level of interest is medium, as in the previous diagram.
- Patients (15) are highly interested in regenerative medicine translation with ethical considerations. They can slightly influence the process of the translation of regenerative medicine by participating in or refusing clinical research. Also, they can approach or lobby politicians, ministries, and other organisations to change the system. Yet those actions need to be aggregated to become an actual power and are limited in Japan, where such examples have not appeared.
- The public (16) may be concerned about the ethical usage of emerging technology, especially by the government. However, they are not proactive, and their level of interest is located on the medium line. Also, their power is limited as long as they are not aggregated, which is rare in Japan compared to that of patients (this information is from the online questionnaire results).

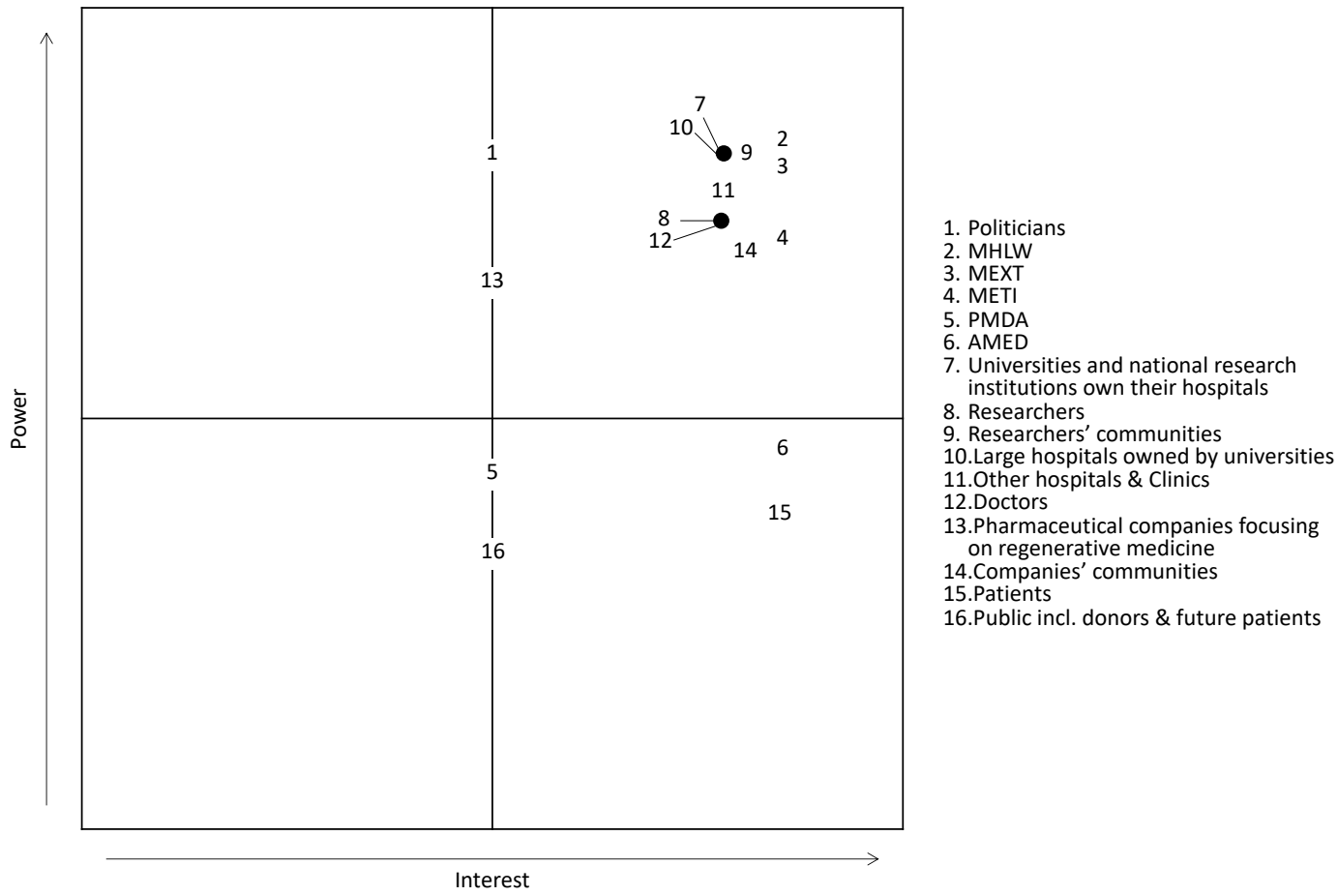


Figure 3-5. Actors' positions regarding the power to initiate change in the current situation and the interest in translating regenerative medicine with ethical considerations in Japan.

When it comes to the power to enforce regulations, ministries can manage them and are apparently influential on the system. However, in terms of initiating changes in the current system, organisations of players on the ground, such as hospitals and research institutions, increase their presence through potential bottom-up chances.

According to the findings so far, actually, no actor intends to hinder the ethically favourable translation of regenerative medicine. This means there seem to be difficulties or oversights in the whole system rather than opposite actors.

3.4. Key Processes and Actors

Considering the information so far, the critical process of the translation of regenerative medicine in Japan would be the process from the clinical research phase to the start of marketing. The former phase is under the ethics guidelines, but the guidelines are sometimes treated like a procedural manual and do not have the power of enforcement. The latter is out of the scope of the guidelines, and the laws that should cover it only require procedural things (not assessment), supposing the committee has problems, as stated by some articles. Moreover, this process involves two ministries, which may cause silos and confusion among practitioners even though the ministries do not intend that (Sugarman et al., 2018). Therefore, documents or organisations which can play as an anchor to be referred to when incorporating ethical considerations into this process are ambiguous.

To consider the key actors, examine the situation from the perspectives of actors located in the first quadrant of the diagrams (Figures 3-4 and 3-5). In both diagrams, the three ministries, MHLW, MEXT, and METI, have high power and interest. Since they have regulations and a duty to promote regenerative medicine but are not practical players, they need to encourage the practitioners' group to proceed with their research and development. Therefore, they offer projects with budgets and construct regulations and guidelines to enable them to carry out their activities easily and appropriately.

The four main laws target the process of clinical research. However, they are procedural requirements, meaning they are not scientific assessments or approvals except for the post-marketing assessment for products stipulated in Law 4. Therefore, from the practitioners' group's perspective, the decision of whether the research can proceed or not is up to them. Also, how much ethical considerations are incorporated or how ethical issues are treated depends on the practitioners as long as they adhere to regulations. Hence, they do not have an anchor to conduct research in "a good" manner. On the other hand, it can be considered that they could influence the ministries in terms of regulations that would fit the practical situations better by informing practical experiences. This especially applies to large hospitals owned by universities, and universities and national research institutions own their hospitals, based on the diagrams.

Consequently, the key actors are the ministries that oversee regulations, including the guidelines. Especially, MHLW, which is involved with the approval process of products and is in charge of Law 3 and Law 4, and MEXT, which is the main player in the Ethical Guidelines and the research sector in Japan, are considered influential. In addition, large hospitals owned by universities and universities and national research institutions own their hospitals, which conduct the critical process practically and potentially influence the system, are also important actors.

4. Result II: Ethical Issues and Possible Approaches

This chapter identifies ethical issues and possible approaches through the literature reviews, the online questionnaire, and the interview (the latter two are mentioned in Chapter 5) to answer sub-questions 2 and 3. Section 4.1 presents an overview of ethical issues and approaches, and the latter sections add explanations for them. Sections 4.2 and 4.3 provide additional explanations about the issues and concerns in the literature and possible approaches related to other countries' policies, respectively.

4.1. Extensive List of Ethical Issues and Possible Approaches

The literature related to the translation of regenerative medicine, which was found through literature reviews 1 and 2, focuses not on the whole system but on specific phases in general or specific laws in Japan and observes the situation to indicate issues and generate suggestions. Therefore, the identified ethical issues and solutions/suggestions as possible approaches were divided into the phases of the translation and grouped by theme through Thematic analysis. Considering the results of Chapter 3, since this research targets the process between the clinical research phase and the start of marketing, only issues and solutions/suggestions in those phases were identified. The results are shown in Table 4-1. The grey-marked issues overlap with issues in former phases.

Table 4-1. Ethical issues arise in translating regenerative medicine and suggested approaches to address the issues. Grey-marked issues overlap with other issues.

Issues	Approaches	Sources & specific topics/regions
Preclinical research - Clinical research		
Safety.	Thorough basic research should be addressed before translating the technology into the clinic.	(Zamborský et al., 2018)
Clinical research		
Need for regulation of patent.	(No specific explanation)	(Zamborský et al., 2018)
Patient's consent - There are several ways of consent, but it is still unclear which one is appropriate in the specific case. - Patient's understanding of uncertainties of regenerative medicine as an emerging technology.	- Training on ethical, legal, and societal issues in RM, including how to involve other stakeholders, especially patients, in research design and review. - Engaging with the public and patients in order to counter misinformation. - Careful communication.	(Hermerén, 2021): in EU (Zamborský et al., 2018) (De Kanter et al., 2023): tissue engineering for regenerative purposes (Riva & Petrini, 2019): gene and cell therapy (King & Perrin, 2014) Online questionnaire
Criteria of safety and effectiveness - Safety and efficacy (limited research evidence and little clinical experience of use; lack of knowledge of the appropriate dosage and other interventions required to make a drug safe and effective, particularly concerning long-term effects). - Difficluty in evaluating preclinical research. - Difficulty in assessing the risk to benefit ratio.	- Boards have the necessary competencies for assessments. - Professional communities should also promote the adoption of standards that lead to ethical conduct, because even physicians themselves might be at risk of serious bias or conflict of interest. - Adaptive trialing: clinical research designed to permit a range of variables to explore the appropriate criteria. - Continuous consideration and verification from the basic research phase and conducting such research projects.	(Hermerén, 2021): in EU (Riva & Petrini, 2019): gene and cell therapy (Gardner et al., 2015): in UK (Lowenthal & Sugarman, 2015): Pulmonary Medicine (King & Perrin, 2014) Online questionnaire
Scientific limitation - Uncertainties of application (lack of prior examples). - Unknown mechanisms of action and interactions. - Known burden and risks. - Unknown and unanticipated effects (differing efficacy and effectiveness).	- Adaptive trialing: clinical research designed to permit a range of variables to explore the appropriate criteria. - Whereas especially in later trial phases a focus can be placed on clinical outcome measures (progressive value), the value of a study should be enhanced by also collecting information to promote further (pre)clinical studies, as is also proposed in the ‘‘translational model of value.’’	(Shook & Giordano, 2024): neuroscience (De Kanter et al., 2023): tissue engineering for regenerative purposes (Riva & Petrini, 2019): gene and cell therapy

- Difficulties related to distinctive characteristics (Need for relatively invasive procedures, Preclinical data not informative as for small molecule pharmaceuticals, Unique complexities of cell therapy products due to the dynamic nature of living cells). - Difficulties in setting relevant goals for measuring outcome (varying from regenerating tissue to improving well-being of patients).	- The disclosure of conflicts of interest in reported studies, and improving the review of research protocols and editorial review of manuscripts. - Incorporation of education about RM, surgical clinical studies, and ethics in the specialization trajectory to orthopedic surgeon is important. - Research programs which aim to stimulate collaborations between scientists and orthopedic surgeons to promote translational research. - Rather than directly designing for safety, it is better to design for the responsibility for safety	(Gardner et al., 2015): in UK (Niemansburg et al., 2014) (Baker et al., 2016) (Van De Poel & Robaey, 2017)
Scientific integrity - Conflicts of interest (e.g., medical professionals are incentivised to provide innovative approaches in ways that may conflict with their responsibilities including those to avoid hyperbole and to report adverse effects). - Responsible conduct. - Transdisciplinary collaboration.	- The disclosure of conflicts of interest in reported studies, and improving the review of research protocols and editorial review of manuscripts. - Incorporation of education about RM, surgical clinical studies, and ethics in the specialization trajectory to orthopedic surgeon is important. - Research programs which aim to stimulate collaborations between scientists and orthopedic surgeons to promote translational research.	(Hermerén, 2021): in EU (Zamborský et al., 2018) (De Kanter et al., 2023): tissue engineering for regenerative purposes (Niemansburg et al., 2014)
Patient selection - Equity and fairness (patient access to experimental treatment). - Criteria for inclusion/exclusion of participants. - Patients are sometimes required to pay to participate in clinical research. - Few patient and public involvement.	- Ensuring that patients do not have to pay to be enrolled in clinical trials. - Boards have the necessary competencies for assessments. - Professional communities should also promote the adoption of standards that lead to ethical conduct, because even physicians themselves might be at risk of serious bias or conflict of interest. - Advanced-stage patients are probably most eligible, because these patients have least functionality to lose when harms occur, and also diagnosis in these participants is easier. - The Internet and social media are key ways in which patients looking for regenerative medicine treatments interact and raise consumer power against providers.	(Hermerén, 2021): in EU (Riva & Petrini, 2019): gene and cell therapy (Niemansburg et al., 2014) (Chan, 2017) (De Kanter et al., 2023): tissue engineering for regenerative purposes (Lowenthal & Sugarman, 2015): Pulmonary Medicine (Baker et al., 2016)
Use of donated cells - Unclear usage of donated biological material (donated material like cells should be treated with transparent information and clear rules).	(No specific explanation)	(Hermerén, 2021): in EU

- Leakage or abuse of donor's personal information, including discrimination based on genetic characteristics. - Ownership of cells.		(Lowenthal & Sugarman, 2015): Pulmonary Medicine Online questionnaire
Societal effect - Societal impact related to distributive justive, impact on healthcare and market, concerns for biosecurity - Extreme expectations of patients and society for new treatment.	- The public discussion involves researchers, ethics professionals, patients and the public. - Clarify the issues based on the practical cases and then communicate with the public by collaborating with involved actors. - Utilise mass media or SNS tools.	(De Kanter et al., 2023): tissue engineering for regenerative purposes (Higuchi, 2013) Online questionnaire
Unclear ethically acceptable extent of research - Manufacturing brains or germ cells. - How to define human experience and identity.	- The public discussion involves researchers, ethics professionals, patients and the public. - Utilise mass media or SNS tools.	(De Kanter et al., 2023): tissue engineering for regenerative purposes (Volarevic et al., 2018) Online questionnaire
Researchers' anxiety - A challenge for some scientists accustomed to conventional academic research is that entrepreneurial science also increases the expectations for impact measured in commercial or social terms. - Researchers may not feel qualified to make and which may contribute to overpromising or “hype.”	(No specific explanation)	(Hogle, 2014)
Review committees' responsibility - High pressure on review committees due to the high expectation from public and government and complex nature of risks makes the assessment challenging. - Therapeutic misconception of participant might occur because of unappropriate communication of benefits and risks between the committees and particiapnts.	- Clear distinguishment of mandatory test for safety or desirable test for broader scientific knowledge. - Balanced information on potential benefits and risks. - Ensure participants' understanding and support for them.	(Takashima et al., 2018)
Clinical research - Treatment		
Scientific integrity - Danger that the emphasis on advancements in scientific knowledge might prevail over the protection of the people who participate in research. (The risk of this danger can introduce complications in the regulations governing the use of materials obtained from clinical patients for medical research.)	- A holistic concept to develop new treatment methods and a means to cultivate the development and management process. - The cooperation of researchers in various fields, and the optimization and integration of research resources.	(Chen et al., 2012) (Hogle, 2014) (Illes et al., 2017)

- Financial and commitment conflicts of interest, as academic entrepreneurs become involved in marketing their inventions. In a still-growing field, academics often take on policy advocacy or expert testimony roles, making it difficult to know when the effect of such activities might benefit a potential entrepreneurial interest.		
Science hype in which the state of scientific progress, the degree of certainty in models or bench results, or the potential applications of research are exaggerated.	Following the International Society for Stem Cell Research (ISSCR) guidelines: - Researchers should promote accurate, balanced, and responsive public representations of the research and ensure that the technology's benefits, risks, and uncertainties are not misrepresented. - Clinical researchers should avoid confusing the language of research with the language of care. - Researchers should make timely corrections of inaccurate or misleading public representations of research projects, achievements, or goals.	(Caulfield et al., 2016)
Due to the rigid design and criteria for trials that are submitted for regulatory approval, the results of such studies may not predict the effectiveness of a product or technology in the clinical practice setting, leading to frustrations from practitioners.	- A holistic concept to develop new treatment methods and a means to cultivate the development and management process. - The cooperation of researchers in various fields, and the optimization and integration of research resources.	(Chen et al., 2012)
Lack of standardised process from clinical reserach to treatment - An unclear idea or concept, a non-standardized process, a lack of a unified, standardized criteria and arbitrary, sometimes utilitarian application - A lack of communication and cooperation between basic researchers (cell biologists/biomaterial scientists) and clinicians. - Inappropriate existing templates related to costs and regulations. - Stem cells are biochemically and pharmacokinetically complex and may fit poorly with Phase I–IV models; while medical innovation is inherently risky.	- A holistic concept to develop new treatment methods and a means to cultivate the development and management process. - The cooperation of researchers in various fields, and the optimization and integration of research resources to solve practical problems. - At the management level, academic research institutions and government departments should adapt to the development of translational medicine and re-establish a set of management practices. - Centralisation of expertise related to the studies and RM-specific costing and contract documentation. - A stem cell-based learning health system.	(Chen et al., 2012) (Gardner et al., 2015): in UK (Touré et al., 2018) (Chan, 2017) (Jacques & Suuronen, 2020)
Few professionals or knowledge for the translation - The lack of translational medicine professionals with a global perspective who are well versed in international	- Further education is required to train these "vanguards" to lead the development of translational regenerative medicine.	(Chen et al., 2012) (Matsuyama, 2013) (Tsubouchi et al., 2008) Online questionnaire

regulations and are responsible for directing the entire development process. The difficulties faced in translational regenerative medicine are largely due to this reason. - The academic researchers are less familiar with the project and/or product management demands of the industry. - Few job chances for ethics professionals and few ethics professionals themselves, due to the unclear outputs of interventions of ethics.	- Establish a system whereby individuals can move easily between academia and industry.	
(No specific explantion)	Well-structured and independently funded registries, engaging in social media discussions, and finding ways for informed patients to have meaningful conversations with other patients, which would be also helpful to understand hematopoietic stem cell transplants and to assess the long-term benefits and harms.	(Sugarman et al., 2018): stem cell-based therapy
Clinical research - Treatment (About Law 3 in Japan)		
- Lack of scientific verification. - Failure to define and distinguish between "research" and "treatment" (It is entirely up to the practitioner to decide). - Neglecting to define and distinguish between "medical innovations" and "unproven interventions" (allowing both to be regarded as treatment, resulting in limited conditions under which medical innovations can be provided are not shared among the medical institutions, physicians, and committees stipulated in Law 3 in Japan). - Concerns about the independence, integrity, and quality of reviews of RM provision plans submitted by the certified (special) committees with inappropriately close relationships to medical institutions and third-party cell providers. - The large number of certified (special) committees leaves considerable scope for variation in how the regulatory guidance is interpreted and applied to specific provisions. - The weaker pre-market evidentiary requirement thresholds that private clinics currently enjoy may enable them to attract patients away from participation in clinical trials. Moreover, the lower evidence bar under Law 3 may enable the continued expansion of the private-practice regenerative medicine industry, with concomitant increases in diversity of clinical offerings, price competition, and political lobbying power.	- More robust review of clinical research and treatment, including surgical elements and devices.. - Other countries typically adopt regulatory frameworks that clearly distinguish between research and therapy. - 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. - 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. - The MHLW should place stricter limits on the discretionary use of regenerative medicine (especially class 3) techniques by private businesses. - Medical professional organizations, such as the Japan Medical Association and the JSRM, should step up their monitoring of and disciplinary activity against practitioners who take undue advantage of the current regulatory looseness. - Careful informed consent. - Support for small clinics to improve the speed and accuracy of data entry to the national database of	(Fujita et al., 2022) (Takashima et al., 2021) (Ikka et al., 2023) (Sipp & Okano, 2018) (Cyranoski, 2019) (Morrison, 2024) (Ikka et al., 2023-b) (Lysaght & Sugii, 2016) Online questionnaire

- A risk that patients will view the registry as a kind of validation. - Follow-up, including adverse event report which is mandatory, is presently limited in scope and quality.	experimental therapies and to conduct more robust long-term patient follow up.	
Clinical research - Treatment (About Law 4 in Japan)		
- Dispropotionaly emphasise safety over the efficacy which means losing clinical benefit for patients. - Conditional approved products have significant uncertainties regarding safety. - Insufficient quality of studies after marketing of contidional approved products. - The system, which could provide unproven regenerative medicine products, potentially undermine public trust. - Subsidising the costs of full manufacture and availability of insurance coverage is an unusual feature and will strain healthcare systems. - Conditional approval may erode confidence in the scientific standards of the field. - Difficulty in recalling conditional approaved products when new evidence shows they are ineffective. - Conditional approval may lead that Japanese patients and the Japanese health system bear the costs of research for foreign companies that can then realise their profits on the global market. - Exclusive system of regenerative medicine products may lead to inferior regenerative medicine products being rewarded at the expense of superior alternative modalities.	- The evidentiary standards for conditional approvals should be at a minimum level that would be suitable for an investigational product to enter into Phase3 trials. The standards should apply to only products where there is an insufficient patient population to recruit subjects into large-scale efficacy trials, or where the intervention involves high-risk surgical procedures to justify testing in large numbers of patient without clinical benefit. - Where products with conditional approvals, regulators must be vigilant in enforcing the conditions and ensuring products that fail to demonstrate efficacy with primary endpoints, or no longer support a positive risk-benefit ratio, are withdrawn from the market expeditiously. - Public funding with market authorisation should be fully evaluated for cont-effectiveness in health technology assessment with the clinical end points and benefit and public funding for clinical research or trials with novel products should continue to be granted competitively. - Regulations at national and international level should be reqired. - Careful informed consent. - A number of refinements of regulations should be made.	(Lysaght, 2017) (Cyranoski, 2019) (Cyranoski et al., 2023) (Chan, 2017) (Sipp, 2015) Online questionnaire
Treatment/Manufacturing products		
Economic burden associated with every new advanced therapy.	The development of new cultivation protocols and expansion media, as well as by the automation of laboratory processes.	(Zamborský et al., 2018) (Shook & Giordano, 2024): neuroscience
Patients or their relatives have high hopes of curing various diseases with stem cells but they are usually not aware of the concerns and potential problems associated with stem cell use.	Establish proper guidelines and regulations globally to effectively protect patients and to ensure proper use of stem cells in the clinic.	(Zamborský et al., 2018)
Regulatory challenge	- Regulatory agency to adopt clearer specification.	(Gardner et al., 2015): in UK

- Heterogeneity in implementation of provisions (a lack of clarity regarding certain regulatory requirements). - Difficulties associated with classification of products. - Deregulation, such as conditional approval, may allow low-efficacy treatments/products and lead to a lack of patient benefits.	- Adaptive licensing. - Stakeholder groups at the national and international levels work together; Local organisations can monitor local situations, establish regulatory standards incorporating advice from international stakeholders, and contribute to public outreach. Global organisations can support the development of national regulations and coordinate regulatory harmonisation.	(Sipp et al., 2017) (Higuchi, 2013)
Manufacturing challenge - Undeveloped infrastructure or scale-up and transport to the clinic. - Lack of consensus regarding the quality assurance. - No geographically consistent or harmonized manufacturing and quality assurance standards (due to the high variability of cells between individuals and difficulties in characterizing cells that are made in batches for single-use applications).	- New systems and logistics with quality assurance. - Uniform standards for cell processing, manufacture, and control should be harmonized by international groups of scientists, cell banks, and regulators since stem cells react in response to different stimuli, requiring uniformity and definition of references to assure a realistic prediction of risks and benefits in clinical translation. - It is essential for regulators to work closely with manufacturers as well as scientific and medical communities with relevant expertise across regional jurisdictions to generate evidence-based standards that can be adopted and enforced within national frameworks.	(Gardner et al., 2015): in UK (Sugarman et al., 2018): stem cell-based therapy
Assessment involves a sensitivity analysis taking account of particular uncertainties, may disadvantage RM with high upfront costs and for which there is limited information on long-term clinical effectiveness.	Move to risk-sharing, refine health economic model, introduce managed entry agreements.	(Gardner et al., 2015): in UK
Practical challenge in hospitals - Need for knowledge for clinicians. - Need for integrating with existing workflows.	Specific centres of excellence.	(Gardner et al., 2015): in UK
Inappropriate clinics - Inappropriate use in practice. - The separation of regulatory responsibilities reflect ‘‘silos’’ that may have not only enabled the growth of the DTC(direct-to-consumer) market for stem cells, but may also be hampering the translation of stem cell research into demonstrably safe and efficacious products. - Different obligations in healthcare settings. - Few guidelines are available on the innovative use of autologous stem cells in clinical practice (There are guidelines, but do not have legal effect while it is unclear	- A cooperative regulatory model that spans multiple domains of regulation is needed (the model could potentially bridge the current silos that regulate innovation pathways in clinical research and practice through the establishment, implementation, and enforcement of evidence-based standards for cell processing and manufacturing, for the market, and for introducing them into routine clinical care.). - National governance bodies and licensing boards that have statutory powers to generate umbrella codes of practice for all medical practitioners and sanction those found practicing outside of those standards.	(Shook & Giordano, 2024): neuroscience (Sugarman et al., 2018): stem cell-based therapy (Lysaght et al., 2018): autologous stem cell (Ventura-Juncá, 2011) (Fears et al., 2021) (Chan, 2017) (Sipp et al., 2017) (Ikka et al., 2015)

who should have responsibility of disciplining wrong practitioners).
- Medical tourism, in which clinics would set up their operations in countries with more permissive regulatory environments and patients would travel to access them.
- Inappropriate drug advertising.
	- Establishing global regulations, which implies agreements among countries to effectively protect patients and ensure the proper use of the impressive developments.
	- Not all problems can be resolved through legal regulations alone. Therefore,
	  - Researchers' communities have a responsibility to transmit and disseminate more effective information regarding inadequate clinics.
	  - Patients should make the decision to undergo RM only after gaining an adequate understanding of the actual status of RM and of the therapy he/she is seeking to undergo.
		(Lowenthal & Sugarman, 2015): Pulmonary Medicine

Distribution challenges - Economic inequalities and cost manupulation. - Provision of resources (based on economics and political direction). - Cultural difference in needs, values, use and access. - Vulnerability of particular individuals.	(No specific explanation)	(Shook & Giordano, 2024): neuroscience
An evidence crisis as a result of premature marketing approval and commercialization of expensive approaches based on insufficient scientific rationale and clinical evidence, facilitated by regulatory authority initiatives for accelerated access.	Hospital exemption (like UK).	(Fears et al., 2021)
Overall		
Public acceptance - Perceived breach of public trust if the expectations of public-private partnerships are not clearly spelled out; that is, a for-profit entity answering to the demands of private capital might define public goals quite differently than not-for-profit or academic researchers and thus there is a question about what constitutes a return on the taxpayers' investment in science. - Public concern and mistrust of government technology policies would be on the rise in Japan (in the wake of the Fukushima nuclear disaster, there has been a persistent perception of lack of community involvement in decisions that affect citizens' health and lives).	- There is a need for public policy discussion more broadly to resolve potential conflicts between stated priorities of translational science and novel ways to achieve translation into public goods through a variety of public-private partnerships, for-profit organizations or other forms. - Facilitate internationally agreed frameworks for robust, interdisciplinary assessment of research protocols and evidence collection. - Renewed and inclusive efforts world-wide involving multiple stakeholders and researchers, regardless of their locations. Scientists must also engage with policy makers. - The ELSI community should play a role both by studying the impact of new popular media, such as SNS, and engaging directly with the broader public and patient	(Hogle, 2014) (Fears et al., 2021) (Illes et al., 2017)

	communities through participation in virtual communities and networks and take effort not only to point out misinformation or ethical concerns, but also serve to highlight new opportunities for the field to better integrate public and patient perspectives and interact with society.	
Difficulties for policy-makers to catch up with rapid advances in biomedical R&D.	Leaders in the international regenerative medicine community should undertake a broad survey of relevant regulations relating to the R&D of regenerative medicine and related biomedical technologies, issue policy statements, and consider action in reforming extant policies.	(Illes et al., 2017)

4.2. Ethical Issues

When looking at specific issues in Japan, several problems with the structure stipulated by law have been identified. Fujita et al. (2022) point out that Law 3 does not prohibit agents from providing regenerative medicine interventions to patients as long as they follow the process the law prescribes. This situation is "unusual" compared to other countries which are struggling to control clinics that intend to find loopholes in regulations (Fijita et al., 2022). In addition, there is no scientific verification requirement during the process (Fujita et al., 2022), which is necessary to produce and sell the technology as products (regarding Law 4). Takashima et al. (2021) consider this situation to be caused by the lack of clarification of the concept of “ensuring safety.”

The certified committee and the certified special committee, which review the provision plan of regenerative medicine by Law 3, are sometimes considered to be problematic points. They consist of specialists in regenerative medicine and technology or law who have high skills for assessment and are outsiders. In addition, they have to include members who have experience in work related to the protection of persons undergoing regenerative medicine or respect for human rights in the field of medicine or healthcare and who have knowledge about bioethics. However, a report from outside Japan analysed that the committees lack transparency and independence (Lysaght & Sugii, 2016, as cited in Fujita et al., 2022). Ikka et al. (2023) also raise concerns about the committee’s independence, integrity, and quality of reviews in several cases.

The literature contains some concerns regarding the system in Japan that should be mentioned here, while they are not indicated as issues. One concern is related to Law 4; in fact, there are relatively few successful examples (products/companies) so far, and the market is still immature in Japan. A major challenge in establishing it as a business model is the cost of development and production (Igarashi & Sato, 2018). Another one is related to the guidelines; they do not have the power to enforce, and there is no monitoring governance system in the government. Each institution is to govern itself so that its research aligns with the guidelines. In addition, the guidelines may end up being a procedural manual to be followed blindly due to their power, lengthy and complex structure and description (Ikka, 2018). Besides, while Law 2 and Law 3 stipulate that "bioethical considerations" must be taken into account, the meaning of these words remains ambiguous. Ikka (2017, as cited in Shineha, 2020) says that “considerations” seem to mean only general topics such as informed consent, protection of personal information, and risk and benefit assessment. Shineha (2020) also states that ethical considerations are generally included in the process argument and treated as the periphery based on his studies.

As practical issues in the Treatment/Manufacturing products phase in Table 4-1, hospitals face challenges in being ready to provide regenerative medicine, such as changing workflows to accommodate new regenerative medicine products and treatment (Gardner et al., 2015). Pharmaceutical companies also face hurdles of financial burdens and risks when manufacturing products (Zamborský et al., 2018; Shook & Giordano, 2024; Gardner et al., 2015; Sugarman et al., 2018). However, these are related to the business phase, where the government (especially MHLW and MEXT) should not intervene so much. Therefore, these issues are considered a low priority in this research.

4.3. Possible Approaches to the Issues

Some of the possible suggestions in Table 4-1 were found in the literature that mentions other countries' policies. Here is an additional explanation about them.

One of the suggestions proposed by Gardner et al. (2015) is adaptive trialling, while the current situation in Japan can be categorised as one of the ways of adaptive trialling. In terms of other systems related to adaptive trialling suggested in the literature, the U.K. and EU have a different system of conditional market approval from Japan. They allow for the provision of cellular medicinal products to individual patients in a European hospital under the exclusive professional responsibility of a doctor. This approach is stricter than

the relatively wide approval of the provision in Japan and more agnostic than that of Japan. It does not intend to have high expectations but pursues a less risky and more beneficial measure (Umemura & Morrison, 2021). However, they also have a challenge with the variation in the criteria of the balance of benefits and risks (Fears et al., 2021).

Japan's premise or starting point of regulations is unique compared to other countries' systems regarding the translation of regenerative medicine. The regulations in Japan were created by the government's and professional communities' desire to take a global lead in regenerative medicine. On the other hand, the system in the U.S., which shifts to allow flexible pathways to implement regenerative medicine, has been driven by long-term advocacy and pressure from patients and the pharmaceutical industry (Rosemann et al., 2018; Sipp et al., 2017). The U.S. decided to change the policy based on the health consumer needs, contrary to Japan's partly top-down policy. This fact implies that broad public policy discussion could be one approach for Japan to mainly communication and other issues, which is also suggested by Hermerén (2021) and Hogle (2014) in general, before the wider distribution of regenerative medicine to embrace the ethical considerations regarding societal influences, considering public acceptance.

5. Result III: Online Questionnaire and Supplementary Interview

This chapter briefly provides the results of the online questionnaire and supplementary interview. The summary of answers for each question is presented in Appendix 3. Here is mainly the explanation of how the results of the online questionnaire and supplementary interview were utilised for the analysis. Overall, answers were aligned with the findings from literature reviews 1 and 2. There was no significant difference, but some information to be added to the results of the literature reviews.

5.1. Perception of the current Japanese situation

Perceptions of changing the current Japanese situation of the translation of regenerative medicine tended to be neutral or negative. Also, most participants in the questionnaire were neutral or had no priorities when comparing critical ethical aspects: safety, efficacy, and prompt provision. At the same time, there were relatively negative perceptions against focusing on prompt patient provision more than now.

These results suggest a relatively negative stance towards changing priorities in the current Japanese context.

5.2. Actors' Positions

The results of actors' relative influences on addressing general ethical issues in the translation of regenerative medicine in Japan showed that the government and related organisations have the strongest influence compared to other actors. Research institutions/hospitals and researchers/doctors were evaluated as equal or slightly less influential than the government and related organisations. In terms of the categories of participants, which include Researcher or Doctor, Promoter or Regulator, and Patient or Public, Participants who are Researchers or Doctors tend to identify research institutions/hospitals and researchers/doctors as influential as the government and related organisations, while other participants answered that the government and related organisations are the most influential and institutions/hospitals and researchers/doctors are the second. Since the number of participants is small, it is difficult to say something from that. However, there might be a perspective gap between practitioners and others in the translation of regenerative medicine. Since the answers about pharmaceutical companies varied, they did not affect the findings of literature reviews. The general public's influence was assumed to be weaker than others. While there was a comment that patients and the public are as influential as others if some triggers aggregate them, few examples were found in literature reviews. There is also a comment that their influence has been limited in Japan. Hence, it can be said that the trend of the questionnaire and interview results is following with the analysis in Sections 3.3 and 3.4.

5.3. Ethical Issues and Possible Approaches

Ethical issues and possible approaches raised in responses to the questionnaire were related to those identified through literature reviews in Section 4.1. “Online questionnaire” has been added in the column “Sources” of rows of relevant issues and approaches in Table 4.1.

As additional information, a shortage of job opportunities for ethical professionals was raised. This might be caused by the fact that the value or impact of ethical considerations and ethical professionals would create is unclear for society and researchers in regenerative medicine, and also, there are gaps between ethical professionals' interests and the expectations of others.

6. Discussion

This chapter discusses all of the findings so far. Section 6.1 synthesises the results from previous chapters to suggest steps to improve the approaches to ethical consideration in Japan, which is the answer to sub-question 4. Then, in Section 6.2, the results are organised, and a conceptual framework is constructed as a recommendation for Japan to answer the main question of this research. In this way, while the literature reviewed so far has provided issues, suggestions and ideas based on observations of the situation around regenerative medicine in Japan or in general, this research synthesises and examines findings from such literature and the questionnaire, incorporating a practical perspective and considering the context of current Japan's policies, to find feasible ways to improve the approach that Japan could take.

6.1. Synthesis of Findings

In this section, the findings are synthesised to identify a set of steps for Japan to incorporate ethical considerations into the translation of regenerative medicine step by step.

Target Points

First, review the focused process of this research and critical actors in the system of the translation of regenerative medicine in Japan.

To incorporate ethical considerations in Japan's current system of translation of regenerative medicine, the process between clinical research and the starting point of marketing should be focused on. This process does not currently have an anchor for incorporating ethical considerations, such as clear uniformed documents or one responsible organisation, so intervening in this process could effectively affect the whole system.

The actors who are influential in the system are the related ministries, MHLW and MEXT, which regulate and promote the translation of regenerative medicine in Japan, and large hospitals owned by universities, which work together or are the same as universities and national institutions that own their hospitals, as practical players in the translation of regenerative medicine.

Relations among Ethical Issues

Next, within the key process, ethical issues were explored deeply to understand their relations for finding the leverage points.

While the identified ethical issues in the translation of regenerative medicine (Table 4-1) are broad, some of them can be connected with others. Exploring these relations could lead to a compelling synthesis of findings and finding room to address issues effectively. First, look at specific issues related to Japan directly and then focus on related issues.

Lack of scientific verification and standardised process, scientific limitations

Regarding Law 3, as already mentioned, the lack of scientific verification in the process of the provision of regenerative medicine is one of the main issues (Fujita et al., 2022; Takashima et al., 2021; Ikka et al., 2023; Sipp & Okano, 2018; Cyranoski, 2019). Besides, the certified (special) committees stipulated in Law 3 to review the provision plans have concerns about their independence, integrity and quality. To address this committee's possible problem, the government plans to amend Law 3 so that the authority will establish guidelines for operating the committees and make duties for the committees to report their conditions constantly and be examined when the authority finds it necessary (Ministry of Health, Labour and Welfare, 2024). However, one cause of this issue is the lack of a standardised translation process for regenerative medicine worldwide (Chen et al., 2012; Touré et al., 2018; Gardner et al., 2015). Moreover, this lack is

caused by scientific limitations, such as uncertainties about reactions and risks that are difficult to address with current technology. As listed as other issues in Table 4-1, regenerative medicine has difficulty in building the safety and efficacy criteria due to the heterogeneity and novelty of regenerative medicine and possible differences in the environment between tests and practical settings (Zamborský et al., 2018; Hermerén, 2021; Riva & Petrini, 2019; Gardner et al., 2015; Niemansburg et al., 2014; Shook & Giordano, 2024; De Kanter et al., 2023). Since emerging technologies always start from an unproven status, this difficulty might not be rare. However, there is a trigger which encourages the problematic situation.

That is confusion or lack of definition between the words “unproven,” “innovative”, and “experimental” in the current Japanese regulations (Fujita et al., 2022; Takashima et al., 2021). According to the study by Takashima et al. (2021), “unproven” is used when describing conditions under which safety and/or efficacy are uncertain or unknown in a narrow sense, while “innovative” presents the novelty of the technology, which differs from the standard or existing things and is not yet validated. This confusion leads to unclear definitions and distinctions between “research” and “treatment” (Fujita et al., 2022).

Namely, the current regulation allows both unproven treatments that need to be conducted research and innovative treatments to be regarded as treatments. These unclear definitions encourage the issues caused by the newness of emerging technologies and, therefore, could be identified as the key point of the issues regarding Law 3. By the way, the International Society for Stem Cell Research (ISSCR) established guidelines that contain the limited conditions under which medical innovations can be provided (International Society for Stem Cell Research, 2021). However, since the definitions of "innovative" and the distinctions between "research" and "treatment" are unclear in Japan, the principles of these guidelines may not be shared among hospitals/clinics which provide patients with regenerative medicine (Takashima et al., 2021).

Communication issues

The situation under Law 3 also leads to general issues related to communication with patients/participants and donors and the way to obtain consent (Hermerén, 2021; Zamborský et al., 2018; De Kanter et al., 2023; Riva & Petrini, 2019). Due to uncertainties and further scientific innovation, especially in the clinical research phases, it is challenging to determine the optimal type of consent. This is also connected with patients’ misunderstandings and unawareness of risks due to the high expectations of regenerative medicine technology (Zamborský et al., 2018).

Inappropriate provision

In terms of issues not specific to Japan, inappropriate clinics which provide regenerative medicine as treatment despite less evidence of effectiveness are raised as issues (Shook & Giordano, 2024; Sugarman et al., 2018; Lysaght et al., 2018; Ventura-Juncá, 2011; Fears et al., 2021). This happens when there are loopholes in regulations, and the loopholes are sometimes caused by the separation of regulatory responsibilities and few guidelines (Sugarman et al., 2018). Looking at the situation in Japan, Law 3 is criticised that it may allow such inappropriate clinics (Fujita et al., 2022; Takashima et al., 2021; Ikka et al., 2023; Sipp & Okano, 2018; Cyranoski, 2019). The distinctions between “research” and “treatment” are ambiguous in Law 3 and related regulations, and the scope of the Ethical guidelines is only in the “research” phase and is not legally binding. Therefore, the bridging process between research and treatment/product, which Law 3 is considered to target, is blurred from an ethical perspective and does not have any anchor for ethical considerations. Moreover, this bridging process is overseen by multiple ministries. Hence, the argument about inappropriate clinics by Sugarman et al. (2018) can apply to the situation in Japan.

Related to Law 4, which requires the results of clinical tests of the products, Law 3’s weak evidentiary requirement may discourage patients from participating in tests and practitioners from conducting tests (Sipp & Okano, 2018). Related to public trust, trust in the experts' testimonies about the safety of regenerative medicine in Japan is relatively lower than in other countries, such as the U.S. and the U.K., partly because of the big fabrication issues concerning regenerative medicine in Japan (Shineha et al.,

2022). Since trust has been pointed out as one of the most critical factors for social acceptance and participation in emerging technologies (Shineha et al., 2018; Drummond & Fischhoff, 2017, as cited in Shineha et al., 2022), the current condition between regenerative medicine and the public in Japan is challenging.

Issues related to the conditional approval system

In terms of Law 4, the accelerated approval process (conditional approval) has pros and cons, while some countries employ similar systems. It allows patients to access regenerative medicine products promptly, which could address an ethical issue, such as the unfair distribution of treatment/products when translating new technologies (Hermerén, 2021; Shook & Giordano, 2024). Yet, the clinical/patient benefits, which means living longer or better than that without the intervention, are not evaluated enough as a result of the low evidentiary standards (Cyranoski, 2019; Lysaght, 2017). In addition, insurance coverage of such products with conditional marketing approval may burden the already severe healthcare system in Japan, including unequal chance for patients to access products and unfair distribution of benefits from taxpayers' perspective (Lysaght, 2017).

Health technology assessment has been adopted in the Japanese healthcare system since 2019. It assesses selected products after their distribution and collection of enough data to evaluate their efficacy and overall costs. This design, in which products are covered by the insurance at first and then assessed, intends not to hinder the patient's prompt access to the products (Ministry of Health, Labour and Welfare, 2021). However, it still burdens the healthcare system during the distribution.

Also, the system, which allows products with evidence under low evidentiary standards to be provided, may not be accepted by the public favourably (Lysaght, 2017). The same goes for Law 3. Moreover, especially in Japan, after the Fukushima 1st nuclear power plant accidents, the communities are sensitive to the involvement in a discussion of technologies that affect citizens' health and lives (Hogle, 2014). These, including the burden on the social healthcare system, lead to public concern/acceptance and trust in government technology policies and science itself (Lysaght, 2017), which have the potential power to change policies when the movement becomes wide and aggregated.

Extent of future research

Related to the public impact, concerns about the impacts of future research in regenerative medicine, such as manufacturing brains by using regenerative medicine technology, arose in the literature (De Kanter et al., 2023; Volarevic et al., 2018) and the online questionnaire. Regenerative medicine could manufacture elements of the human body, including brains, in theory, which might lead to cloning or artificial humans. The ethical limitation of research in the future would need to be argued, while it needs not only regenerative medicine researchers but also ethical professionals. These concerns are related to the issues of biosecurity, human welfare, experience and identity, which may have influences on society through the development and wide distribution of regenerative medicine in the near future, as mentioned by De Kanter et al. (2023), Hogle (2014), and Fears et al. (2021).

Shortage of ethical professionals

One practical issue which is not related to Law 3 and Law 4 directly but is important is the lack of professionals with the knowledge required for the translation of regenerative medicine, such as regulations, ethics, and cost management in the research sector. This is mentioned in the questionnaire as well as the literature (Chen et al. ,2012; Matsuyama, 2013; Tsubouchi et al., 2008). This lack discourages establishing a standardised process for the translation of regenerative medicine and also causes unclear ethical anchors in the key process. In the questionnaire, there is also a concern about the few chances of working for ethics professionals in Japan. This concern would discourage people from being ethical professionals and result in a shortage of such professionals. Since there are few professionals, the job chances naturally become small. Namely, there is a negative loop of the professional shortage. This may be partly because the

awareness of ethical perspective regarding science and technologies in Japan arose relatively late compared to other countries in Europe and North America (Center for Research and Development Strategy, Japan Science and Technology Agency, 2022), and the focus of ethical considerations have been prioritised on the science integrity due to some actual cases of misconducts in healthcare and medical research that happened in Japan (Ikka, 2018). Combined with those, people might not yet understand the practical importance of ethical considerations. While there are examples in Europe and North America that Japan can follow, as mentioned above, people already perceive ethical considerations as included in the process argument and not placed at the centre or main way of their research (Shineha, 2020), as mentioned in Section 4.2. Hence, the unclear results or effects (from practitioners' perspectives in Japan) of taking ethical considerations into account discourage hospitals or research institutions from continuously involving ethics professionals in research projects or creating job opportunities for them. This could be applied not only to the regenerative medicine field but also to other emerging technologies.

According to the arguments related to Law 3 and Law 4, the regulations are struggling with the dilemma of developing regenerative medicine to ensure patients' prompt access to it and evidence-based medicine, connecting to other issues. Summarising the argument above, the relations among issues are shown as a diagram (Figure 5-1).

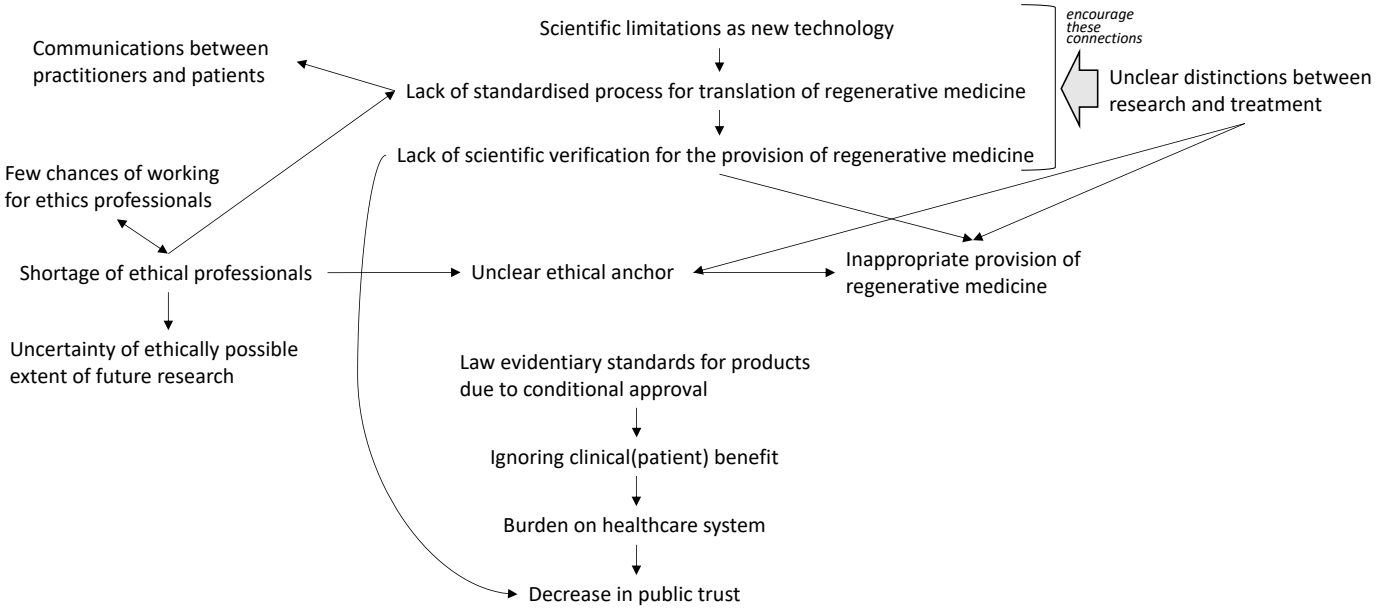


Figure 5-1. Relations among issues related to the translation of regenerative medicine in Japan

Other than issues directly related to issues in Japan, some are identified through the literature reviews. In this research, these can be categorised as the second priority compared to the issues argued above as directly related to Japan.

Issues related to scientific uncertainties, combined with high expectations of regenerative medicine, cause researchers to be anxious about proceeding with their research with humans (Hogle, 2014). This includes the appropriate selection of research participants, which is a general ethical issue (Riva & Petrini, 2019; Niemansburg et al., 2014). Also, ethical committees that review the research, which are usually established in research institutions and consist of experts, feel too much pressure from the public's and the government's high expectations for approval (Takashima et al., 2018).

On the other hand, the scientific integrity of researchers' appropriate conducting research and the review committees' independence and quality arise as one issue (Hermerén, 2021; Zamborský et al., 2018; De Kanter et al., 2023; Niemansburg et al., 2014; Chen et al., 2012). Since ethical viewpoints in Japan have focused on scientific integrity so far, as mentioned above, these issues will not be addressed in this research.

Possible Approaches to Main Issues in Japan

Next, based on possible approaches identified in Chapter 4, the feasible ways for Japan to address the issues elaborated in the previous sub-section were explored.

Based on the questionnaire, participants considered there was no strong need to change the situation in Japan, especially regarding the priority of discussed points, i.e., safety, efficacy, and prompt provision of regenerative medicine. While the questionnaire's results were very limited, considering the global trend of developing regenerative medicine and the practical feasibility of changing policies, the current Japanese approach aiming to accelerate the translation of regenerative medicine should be maintained as much as possible. Assuming this, the approach to ethical considerations needs to be improved.

Interdisciplinary research project for standardised process

To address most of the issues, the most direct suggestion from the literature is to establish clear standards through the collaboration of experts in various fields related to the translation of regenerative medicine (Riva & Petrini, 2019; Takashima et al., 2018; Chen et al., 2012; Zamborský et al., 2018; Gardner et al., 2015). However, this is also the most difficult since the technology is novel, which means there are few experts or insufficient scientific knowledge to make clear criteria. The situation is going around in circles while the research is gradually developing. Therefore, it is difficult to establish standards immediately only by the interdisciplinary research project in practice. The issue of patient/participant selection is in the same situation.

Nevertheless, aiming to establish standards at either the national or international level and incorporating interdisciplinary perspectives are important in the long term. Interdisciplinary teams working is also indicated in the study of other medical technology: Ankeny et al. (2021) analyse the ethical matters regarding iBlastoids using viewpoints of responsible research and innovation (RRI) as a case of emerging technology and highlight the importance of interdisciplinary dialogues for the research of emerging technologies. They conclude that issues regarding emerging technologies, such as how to understand intention and anticipation in serendipitous and novel discoveries related to emerging technologies and the ethical and social implications of the mission-based science of emerging technologies, can only be understood by interdisciplinary teams working together from the early stages of research and throughout the research process.

Interdisciplinary research project for issues related to ethical professionals and communication

Related to the incorporation of experts in various fields, research projects, which are designed to involve not only regenerative medicine researchers but also professionals in ethics and entrepreneurship (Niemansburg et al., 2014; Chen et al., 2012; Fears et al., 2021), could mitigate each stakeholder's pressures and become a chance for education or training, tackling the shortage of experts with the knowledge required for translating regenerative medicine (Hermerén, 2021; Chen et al., 2012). Ethics professionals could find the practical value of ethics in the translation of regenerative medicine by working in translational research with researchers of other disciplines. Other researchers would also realise ethical perspectives thanks to the ethics professionals, which they did not have before, leading to incorporating such perspectives by themselves. This small step would lead to dedicated communication between practitioners and patients/participants in clinical research, as suggested in literature (Chen et al., 2012) and the results of the questionnaire. Furthermore, these would lead to job opportunities for ethical professionals and addressing the shortage of them in the long term.

The three ministries, MHLW, MEXT, and METI, have already launched a research project with the national budget in Japan. This project aims to promote research and development in regenerative medicine, incorporating multidisciplinary researchers and experts as a team (for example, the project mentioned in Japan Science and Technology Agency, n.d.-b). Given that the whole budget is shrinking, and the national bond is increasing, accelerating or scaling up such a project is unrealistic for the government. Therefore, the government can only show the model case of the research projects incorporating multidisciplinary

experts so that stakeholders in practitioners' groups will follow the model by themselves. While these projects' outcomes have not had a drastic influence on the healthcare field so far, continuous effort is important in the long term.

Clear distinction between research and treatment and introducing anchors

Looking at the root cause of the specific issues of Law 3, possible suggestions are clearly distinguishing between research and therapy (treatment) and introducing systems from other countries that are modelled on Japan but differ (Fujita et al., 2022; Takashima et al., 2021; Ikka et al., 2023; Sipp & Okano, 2018; Cyranoski, 2019). Especially the former can be adopted through the guidelines of the certified (special) committees in the provision process stipulated in Law 3, which are planned to be established as part of the law amendment. Under the current regulations, practitioners decide whether their activities are treated as research or treatment, which causes confusion. To address this situation, for example, by the committees' examination and decision of the distinction based on the new guidelines, at least the borders between research and treatment of regenerative medicine can be clear.

This clear border enables practitioners to find the appropriate regulations or ethical guidelines established by the government or the international organisation as the ethical anchor for their research or treatment. If the appropriate guidelines do not exist, the ministries should engage in establishing them, which should be relatively feasible compared to making the whole standards since the target point is clear. Also, interdisciplinary research projects could encourage or help the government to establish or introduce ethical anchors through their experiences in the practical field and ethical professionals' works, as mentioned above.

The stricter limits or monitoring by the authorities, like the systems of other countries, such as Taiwan (Ikka et al., 2023), will be considered after the clear distinction. Also, it is difficult for the government or society in Japan to force companies and researchers to assume additional responsibilities or tasks in the provision of regenerative medicine (which is suggested by Riva & Petrini (2019) and Sipp & Okano (2018)) since such communities have collected knowledge and experiences but not practical power and resources.

Stricter regulation or public discussion

To address the possible issues related to Law 4, i.e., the distribution of products assessed with low evidentiary standards and other issues caused by this, scientifically strict selection for conditional approval by regulations is suggested (Lysaght, 2017; Cyranoski, 2019). In current Japanese regulation (Law 4), there are no classifications of risks within "regenerative medicine products." Also, strict health technology assessment for clinical benefits is recommended to address this issue (Lysaght, 2017; Cyranoski, 2019). However, the suggestions do not take into account the prompt access of patients, which the current regulation prioritises. This current regulation's priority has been decided in a relatively top-down process. Therefore, considering the situation in the U.S. and suggestions in the literature and questionnaire results, Japan's government should make an effort to have a broad public policy discussion to consider the priority of translating regenerative medicine before just changing the direction of regulations.

Also, public discussion would contribute to considering ethical limitations or extent of future research in regenerative medicine, i.e., how much we can proceed with research in regenerative medicine ethically, as suggested by literature (De Kanter et al., 2023) and the results of the questionnaire. Ankeny et al. (2021) state that it is crucial to reflexively engage with multiple actors, including the public, in order to facilitate innovative and transformative scientific research in rapidly changing domains and prepare our minds for change. This idea could be applied to continuously advancing regenerative medicine.

Research design

Apart from the specific topics in Japan, a clear distinction between research and treatment would contribute to the design of research projects. A robust design may mitigate researchers' anxieties and eliminate spaces for accidental inappropriate research. The aim of research and test criteria, for example,

distinguishing mandatory tests for safety and desirable tests for scientific knowledge (Takashima et al., 2018), would be identified, while this distinguishment may also be controversial.

Based on the reflections above, relations among issues and possible approaches to them are shown as a diagram (Figure 5-2).

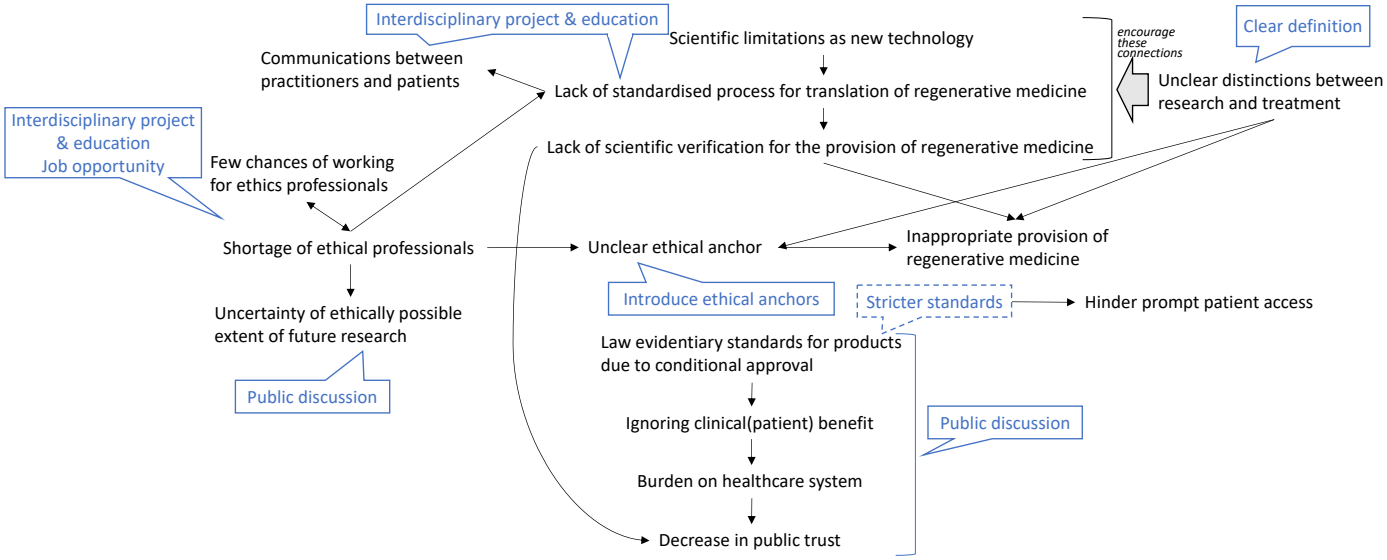


Figure 5-2. Relations among issues and possible approaches to the issues. Blue rectangular callouts mean the possible approaches to the issues.

Responsibility for Each Approach

Based on the findings from the Actor analysis in Section 3.3, responsibility for each approach identified so far in Figure 5-2 was considered to make the set of steps more practical.

- Making clear definitions: As already mentioned above, since this approach would be a part of the process by Law 3, which is overseen MHLW, the responsibility is on MHLW.
- Introducing ethical guidelines to address unclear ethical anchor: This issue exists between clinical research and treatment/products. Therefore, MHLW and MEXT take responsibility for covering both research and treatment in terms of their jurisdictions.
- Public discussion to address the decrease in public trust: This discussion needs to talk about the regulatory balance of prompt patient access, safety, efficacy, and other important points related to regenerative medicine products. Those products are overseen by MHLW and related organisations. Therefore, MHLW has the responsibility.
- Public discussion for future research: The issue would occur from the phase of (mainly basic) research, which is MEXT's jurisdiction. Hence, MEXT is responsible for this approach.
- Interdisciplinary project and education for communications between practitioners and patients: The ministries have already launched the projects and would show them as a model case. Therefore, this time, large hospitals and universities and national research institutions should take the initiative to utilise such model cases for their own projects.
- Interdisciplinary project and education for addressing the shortage of ethical professionals: Similar to the previous suggestion, large hospitals and universities and national research institutions have the main responsibility.

Figure 5-3 shows the main responsibilities of each approach in green letters.

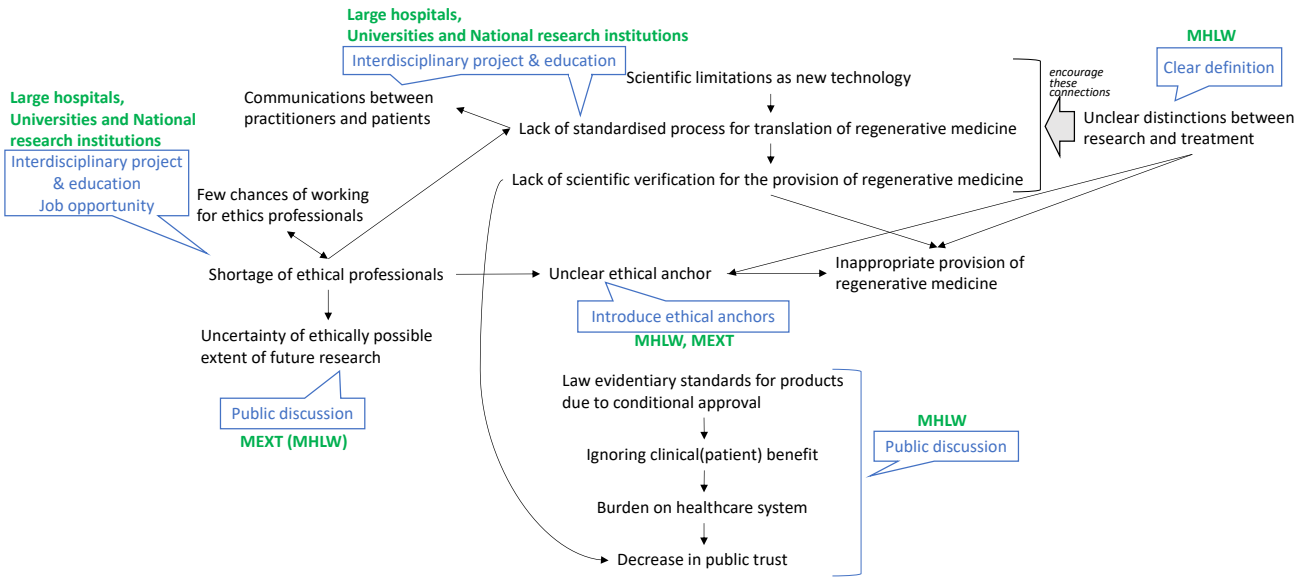


Figure 5-3. Relations among issues and possible approaches with responsible actors. Green letters are actors who are responsible for approaches.

Steps to Improve the Approach to Ethical Considerations

Approaches examined in the previous sections (Figure 5-3) will be elaborated as a set of steps to incorporate ethical considerations into the translation of regenerative medicine in Japan.

In summary, the issues that arise in the translation of regenerative medicine in Japan are encouraged by unclear definitions of important terms in regulations, such as “unproven,” “innovative,” “research,” and “treatment.” This ambiguous situation causes players on the ground to have difficulties finding an anchor for conducting research or treatment with ethical considerations in the process between clinical research and the starting point of marketing, namely the process where research and treatment are confused in practice. Therefore, the first step is to make clear distinctions between those words, and MHLW is responsible for this step.

By clear definitions of terms as the first step, the certified (special) committees are to categorise the provision plans submitted by hospitals or clinics as research or treatment, and the practitioners could find the appropriate regulations or guidelines and responsible organisations to follow as ethical anchors. If such appropriate guidelines do not exist, MHLW and MEXT should introduce them by reviewing the existing guidelines or following the international guidelines. This is the second step.

Since no actor intends to hinder ethical considerations in the translation of regenerative medicine, and issues seem to arise from the current system as a whole, the steps incorporating ethical considerations into the translation should be considered as the system. In addition, as mentioned above, large hospitals owned by universities are key actors in incorporating ethical considerations. Hence, it is important to let them be involved with the approach to realise in practice. As the third step, but in parallel with clarifying the definitions of important words, such as research and treatment, hospitals should present their reflections on the current regulations and guidelines by aggregating the information from researchers and doctors who are conducting research or treatment practically. MHLW and MEXT could modify the guidelines based on the reflections from practitioners (not only more flexible but also stricter), which would benefit both ministries and practitioners.

Communication between ministries and hospitals is necessary to realise this third step, though this communication should have been tried so far. As the broker, researchers’ communities and AMED could assist with this communication, which is the third step. For AMED, it would be especially possible to collect opinions and flexibility when conducting clinical research from researchers and doctors involved with the

projects, which are supported by the national budget and managed by AMED, while the number of such projects is limited. Through this cycle of steps, Japan could incorporate ethical considerations into the translation of regenerative medicine in a better way.

In parallel to the third step, large hospitals owned by universities and universities/national research institutions own their hospitals also need to utilise experiences and results of existing interdisciplinary research projects, especially which the ministries support, for their research project and treatment. These model projects should show hints to address challenges related to communication, process of the translation, and the importance of ethical perspectives.

On the other hand, considering the small number of (conditional) approval cases of regenerative medicine products and the regenerative medicine industry in Japan that is not thriving yet based on literature, the issues related to the approval process of regenerative medicine products indicated in the literature are not as critical as they need to be addressed urgently. Therefore, the approach for addressing ethical issues could be not to modify the current regulations (to make them stricter) but to focus on public understanding or collecting opinions of people who are not involved in translating regenerative medicine directly. While the current regulations seem to prioritise patients' prompt access to regenerative medicine based on a partly top-down policy-making process, ministries, especially MHLW, should understand perceptions from the bottom. This time, communication between regulators and involved people is required. Ishihara et al. (2016) suggest the importance of a social approach to improving QOL in society by developing the public understanding of regenerative medicine for establishing systems to promote this field in Japan. Studies and general opinions often indicate the importance of communication involving the public, but it has been difficult to implement in practice. This is because there are few facilitators and few motivations (usually, people are busy with their business) (Shineha, 2016; Committee on Social Cooperation in Science and Technology, 2019), while some topics which have had a significant impact on society, like nuclear power, tend to get people's attention. There was also a comment in the interview that only after experiencing a large problem do people realise their daily lives are connected with technology and the importance of incorporating ethical considerations into the use of new technologies. As the most realistic first step for this, careful explanations for patients by practitioners and informed consent before providing products are essential, though this is hoped to have already been done. This can be supported by practical lessons through interdisciplinary projects which ethics professionals join and education. The important thing is that the balance or priorities of current regulations or policies are disseminated among at least people involved with regenerative medicine. Besides, it is crucial that patients who receive regenerative medicine as treatment or participants in clinical research understand its benefits and risks and make decisions. Also, there is an example of a platform to bridge between patients and researchers/doctors to promote clinical research[2], while the scope is based on diseases (some rare diseases) and is not directly connected to regenerative medicine. Since this platform could reach patients who are not involved with the research or treatment now, it could be a way to make communication broader as the next step. Hospitals would also be aware of the importance of ethics professionals through these practices, which would lead to job opportunities for the professionals and active education.

Broader communication is desired as the next step in the near future in this research. Some universities and research institutions which have ethics professionals have held public discussions about regenerative medicine for various purposes, such as promoting the public's understanding and collecting public opinions[3]. One researcher's community has facilitated interactive events between researchers and the public, including patients, to cultivate public acceptance of regenerative medicine with partial support from related ministries (The Japanese Society for Regenerative Medicine, 2024). These activities contribute to a

[2] RUDY JAPAN aims to collect information on patients with rare diseases via the online website to promote understanding of such diseases. The project started at the University of Oxford in the U.K., and Osaka University in Japan has set up and carried out a Japanese version, collaborating with the project in the U.K. https://rudyjapan.info

[3] For example, the Center for iPS Cell Research and Application, Kyoto University, is holding a symposium targeting the public, including high school students, to introduce research using iPS cells and facilitate interaction between researchers and the public. https://www.cira.kyoto-u.ac.jp/j/pressrelease/seminar/240515-000000.html

bottom-up policy-making process, which would benefit both the public, who perceive the current situation around regenerative medicine negatively concerning ethical issues, and ministries, which struggle with balancing ethical priorities for translating regenerative medicine. As a further step, while learning from other countries' examples, Japan needs to create opportunities for a broad public discussion about emerging technologies, how much extent we can explore from an ethical perspective, and how much they should be promoted by the public budget.

6.2. Recommendations

By reviewing the activities and responsible actors of each step identified in Section 5.1 and clarifying the interactions of activities and actors, the steps identified in Section 5.1 can be presented as a conceptual framework for the desirable system between clinical research and pre-marketing, which would help Japan to incorporate ethical considerations into the translation of regenerative medicine (Figure 5-4).

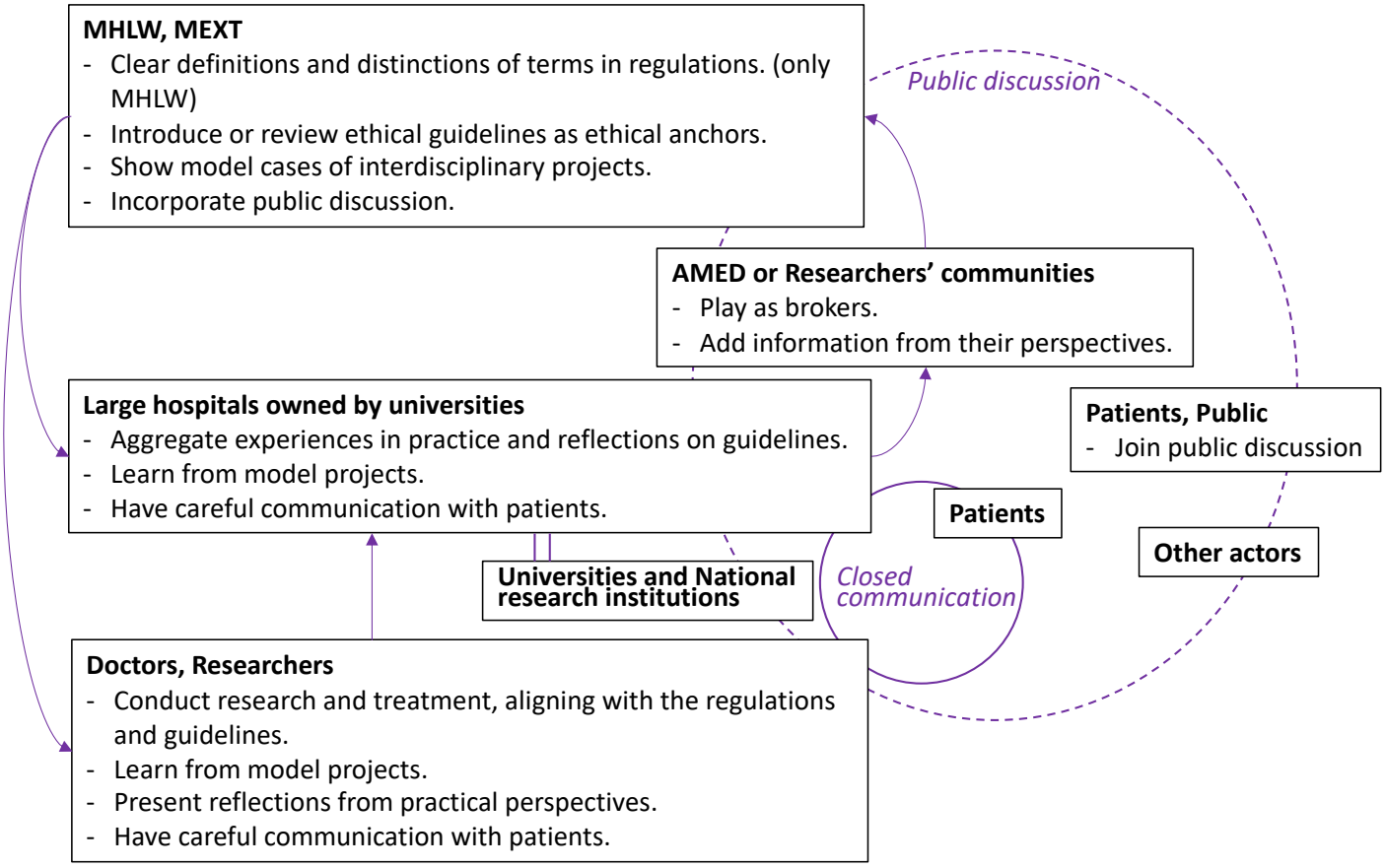


Figure 5-4. The framework of the desirable system in Japan

Since the translation of regenerative medicine in Japan involves multiple actors, the recommendations target not one but multiple actors, mainly the key actors; MHLW, MEXT, large hospitals owned by universities, and universities and national research institutions own their hospitals. Also, considering that Japan has cultivated the environment aiming to prompt patient access to regenerative medicine as its policy and the perceptions of participants in the online questionnaire, it is not realistic to drastically change the policy's direction and current regulations. Hence, the recommendations aim to incorporate ethical considerations into the current translation of regenerative medicine in Japan.

First of all, MHLW should clearly define and distinguish the terms in the current regulations, such as "unproven," "innovative," "research," and "treatment." Then, MHLW, MEXT, and large hospitals owned by universities are expected to take a few additional considerations or actions to incorporate ethical perspectives in the system for the translation of regenerative medicine. Hospitals should aggregate

experiences in practice and reflections on guidelines to enable the ministries to review guidelines if necessary. Also, hospitals should elaborate their provision plans, including communication with patients, and research projects related to regenerative medicine, which usually work together with universities or national research institutions where hospitals connect, by learning from the model cases of interdisciplinary research projects that the ministries have presented. Ministries should collect opinions from practitioners by sometimes cooperating with AMED or researchers' communities and utilise such information to introduce or review ethical guidelines.

Other than the key actors, doctors and researchers are expected to work with the government's policy and their institutions by presenting reflections on guidelines from practical experiences and incorporating the lessons from interdisciplinary model cases when promoting regenerative medicine, as expected in Law 2.

Public discussion, presented with dot lines in Figure 5-4, is recommended as a further step. Translating regenerative medicine is connected to societal challenges, and it is difficult to proceed without public acceptance. Not only patients but also the public should be aware of this and join the discussion for better approaches to ethical consideration in Japan. Ministries also need to incorporate such discussions to make policy from the bottom-up perspective.

7. Conclusion

This final chapter summarises this research's process and final conclusion. It also lists its limitations and future prospects.

7.1. Conclusion

This research explored how to incorporate ethical considerations into the translation of regenerative medicine in Japan, a technological response to multiple healthcare problems. It proceeded by answering the four sub-questions through a mixed qualitative analysis and finally answering the main question, "*How can ethical considerations be incorporated into the translation of regenerative medicine in Japan?"*

To answer the first sub-question, "*What are the key processes and actors involved in translating regenerative medicine in Japan?"* a literature review, including grey literature, and an online questionnaire with a supplementary interview were conducted. The key processes were identified as those from the clinical research phase to the start of marketing. In this process, there is no solid ethical anchor to be followed by practitioners. Due to Japan's situation involving multiple actors, there are also multiple key actors. Based on the Actor analysis using information from the literature and websites of actors, MHLW and MEXT, as regulators, and large hospitals owned by universities and universities/national research institutions who own their hospitals, as practitioners, are considered the key actors.

The answer to the second sub-question, "*What ethical issues could arise in the translation of regenerative medicine in Japan?*" was identified with the answer to the third sub-question, "*How could ethical issues that would arise in the translation of regenerative medicine in Japan be addressed?*" through another literature review and the online questionnaire. The issues are broad, from scientific limitations due to the novelty of the technology, such as unclear criteria for the safety and effectiveness of regenerative medicine, to the burden on the healthcare system or anxiety of people by the technological development of regenerative medicine in the future. While they could be categorised by phases of the translation based on the original studies' focusing points, some of them overlap and connect to each other. The possible approaches were also identified through the comparison with other countries' policies.

The findings were synthesised and examined from a practical perspective of Japan to provide a set of steps to incorporate ethical considerations into the translation of regenerative medicine, which is the answer to the fourth sub-question, "*What steps could be taken to improve the approach to ethical considerations for translating regenerative medicine in Japan?*" Ambiguous definitions and distinctions of terms in regulations, such as research and treatment, have encouraged issues which are caused by the nature of emerging technologies in Japan. Therefore, clarifying such definitions by MHLW is one of the steps to improvement. Also, bottom-up reflections on the regulations by hospitals and universities/national research institutions enable MHLW and MEXT to present appropriate ethical anchors for practitioners, which is also one step. This bottom-up process has not been employed in Japan compared to other countries like the U.S. In parallel, hospitals and universities/national research institutions need to learn from interdisciplinary research projects, which the ministries support and show the results and experiences, and utilise them for improving their own research projects, especially by addressing communication and ethical professional issues. On the other hand, considering the current marketing situation of regenerative medicine products in Japan, which is still developing, policies that have aimed to prompt patient access to regenerative medicine, and the negative perception of the online questionnaire to change the policies, the issues related to the conditional approval of products could be addressed by communication between practitioners and patients or ministries and the public rather than just shifting regulations stricter. As the future step, broad public discussion managed by the ministries is expected to address the uncertainty of the ethically possible extent of research in regenerative medicine.

These steps were translated into a conceptual framework as recommendations for actors with expected actions to realise the desired system between clinical research and pre-marketing that would help Japan to incorporate ethical considerations into the translation of regenerative medicine (Figure 5-4). This framework is the final deliverable of this research and the answer to the main question. In conclusion, implementing the framework which indicates clear definitions of ambiguous words by MHLW, review and introduction of ethical anchors by MHLW and MEXT, and the bottom-up feedback on ethical anchors by practitioners is the answer to the main research question.

This research sheds light on the system of Japan from an ethical perspective, where a knowledge gap exists. Besides, this research reviews the system of the translation of regenerative medicine in Japan and incorporates a practical perspective. This attitude enables the research to provide feasible ways to improve the system in Japan, which mainly differs from the results of existing studies.

7.2. Limitations

This research has certain limitations, as follows.

- This research employs a mixed qualitative analysis, in which certain subjectivity and the influence of the research conductor's bias are inherent. While collecting data from multiple resources, namely, conducting a literature review and an online questionnaire with a supplementary interview, as a partial mitigation plan, it is difficult to address this limitation fully.
- The exhaustiveness of the literature reviews, including grey literature might not be enough. While the literature was filtered by certain terms and, for the academic literature, use two aggregating databases, which contains journals familiar with this research's topic, there could have been other ways of filtering or information source of grey literature.
- The number of responses to the online questionnaire was lower than expected. The motivation of possible participants should have been considered more. For example, the questionnaire could have got more responses if it had been conducted at other times by consulting with the contact points beforehand.
- The online questionnaire was distributed via the contact points of related researchers' communities and the author's SNS account. This method of distribution may have a bias in the selection of participants. To mitigate this, the results were used as a supplement to the findings of the literature review from a qualitative perspective.

7.3. Reflection

This research used Grammarly and ChatGPT to write this report. Grammarly was used to check the spelling and grammar of the author's original sentences. Grammarly suggests the correct spelling or sentences with appropriate grammar if there is a possible mistake in the original sentences. It also provides paraphrase ideas for some sentences which are identified as unnatural sentences. The author checked each suggestion from Grammarly and distinguished if it was a correct or appropriate change rather than accepting it automatically. ChatGPT was utilised for getting ideas of paraphrasing when the author wanted to make original sentences more sophisticated, for example, to make too long sentences shorter or divided into multiple sentences. Each time, the author reviewed the answers of ChatGPT and decided whether to employ the paraphrasing idea.

7.4. Future Research

There is still room to explore within the scope of this research. Some of it is related to the limitations mentioned above. Possible future research points are as follows.

- This research did not objectively assess the validity of the final deliverable, such as collecting feedback from actual actors. Therefore, future research can examine validity and refine the framework, for example, by conducting critical reviews or in-depth interviews with actual actors.

- Delving into more scientific aspects of regenerative medicine based on the results of this research, such as aiming to generate ethical standards or practical research processes by focusing on a specific technology within regenerative medicine.
- Focusing on the distribution of regenerative products, which would be a later process of this research's focused processes, regulatory pharmaceuticalisation in Japan could be explored more from an ethical perspective. This would involve more deeply analysing especially Law 4, perceptions of pharmaceutical companies, and the health technology assessment system in Japan.
- Exploring a better and more practical way of public discussion or science communication aims to improve the approaches to ethical considerations regarding the translation of regenerative medicine in Japan, compared with other countries' examples or conducting practical workshops. Also, the exploration of addressing the shortage of ethics professionals is possible with a similar method.
- This research focused on regenerative medicine in Japan. The research processes or results could be used to analyse other emerging technologies or technologies generally in the healthcare field.
- In this research, "safety" means only scientific or technical safety and societal safety, including the pressure on people to harm themselves through introducing enhancing technologies to reduce a societal problem. This perspective can be incorporated into future research to analyse the situation more deeply.
- This research brought together practical analytical tools from policy analysis with an ethical analysis. This combined way could be elaborated by being utilised for other topics and lead to a new research approach.

References

Aboelela, S. W., Larson, E., Bakken, S., Carrasquillo, O., Formicola, A., Glied, S. A., Haas, J., & Gebbie, K. M. (2006). Defining Interdisciplinary Research: Conclusions from a Critical Review of the Literature. *Health Services Research*, *42*(1p1), 329–346. https://doi.org/10.1111/j.1475-6773.2006.00621.x

Anderson M, Pitchforth E, Edwards N, Alderwick H, McGuire A, Mossialos E. (2022). The United Kingdom: Health system review. *Health Systems in Transition, 24*(1), WHO Regional Office for Europe. https://eurohealthobservatory.who.int/publications/i/united-kingdom-health-system-review-2022

Ankeny, R. A., Munsie, M. J., & Leach, J. (2021). Developing a Reflexive, Anticipatory, and Deliberative Approach to Unanticipated Discoveries: Ethical Lessons from iBlastoids. *The American Journal of Bioethics*, *22*(1), 36–45. https://doi.org/10.1080/15265161.2021.1974976

Baker, H. B., McQuilling, J. P., & King, N. M. (2016). Ethical considerations in tissue engineering research: Case studies in translation. *Methods*, *99*, 135–144. https://doi.org/10.1016/j.ymeth.2015.08.010

Baldus, M. (2023). “Overestimated technology – underestimated consequences” – reflections on risks, ethical conflicts, and social disparities in the handling of non-invasive prenatal tests (NIPTs). *Medicine Health Care and Philosophy*, *26*(2), 271–282. https://doi.org/10.1007/s11019-023-10143-1

Braun, V., Clarke, V., & Weate, P. (2016). Using thematic analysis in sport and exercise research. In *Routledge handbook of qualitative research in sport and exercise* (1st ed., pp. 213–227). Taylor & Francis (Routledge). https://doi.org/10.4324/9781315762012.ch15

Broom, J., & Broom, A. (2024). Qualitative research methods: Powerful tools for understanding practice and informing change. *Journal of Hospital Infection*, *149*, 182–183. https://doi.org/10.1016/j.jhin.2024.02.031

Buzdugan, A., Railean, S., & Buzdugan, A. (2022). Nanotechnology and nonproliferation. In *IFMBE proceedings* (pp. 463–469). https://doi.org/10.1007/978-3-030-92328-0_60

Cabinet. (2021). *Healthcare Policy.* https://www.kantei.go.jp/jp/singi/kenkouiryou/suisin/ketteisiryou/kakugi/r030406senryaku.pdf

Cabinet Office. (2015). 国立研究開発法人日本医療研究開発機構及び日本医療研究開発機構審議会について（概要） [About the Japan Agency for Medical Research and Development and the Council for Japan Agency for Medical Research and Development (Summary)] [Slide show]. Council for Japan Agency for Medical Research and Development (1st Session). https://www8.cao.go.jp/iryou/council/20150804/agenda.html

Cabinet Secretariat. (n.d.). *ミミズク博士と社会科を学ぼう![Let’s learn social studies with Dr. Mimizuku]*. 首相官邸きっず. https://www.kantei.go.jp/jp/kids/seifu_hajimeni.html

Caulfield, T., Sipp, D., Murry, C. E., Daley, G. Q., & Kimmelman, J. (2016). Confronting stem cell hype. *Science*, *352*(6287), 776–777. https://doi.org/10.1126/science.aaf4620

Center for Research and Development Strategy, Japan Science and Technology Agency. (2022). *The Beyond Disciplines Collection ELSI から RRI への展開から考える科学技術・イノベーション の変革* (CRDS-FY2021-RR-07) [The transition of science and technology/innovation through considering the transformation from ELSI to RRI]. https://www.jst.go.jp/crds/report/CRDS-FY2021-RR-07.html

Chamuah, A., & Singh, R. (2022). Responsible governance of civilian unmanned aerial vehicle (UAV) innovations for Indian crop insurance applications. *Journal of Responsible Technology*, *9*, 100025. https://doi.org/10.1016/j.jrt.2022.100025

Chan, S. (2017). Current and emerging global themes in the bioethics of regenerative medicine: the tangled web of stem cell translation. *Regenerative Medicine*, *12*(7), 839–851. https://doi.org/10.2217/rme-2017-0065

Chen, F., Zhao, Y., Jin, Y., & Shi, S. (2012). Prospects for translational regenerative medicine. *Biotechnology Advances*, *30*(3), 658–672. https://doi.org/10.1016/j.biotechadv.2011.11.005

Committee on Social Cooperation in Science and Technology. (2019). *今後の科学コミュニケーションのあり方について[Future prospects of science communication]*. https://www.mext.go.jp/b_menu/shingi/gijyutu/gijyutu2/092/houkoku/1413643.htm

Cyranoski, D. (2019). The potent effects of Japan's stem-cell policies. *Nature*, *573*(7775), 482–485. https://doi.org/10.1038/d41586-019-02847-3

Cyranoski, D., Sipp, D., Mallik, S., & Rasko, J. E. (2023). Too little, too soon: Japan's experiment in regenerative medicine deregulation. *Cell Stem Cell*, *30*(7), 913–916. https://doi.org/10.1016/j.stem.2023.06.005

De Kanter, A. J., Jongsma, K., Verhaar, M. C., & Bredenoord, A. L. (2023). The ethical Implications of tissue engineering for Regenerative Purposes: A Systematic review. *Tissue Engineering. Part B, Reviews/Tissue Engineering. Part B, Reviews.*, *29*(2), 167–187. https://doi.org/10.1089/ten.teb.2022.0033

Delatycki, M. B., Alkuraya, F. S., Archibald, A. D., Castellani, C., Cornel, M. C., Grody, W. W., Henneman, L., Ioannides, A. S., Kirk, E. P., Laing, N. G., Lucassen, A., Massie, J., Schuurmans, J., Thong, M., Van Langen, I. M., & Zlotogora, J. (2019). International perspectives on the implementation of reproductive carrier screening. *Prenatal Diagnosis*, *40*(3), 301–310. https://doi.org/10.1002/pd.5611

European Academies' Science Advisory Council & Federation of European Academies of Medicine. (2020). *Challenges and potential in regenerative medicine*. https://easac.eu/publications/details/challenges-and-potential-in-regenerative-medicine

European Commission, Directorate-General for Research and Innovation, (2012). *Ethical and regulatory challenges to science and research policy at the global level*, Publications Office. https://data.europa.eu/doi/10.2777/35203

Enserink, B., Bots, P., Van Daalen, E., Hermans, L., Kortmann, R., Koppenjan, J., Kwakkel, J., Van Der Ploeg, T. R., Slinger, J., & Thissen, W. (2022). *Policy analysis of Multi-Actor Systems*. Eleven International Publishing.

Essa, M. M., Chouchane, L., Mifsud, B., Emadi, M. A., & Ismail, S. I. (2020). THE FUTURE OF MEDICINE, healthcare innovation through precision medicine: policy case study of Qatar. *Life Sciences, Society and Policy*, *16*(1). https://doi.org/10.1186/s40504-020-00107-1

Falagas, M. E., Pitsouni, E. I., Malietzis, G. A., & Pappas, G. (2007). Comparison of PubMed, Scopus, Web of Science, and Google Scholar: strengths and weaknesses. *FASEB Journal*, *22*(2), 338–342. https://doi.org/10.1096/fj.07-9492lsf

Fears, R., Akutsu, H., Alentajan-Aleta, L. T., Caicedo, A., De Carvalho, A. C. C., Čolić, M., Cornish, J., Cossu, G., Debré, P., Dierckxsens, G., El-Badri, N., Griffin, G. E., Hsieh, P. C., Inamdar, M. S., Kumar, P., Abraham, C. M., Mačiulaitis, R., Mahtab, M. A., O'Brien, F. J., . . . Ter Meulen, V. (2021). Inclusivity and diversity: Integrating international perspectives on stem cell challenges and potential. *Stem Cell Reports*, *16*(8), 1847–1852. https://doi.org/10.1016/j.stemcr.2021.07.003

Forum for Innovative Regenerative Medicine. (n.d.). *About FIRM*. https://firm.or.jp/en/about/

Forum for Innovative Regenerative Medicine. (2023). *イノベーションの推進に向けた今後の方策について[Future measures to promote innovation]* [Slide show]. Public-private Dialogue for the Creation of Innovative Pharmaceuticals, Medical Devices, and Regenerative Medicine Products, Japan. https://firm.or.jp/wp-content/uploads/2023/12/231113_官民対話.pdf

Fujita, M., Hatta, T., & Ide, K. (2022). Current status of cell-based interventions in Japan. *Cell Stem Cell*, *29*(9), 1294–1297. https://doi.org/10.1016/j.stem.2022.08.003

Gable, L., Ram, N., & Ram, J. L. (2020). Legal and ethical implications of wastewater monitoring of SARS-CoV-2 for COVID-19 surveillance. *Journal of Law and the Biosciences*, *7*(1). https://doi.org/10.1093/jlb/lsaa039

Gardner, J., Faulkner, A., Mahalatchimy, A., & Webster, A. (2015). Are there specific translational challenges in regenerative medicine? Lessons from other fields. *Regenerative Medicine*, *10*(7), 885–895. https://doi.org/10.2217/rme.15.50

Headquarters for Healthcare Policy. (2023). *令和６年度 医療分野の研究開発関連予算のポイント[The overview of the budget for research and development in the medical sector in FY2024]*. https://www.kantei.go.jp/jp/singi/kenkouiryou/siryou/pdf/r051222_yosanpoint.pdf

Headquarters for Healthcare Policy. (2023-b). *令和６年度予算における統合プロジェクトの概要[Overview of projects in the FY2024 budget]*. https://www.kantei.go.jp/jp/singi/kenkouiryou/siryou/pdf/r051222_projectgaiyou.pdf

Health and Global Policy Institute. (2012). *参考資料：オランダの医療制度改革と高齢化対策[Ref: Dutch health care reform and ageing policy.]*. https://hgpi.org/lecture/191.html

Hee Hong, G., & Schneider, T. (2020). *Shrinkanomics: Policy Lessons from Japan on Aging*. IMF. from https://www.imf.org/en/Publications/fandd/issues/2020/03/shrinkanomics-policy-lessons-from-japan-on-population-aging-schneider

Hermerén, G. (2021). The ethics of regenerative medicine. *Biologia Futura*, *72*(2), 113–118. https://doi.org/10.1007/s42977-021-00075-3

Higuchi, N. (2013). Three challenges in advanced medicine. *Japan Medical Association Journal*, *56*(6), 437–447. https://www.med.or.jp/english/activities/pdf/2013_06/434_447.pdf

Hogle, L. a. F. (2014). Regenerative Medicine Ethics. In *Springer eBooks*. https://doi.org/10.1007/978-1-4614-9062-3

Igarashi, Y., & Sato, Y. (2018). Current status of the regulation and development of cell therapy products in Japan. *Folia Pharmacologica Japonica*, *151*(6), 254–259. https://doi.org/10.1254/fpj.151.254

Ikka, T. (2018). 医の倫理の基礎知識 2018 年版 H-10.臨床研究の倫理[Fundamentals of Medical Ethics, 2018 Edition H-10.Ethics of Clinical Research]. In *Japan Medical Association*. https://www.med.or.jp/doctor/rinri/i_rinri/h10.html

Ikka, T., Fujita, M., Hatta, T., Isobe, T., Konomi, K., Onishi, T., Shoji, S., Sato, Y., Tashiro, S., & Tobita, M. (2023). Difficulties in ensuring review quality performed by committees under the Act on the Safety of Regenerative Medicine in Japan. *Stem Cell Reports*, *18*(3), 613–617. https://doi.org/10.1016/j.stemcr.2023.01.013

Ikka, T., Fujita, M., Yashiro, Y., & Ikegaya, H. (2015). Recent court ruling in Japan exemplifies another layer of regulation for regenerative therapy. *Cell Stem Cell*, *17*(5), 507–508. https://doi.org/10.1016/j.stem.2015.10.008

Ikka, T., Hatta, T., Saito, Y., & Fujita, M. (2023-b). Does the Act on the Safety of Regenerative Medicine in Japan ensure “safety”?: Implications of low adverse event reporting. *Stem Cell Reports*, *18*(12), 2297–2299. https://doi.org/10.1016/j.stemcr.2023.10.012

Illes, J., Sipp, D., Kleiderman, E., Benjaminy, S., Isasi, R., Lomax, G., Master, Z., McCormick, J., Ogbogu, U., Ravitsky, V., Robillard, J. M., Rossi, F., Wilson, B., & Zarzeczny, A. (2017). A blueprint for the next generation of ELSI research, training, and outreach in regenerative medicine. *Npj Regenerative Medicine*, *2*(1). https://doi.org/10.1038/s41536-017-0026-z

Inoue, Y., Shineha, R., & Yashiro, Y. (2016). Current public support for Human-Animal chimera research in Japan is limited, despite high levels of scientific approval. *Cell Stem Cell, 19*(2), 152–153. https://doi.org/10.1016/j.stem.2016.07.011

International Society for Stem Cell Research. (2021). *ISSCR Guidelines for Stem Cell Research and Clinical Translation*. https://www.isscr.org/guidelines

Ishihara, K., Ichinomiya, A., Inami, M., Hashimoto, T., Yuzawa, R., Ishizu, M., Hirohara, T., Yashiro, Y., & Takizawa, T. (2016). Recognition of, interest in, and understanding of induced pluripotent stem cells and regenerative medicine in Japanese students. *Regenerative Therapy*, *5*, 96–106. https://doi.org/10.1016/j.reth.2016.09.003

Jacques, E., & Suuronen, E. J. (2020). The Progression of Regenerative Medicine and its Impact on Therapy Translation. *Clinical and Translational Science*, *13*(3), 440–450. https://doi.org/10.1111/cts.12736

James, A., & Whelan, A. (2021). ‘Ethical’ artificial intelligence in the welfare state: Discourse and discrepancy in Australian social services. *Critical Social Policy*, *42*(1), 22–42. https://doi.org/10.1177/0261018320985463

Japan Agency for Medical Research and Development. (2023). *AMED’s Programs on Regenerative Medicine and Cell and Gene Therapies*. https://www.amed.go.jp/content/000110446.pdf

Japan Agency for Medical Research and Development. (2023-b). *「再生医療実用化研究事業」におけるアカデミア発シーズと企業とのマッチング支援[Support for matching the seeds of academia with companies in the “Research Project for Practical Application of Regenerative Medicine”]*. https://www.amed.go.jp/program/list/13/01/matching.html

Japan Science and Technology Agency. (n.d.). *About PROGRAM*. RInCA. https://www.jst.go.jp/ristex/rinca/en/program/index.html

Japan Science and Technology Agency. (n.d.-b*). 再生医療の実現化ハイウェイ[The Highway to Realise Regenerative Medicine Project]*. https://www.jst.go.jp/saisei-nw/highway/index.html

Kanama, D., Itoh, M., Aketani, S., Okamura, A., Shineha, R., Noro, T., Fukui, K., Mitsumori, Y. (2019). A Study on Formation of New Research Areas and Its Acceleration, *The Journal of Science Policy and Research Management*, *34*(3), 258-269, https://doi.org/10.20801/jsrpim.34.3_258

Kato, M., & Sleeboom-Faulkner, M. (2017). Motivations for seeking experimental treatment in Japan. *BioSocieties*, *13*(1), 255–275. https://doi.org/10.1057/s41292-017-0067-y

King, N. M., & Perrin, J. (2014). Ethical issues in stem cell research and therapy. *Stem Cell Research & Therapy*, *5*(4). https://doi.org/10.1186/scrt474

Kishimoto, A. (2021). The Social Implementation of Emerging Technologies. In Research and Legislative Reference Bureau National Diet Library (Ed.), *Genome-Editing Technology and Its Impact* (pp. 101–121). National Diet Library, Japan. https://dl.ndl.go.jp/view/download/digidepo_11656216_po_20200508.pdf?contentNo=1

Kroneman M, Boerma W, van den Berg M, Groenewegen P, de Jong J, van Ginneken E. (2016). The Netherlands: health system review. *Health Systems in Transition, 18*(2), WHO Regional Office for Europe. https://www.who.int/publications/i/item/HiT-18-2-2016

Kuzma, J. (2022). Implementing responsible research and innovation: a case study of U.S. biotechnology oversight. *Global Public Policy and Governance*, *2*(3), 306–325. https://doi.org/10.1007/s43508-022-00046-x

Langman, S., Capicotto, N., Maddahi, Y., & Zareinia, K. (2021). Roboethics principles and policies in Europe and North America. *SN Applied Sciences*, *3*(12). https://doi.org/10.1007/s42452-021-04853-5

Lowenthal, J., & Sugarman, J. (2015). Ethics and policy issues for stem cell research and pulmonary medicine. *Chest*, *147*(3), 824–834. https://doi.org/10.1378/chest.14-1696

Lysaght, T. (2017). Accelerating regenerative medicine: the Japanese experiment in ethics and regulation. *Regenerative Medicine*, *12*(6), 657–668. https://doi.org/10.2217/rme-2017-0038

Lysaght, T., Munsie, M., Castricum, A., Hui, J. H. P., Okada, K., Sato, Y., Sawa, Y., Stewart, C., Tan, L. K., Tan, L. H., & Sugii, S. (2018). A roundtable on responsible innovation with autologous stem cells in Australia, Japan and Singapore. *Cytotherapy*, *20*(9), 1103–1109. https://doi.org/10.1016/j.jcyt.2018.06.004

Lysaght, T., & Sugii, S. (2016). Uncertain Oversight of Regenerative Medicines in Japan under the ASRM. *Cell Stem Cell*, *18*(4), 438–439. https://doi.org/10.1016/j.stem.2016.03.007

Mao, A. S., & Mooney, D. J. (2015). Regenerative medicine: Current therapies and future directions. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(47), 14452–14459. https://doi.org/10.1073/pnas.1508520112

Mariscal, C., & Petropanagos, A. (2016). CRISPR as a driving force: the Model T of biotechnology. *Monash Bioethics Review*, *34*(2), 101–116. https://doi.org/10.1007/s40592-016-0062-2

Matsuyama, A. (2013). Translational research in regenerative medicine: A translational gap. *Pharmaceuticals, Policy and Law*, *15*(3,4), 163–172. https://doi.org/10.3233/ppl-130368

Morrison, M. (2024). *The limits of regulatory pharmaceuticalisation? Global developments supporting clinical innovation with advanced therapies* [Slide show]. EOAR Seminar. https://www.eoar.com.au/seminars

Mikami, K. (2014). State-Supported science and imaginary lock-in: The case of regenerative medicine in Japan. *Science as Culture*, *24*(2), 183–204. https://doi.org/10.1080/09505431.2014.945410

Minari, J., Yokono, M., Takashima, K., Kokado, M., Ida, R., & Hishiyama, Y. (2021). Looking back: three key lessons from 20 years of shaping Japanese genome research regulations. *Journal of Human Genetics*, *66*(11), 1039–1041. https://doi.org/10.1038/s10038-021-00923-z

Ministry of Education, Culture, Sports, Science and Technology. (2022). 再生・細胞医療・遺伝子治療研究の在り方について[The state of regenerative and cellular medicine and gene therapy research]. In *MEXT Life Science Portalsite*. https://www.lifescience.mext.go.jp/files/pdf/n2338_01.pdf

Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, & Ministry of Economy, Trade and Industry. (2021). *Ethical Guidelines for Medical and Biological Research Involving Human*. https://www.lifescience.mext.go.jp/files/pdf/n2373_01.pdf

Ministry of Health, Labour and Welfare. (2019). *OECD 加盟国の保健医療費の状況（2018 年）[Health expenditure in OECD countries in 2018]*. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryouhoken/iryouhoken11/index.html

Ministry of Health, Labour and Welfare. (2020). *臨床研究法の概要[Overview of the Clinical Trials Act]*. https://www.mhlw.go.jp/content/10800000/000647734.pdf

Ministry of Health, Labour and Welfare. (2021). *医薬品等の費用対効果評価について[Cost-benefit assessment of pharmaceuticals and other products]* [Slide show]. The Central Social Insurance Medical Council, Japan. https://www.mhlw.go.jp/content/12404000/000855564.pdf

Ministry of Health, Labour and Welfare. (n.d.). *再生医療等提供機関の情報について[Information on Regenerative Medicine Provider Organizations]*. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000186471.html

Ministry of Health, Labour and Welfare. (n.d.-b). *再生医療等の安全性の確保等に関する法律について[About the Act on Securing Safety of Regenerative Medicine*]. https://www.mhlw.go.jp/content/000679801.pdf

Ministry of Health, Labour and Welfare. (2024). *再生医療等安全性確保法の見直しについて[Review of the Act on Securing Safety of Regenerative Medicine]* [Slide show]. 91st Session of the Regenerative Medicine Evaluation Committee, Japan. https://www.mhlw.go.jp/content/10808000/001191348.pdf

Nakazawa, E., Takimoto, Y., & Akabayashi, A. (2016). The social framework surrounding the development of regenerative medicine in Japan. *Cambridge Quarterly of Healthcare Ethics/CQ. Cambridge Quarterly of Healthcare Ethics*, *25*(3), 466–471. https://doi.org/10.1017/s0963180116000104

National Institute of Health Sciences. (n.d.). *About NIHS*. https://www.nihs.go.jp/english/nihs/index.html

National Institute of Health Sciences. (2023). 日本国内で承認されている再生医療等製品*[Regenerative medicine products approved in Japan]*. http://www.nihs.go.jp/cbtp/home/info.html

Niemansburg, S. L., Van Delden, J. J. M., Öner, F. C., Dhert, W. J., & Bredenoord, A. L. (2014). Ethical implications of regenerative medicine in orthopedics: an empirical study with surgeons and scientists in the field. *The Spine Journal*, *14*(6), 1029–1035. https://doi.org/10.1016/j.spinee.2013.10.016

OECD. (2023-a). *Elderly population* [Dataset]. OECD. https://data.oecd.org/pop/elderly-population.htm

OECD. (2023-b). *Old-age dependency ratio* [Dataset]. OECD. https://data.oecd.org/pop/old-age-dependency-ratio.htm

O'Shaughnessy, M., Johnson, W. G., Tournas, L., Rozell, C. J., & Rommelfanger, K. S. (2023). Neuroethics guidance documents: principles, analysis, and implementation strategies. *Journal of Law and the Biosciences*, *10*(2). https://doi.org/10.1093/jlb/lsad025

Pharmaceuticals and Medical Devices Agency. (2015). *再生医療等製品の製造販売承認制度の概要[Overview of the approval system for the manufacture and sale of regenerative medical products]* [Slide show]. https://www.pmda.go.jp/files/000207261.pdf

Pharmaceuticals and Medical Devices Agency. (n.d.). *再生医療等製品[Regenerative medicine products]*. https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/ctp/0007.html

Pharmaceuticals and Medical Devices Agency. (n.d.-b). *再生医療等製品の製造販売手順について[About the process of producing and selling regenerative medicine products*]. https://www.pmda.go.jp/files/000216666.pdf

Pharmaceuticals and Medical Devices Agency. (n.d.-c). *About PMDA*. https://www.pmda.go.jp/english/about-pmda/outline/0005.html

Post, G., Keestra, M., & Rutting, L. (2016). *An introduction to interdisciplinary research*. Amsterdam University Press. https://doi.org/10.1515/9789048531615

Read, S. A., Kass, G., Sutcliffe, H. R., & Hankin, S. (2015). Foresight Study on the risk governance of new technologies: The case of Nanotechnology. *Risk Analysis*, *36*(5), 1006–1024. https://doi.org/10.1111/risa.12470

Rice T, Rosenau P, Unruh LY, Barnes AJ, van Ginneken E. (2020). United States of America: Health system review. *Health Systems in Transition, 22*(4). WHO Regional Office for Europe. https://eurohealthobservatory.who.int/publications/i/united-states-health-system-review-2020

Riva, L., & Petrini, C. (2019). A few ethical issues in translational research for gene and cell therapy. *Journal of Translational Medicine*, *17*(1). https://doi.org/10.1186/s12967-019-02154-5

Rosemann, A., Vasen, F., & Bortz, G. (2018). Global Diversification in Medicine Regulation: Insights from Regenerative Stem Cell Medicine. *Science as Culture*, *28*(2), 223–249. https://doi.org/10.1080/09505431.2018.1556253

Sakamoto, H., Rahman, M., Nomura, S., Okamoto, E., Koike, S. et al. (2018). Japan health system review. *Health Systems in Transition, 8* (1), World Health Organization. Regional Office for South-East Asia. https://iris.who.int/handle/10665/259941.

Saunders, M., Lewis, P., Thornhill, A., & Bristow, A. (2019). Chapter 4: Understanding research philosophy and approaches to theory development. In *Research Methods for Business Students* (8th ed., pp. 128–171). Pearson Education. https://www.researchgate.net/publication/330760964_Research_Methods_for_Business_Students_Chapter_4_Understanding_research_philosophy_and_approaches_to_theory_development

Sawai, T., Hatta, T., & Fujita, M. (2017). Public attitudes in Japan towards human–animal chimeric embryo research using human induced pluripotent stem cells. *Regenerative Medicine*, *12*(3), 233–248. https://doi.org/10.2217/rme-2016-0171

Sawaji, O. (2021). *Measures to Address Japan's aging Society*. PUBLIC RELATIONS OFFICE, GOVERNMENT OF JAPAN. Retrieved November 30, 2023, from https://www.gov-online.go.jp/eng/publicity/book/hlj/html/202102/202102_09_en.html

Science and Technology Committee of UK Parliament. (2013). *1st Report Regenerative Medicine*. The Authority of the House of Lords. https://publications.parliament.uk/pa/ld201314/ldselect/ldsctech/23/23.pdf

Shineha, R. (2016). *History and Issues of Science Communication : a Review of Discussions and Perspectives in Policy-making*. Graduate School of Literature, Seijo University. https://seijo.repo.nii.ac.jp/records/3763

Shineha, R. (2020). *責任ある科学技術ガバナンス概論*[Overview of responsible science and technology governance]. Nakanishiya Shuppan co.ltd.

Shineha, R., Inoue, Y., Ikka, T., Kishimoto, A., & Yashiro, Y. (2018). A comparative analysis of attitudes on communication toward stem cell research and regenerative medicine between the public and the scientific community. *Stem Cells Translational Medicine (Print)*, *7*(2), 251–257. https://doi.org/10.1002/sctm.17-0184

Shineha, R., Inoue, Y., & Yashiro, Y. (2022). A comparative analysis of attitudes toward stem cell research and regenerative medicine between six countries – A pilot study. *Regenerative Therapy*, *20*, 187–193. https://doi.org/10.1016/j.reth.2022.04.007

Shook, J. R., & Giordano, J. (2024). Ethical and policy issues in practices of regenerative medicine for the treatment of chronic pain. In *Springer eBooks* (pp. 593–599). https://doi.org/10.1007/978-3-031-50357-3_34

Sipp, D. (2015). Conditional approval: Japan lowers the bar for regenerative medicine products. *Cell Stem Cell*, *16*(4), 353–356. https://doi.org/10.1016/j.stem.2015.03.013

Sipp, D., Caulfield, T., Kaye, J., Barfoot, J., Blackburn, C., Chan, S., De Luca, M., Kent, A., McCabe, C., Munsie, M., Sleeboom-Faulkner, M., Sugarman, J., Van Zimmeren, E., Zarzeczny, A., & Rasko, J. E. J. (2017). Marketing of unproven stem cell–based interventions: A call to action. *Science Translational Medicine*, *9*(397). https://doi.org/10.1126/scitranslmed.aag0426

Sipp, D., & Okano, H. (2018). Japan strengthens regenerative medicine oversight. *Cell Stem Cell*, *22*(2), 153–156. https://doi.org/10.1016/j.stem.2018.01.001

Smye, S. W., & Frangi, A. F. (2021). Interdisciplinary research: shaping the healthcare of the future. *Future Healthcare Journal*, *8*(2), e218–e223. https://doi.org/10.7861/fhj.2021-0025

Sugarman, J., Barker, R. A., Kerridge, I., Lysaght, T., Pellegrini, G., Sipp, D., & Tanner, C. (2018). Tackling ethical Challenges of Premature delivery of Stem Cell-Based therapies: ISSCR 2018 Annual Meeting Focus Session Report. *Stem Cell Reports*, *11*(5), 1021–1025. https://doi.org/10.1016/j.stemcr.2018.10.020

Takashima, K., Inoue, Y., Tashiro, S., & Muto, K. (2018). Lessons for reviewing clinical trials using induced pluripotent stem cells: examining the case of a first-in-human trial for age-related macular degeneration. *Regenerative Medicine*, *13*(2), 123–128. https://doi.org/10.2217/rme-2017-0130

Takashima, K., Morrison, M., & Minari, J. (2021). Reflection on the enactment and impact of safety laws for regenerative medicine in Japan. *Stem Cell Reports*, *16*(6), 1425–1434. https://doi.org/10.1016/j.stemcr.2021.04.017

The Japanese Society for Regenerative Medicine. (n.d.). *設立趣旨 [Objectives]*. https://www.jsrm.jp/whoweare/prospectus/

The Japanese Society for Regenerative Medicine. (n.d.-b). *用語集[Glossary of terms]*. 再生医療ポータル. https://saiseiiryo.jp/keywords/detail/post_10.html

The Japanese Society for Regenerative Medicine. (2024). *再生医療を普遍化するためのオープンイノベーションプラットフォームである日本再生医療学会[The Japanese Society for Regenerative Medicine, an open innovation platform for universalising regenerative medicine]* [Slide show].

Tobita, M., Konomi, K., Torashima, Y., Kimura, K., Taoka, M., & Kaminota, M. (2016). Japan's challenges of translational regenerative medicine: Act on the safety of regenerative medicine. *Regenerative Therapy*, *4*, 78–81. https://doi.org/10.1016/j.reth.2016.04.001

Touré, S. B., Kleiderman, E., & Knoppers, B. M. (2018). Bridging stem cell research and medicine: a learning health system. *Regenerative Medicine*, *13*(6), 741–752. https://doi.org/10.2217/rme-2017-0129

Tricco, A. C., Antony, J., Soobiah, C., Kastner, M., Cogo, E., MacDonald, H., D'Souza, J., Hui, W., & Straus, S. E. (2016). Knowledge synthesis methods for generating or refining theory: a scoping review reveals that little guidance is available. *Journal of Clinical Epidemiology*, *73*, 36–42. https://doi.org/10.1016/j.jclinepi.2015.11.021

Tsubouchi, M., Morishita, R., Tabata, Y., Matsui, S., & Kawakami, K. (2008). Critical issues for effective collaboration between academia and industry in the field of regenerative medicine in Japan. *Regenerative Medicine*, *3*(4), 497–504. https://doi.org/10.2217/17460751.3.4.497

Umemura, M., & Morrison, M. (2021). Comparative lessons in regenerative medicine readiness: learning from the UK and Japanese experience. *Regenerative Medicine*, *16*(3), 269–282. https://doi.org/10.2217/rme-2020-0136

Union of Kansai Governments. (n.d.). *諸外国の医療保険制度の比較[Comparison of health insurance systems of countries]*. https://www.kouiki-kansai.jp/material/files/group/3/1378455555.pdf

Van De Poel, I., & Robaey, Z. (2017). Safe-by-Design: from Safety to Responsibility. *NanoEthics*, *11*(3), 297–306. https://doi.org/10.1007/s11569-017-0301-x

Van Dijke, I., Van El, C. G., Lakeman, P., Goddijn, M., Rigter, T., Cornel, M. C., & Henneman, L. (2022). Dynamics of reproductive genetic technologies: Perspectives of professional stakeholders. *PLOS ONE*, *17*(6), e0269719. https://doi.org/10.1371/journal.pone.0269719

Van Noorden, R. (2015). Interdisciplinary research by the numbers. *Nature*, *525*(7569), 306–307. https://doi.org/10.1038/525306a

Ventura-Juncá, P. (2011). Science and Ethics: Bridge to the Future for Regenerative Medicine. *International Journal of Stem Cells*, *4*(2), 79–84. https://doi.org/10.15283/ijsc.2011.4.2.79

Volarevic, V., Markovic, B. S., Gazdic, M., Volarevic, A., Jovicic, N., Arsenijevic, N., Armstrong, L., Djonov, V., Lako, M., & Stojkovic, M. (2018). Ethical and safety issues of Stem Cell-Based therapy. *International Journal of Medical Sciences*, *15*(1), 36–45. https://doi.org/10.7150/ijms.21666

Yamada, S., Behfar, A., & Terzic, A. (2021). Regenerative medicine clinical readiness. *Regenerative Medicine (Print)*, *16*(3), 309–322. https://doi.org/10.2217/rme-2020-0178

Zamborský, R., Kilian, M., Csöbönyeiová, M., & Danisovič, Ľ. (2018). Regenerative Medicine in Orthopaedics and Trauma: challenges, regulation and ethical issues. *Ortopedia, Traumatologia, Rehabilitacja*, *20*(3), 173–180. https://doi.org/10.5604/01.3001.0012.0764

再生医療の産業化に向けリ・スタート 議員の会で提言まとめる [Re-starting the industrialisation of regenerative medicine - Parliamentary group summarises proposals]. (2024). *Project Design Online*. https://www.projectdesign.jp/articles/95e2b20e-ea58-4b1f-b49d-f7d6cb7470cb

Appendices

Appendix 1. Online questionnaire

Opening Statement

（日本語は下部にあります。）
You are being invited to participate in a study titled “Responsible translation of regenerative medicine in Japan”. This study is being done by Misa Aikawa from the Delft University of Technology (TU Delft).

The purpose of this research is to understand how to translate regenerative medicine with ethical considerations in Japan. This survey is aimed at those involved with regenerative medicine in Japan, such as researchers, doctors, promoters, or regulators related to regenerative medicine, patients, and other people familiar with regenerative medicine in Japan. This survey will take you approximately 10 minutes to complete. We will be asking you about the difficulties you perceive in relation to the process of translating regenerative medicine. Translating in this study means those activities required to develop treatments or products from preclinical research, in this case, the translation of laboratory research into regenerative medical treatments. The data will be used for the analysis in the study of the master’s thesis.

As with any online activity, the risk of a breach is always possible. We treat your data confidentially; Your answers are treated as anonymous, and we do not store IP addresses. We store your answers on a secure server within TU Delft, in the Netherlands, which is accessible only to the research team.

Your participation in this survey is entirely voluntary. You are free to stop the survey at any time by closing the page; in that case, your answers will not be recorded.
In the survey, you can go back and forth to modify your answers or skip them by clicking on ‘Back/戻る’ or ‘Next/次へ,’ respectively, except for the first question.

If you have any questions or comments about the study, you can contact Misa Aikawa

By clicking on ‘Go to the survey/調査に進む’ you agree to the above.

このオンライン調査は「日本における責任ある再生医療技術の実現」と題した修士論文研究の一環です。この研究はオランダのデルフト工科大学（TU Delft）の修士課程学生である相川美紗が行っています。

本研究の目的は、日本において、どのようにすれば倫理的視点を踏まえた再生医療技術の実現が可能となるか分析検討・提案することです。この調査は、再生医療に関する研究者や医師、再生医療に関するプロジェクトや規制に関わっている方、患者の方やその他日本の再生医療分野に精通している方など、日本の再生医療に関わりのある方を対象としています。
本オンライン調査では、再生医療の実現に係るプロセスにおいて、あなたが難しいと感じる点等について伺うもので、所要は 10 分程度です。本研究における「再生医療の実現に係るプロセス」とは、研究室での研究（前臨床研究）から実際の治療法や製品を開発するまでの活動を指します。いただいた回答は上述の修士論文研究における分析に使用されます。

オンライン調査には必然的に一定の情報漏洩等リスクが伴いますが、機密性を保持した上で情報を取り扱

います。いただいた回答は匿名で処理され、IP アドレスは保存しません。いただいた回答は、本研究チームのみがアクセス可能な、機密性の担保された大学内サーバーに保存されます。

調査への参加は完全に任意です。ウェブページを閉じることで、いつでも調査への回答を中止することができます。この場合、それまでにいただいた回答は記録・保存されません。
調査中、最初の質問を除き、「Back/戻る」または「Next/次へ」をクリックすることで、回答を修正したり、飛ばしたりすることができます。

御不明点等ございましたら、まで御連絡ください。

「Go to the survey/調査に進む」をクリックすると、上記に同意したものとみなします。

Questions

Q1. [mandatory]
What is your role in terms of translating regenerative medicine? Please choose the closest one that fits you.
あなた自身は以下のどのカテゴリーにあてはまりますか？最も近いものを１つ選択してください。

- Researcher or Doctor: conduct research in regenerative medicine or treatment using regenerative medicine.
  研究者または医師：再生医療に関する研究や治療を行っている方
- Promoter or Regulator: manage research projects related to regenerative medicine or make regulations related to regenerative medicine.
  再生医療に関する研究プロジェクトの管理や促進を行ったり、関連する規制を担当している方
- Patient or Public
  患者または一般の方

Q2-1. [answer by scale] [optional]
Have you experienced any (potential) ethical issues or difficulties during your activities for translating regenerative medicine in Japan? Please choose the closest number that fits your opinion. (“Ethical issues or difficulties” means not only the principles of bioethics but also other considerations, such as an unbalanced chance to participate in clinical research and conflict of interest during a review that evaluates if the research could proceed. Please answer widely, even if you are unsure whether it is ethical or not.)
あなたは、再生医療の実現化に関連して、倫理的に課題が生じ得る・難しいと感じたことはありますか？（生命倫理のみならず、例えば「患者にとって臨床試験に参加する機会が不平等である」、「倫理や研究進捗等の審査の過程で利益相反が生じる可能性がある」等、幅広い意味合いでの倫理的課題について御検討ください。倫理の範疇か否か曖昧なものでも構いません。）

Number: 1 - 5
1: I have never experienced such things. そのようなことは一切ない
5: I always face ethical issues or difficulties. 常に問題に直面している

Q2-2. [If answer 2, 3, 4, or 5, answer this open question] [optional]
Can you give an example or some examples of ethical issues or difficulties you have experienced? Answers can be in English or Japanese.

倫理的な課題や難しさはどのようなものか、例を挙げていただけますか？回答は日本語でも英語でも構いません。

Q2-3. [If answer 2, 3, 4, or 5, answer open question] [optional]
If you have any ideas for addressing such issues, please write them. The ideas can include what should be done by not only you but also other people or organisations. Answers can be in English or Japanese.
上記の難しさに対して、アイデア（あなたが主体的に行えるものに限らず、規制当局やムーブメント等他のプレーヤーに対して望まれるものを含む）がございましたら御教示願います。回答は日本語でも英語でも構いません。

Q3. [information before the questions]
Some studies indicate that the current Japanese system ensures prompt patient's access to new regenerative medicine, but this may be problematic. For example; Scientific evidence for safety may not be required or reviewed by the certified (special) committees stipulated in the Act on Securing Safety of Regenerative Medicine[1]. The Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices requires only basic evidence of safety and effectiveness and leaves questions of efficacy, which lead to patient benefits, to postmarketing studies[2].
現行の日本の制度について、いくつかの研究で、迅速な再生医療の患者への提供を追求していると評価するものの、それに伴う問題点を指摘しているものもあります。例えば、再生医療等の安全性の確保等に関する法律（再生医療等安全性確保法）に規定されている（特定）認定再生医療等委員会では安全性等の科学的検証を明示していない[1]、医薬品、医療機器等の品質、有効性及び安全性の確保等に関する法律（薬機法）では最低限の安全性と有効性のみ検証され、患者利益に繋がる有効性の検討は市場流通後に委ねている[2]、など。

References/参考文献
[1] Fujita, M., Hatta, T., & Ide, K. (2022). Current status of cell-based interventions in Japan. Cell Stem Cell, 29(9), 1294–1297. https://doi.org/10.1016/j.stem.2022.08.003
[2] Lysaght, T. (2017). Accelerating regenerative medicine: the Japanese experiment in ethics and regulation. Regenerative Medicine, 12(6), 657–668. https://doi.org/10.2217/rme-2017-0038

Q3-1. [answer by scale] [optional]
How do you feel about the current situation as a player in translating regenerative medicine in Japan in general? Please choose the closest number that fits your opinion.
再生医療の実用化に関して、現在の日本の制度や環境・雰囲気をどのように感じていますか？あなたの意見に最も近い番号を選択してください。

Number: 1 - 5
1: Keep the current conditions. 現状維持
5: Need changes. 変革が必要

Q3-2. [answer by scale] [optional]
How much do you agree with the following statements? Please answer on a scale from 1 (Totally disagree) to 5 (Totally agree).
あなたは以下についてどの程度同意しますか？ １（全くそう思わない）から５（とてもそう思う）の５段階で御回答ください。

Number: 1 - 5

1: Totally disagree 全くそう思わない

5: Totally agree とてもそう思う

Statements:

- Japan should focus on safety more than efficacy.
  日本は有効性よりも安全性を重視すべきである。
- Japan should focus on efficacy more than safety.
  日本は安全性よりも有効性を重視すべきである。
- Japan should focus on safety and efficacy more than now.
  日本は安全性や有効性を現状よりも重視すべきである。
- Japan should focus on safety and efficacy more than prompt provision to patients.
  日本は安全性や有効性を患者への迅速な提供よりも重視すべきである。
- Japan should focus on prompt provision to patients more than now.
  日本は患者への迅速な提供を現状よりも重視すべきである。

Q3-3. [open question] [optional]
If you have additional comments about the above questions, please write them here. Answers can be in English or Japanese.
上記の質問に関して補足や御意見がございましたらこちらに記入をお願いします。 回答は日本語でも英語でも構いません。

Q4. [answer by scale] [optional]
This question is about general ethical considerations related to the translation of regenerative medicine, including safety and efficacy. How much do you think the following stakeholders can currently have a relative influence on addressing general ethical issues in translating regenerative medicine? Please choose the closest number that fits your opinion. Please answer on a scale from 1 (weak influence) to 5 (strong influence).
この質問は安全性や有効性を含めて、倫理的配慮全般に関するものです。再生医療の実現プロセスにおける倫理的観点での考慮や問題への対処にあたって、以下の各関係者の影響力は相対的にどの程度だと思いますか？あなたの意見に最も近い番号を選択してください。 １（弱い）から５（強い）の５段階で御回答ください。

Number: 1 - 5

1: weak influence　影響力は弱い

5: strong influence　影響力は強い

Stakeholders:

- The government and related organisations 政府や政府関係機関
- Researchers/Doctors 研究者や医師
- Research institutions/Hospitals and clinics 研究機関や病院
- Pharmaceutical companies and other related companies 製薬会社や関連会社
- Patients 患者
- General public 一般の方々

Q5. [open question] [optional]

If you have additional opinions or comments related to the questions, please write them here. Answers can be in English or Japanese.
これまでの質問に関して、追加の御意見等ございましたら、こちらに記入をお願いいたします。 回答は日本語でも英語でも構いません。

Q6. [open question] [optional]
I may want to conduct an online interview with you to understand your answers to this study more deeply. If you can help me by joining the interview, could you give me your name and contact address (e-mail address) for further communication?
いただいた回答を深く分析するために、もし可能でしたらオンラインでのインタビューをさせていただきたいと考えています。御対応可能な場合は、御名前と御連絡先（メールアドレス）をこちらに御記載願います。おって、こちらから御連絡させていただく場合がございます。

Ending Statement

By clicking on 'Finish this survey/調査を終える,' your answers will be recorded.
If you want to change your answers, please click on 'Back/戻る' and modify them.
If you want to stop the survey and do not want to record your answers, please close this page now.

「Finish the survey/調査を終える」をクリックすると、あなたの回答は保存されます。
今までの回答を修正したい場合は、「Back/戻る」をクリックして修正してください。
調査を中止して回答を保存しないことを希望される場合は、今、このウェブページを閉じてください。

Appendix 2. Online Interview Protocol

Opening statement: verbal consent before the interview

（日本語は下部にあります。）
You are being invited to participate in a study titled “Responsible translation of regenerative medicine in Japan”. This study is being done by Misa Aikawa from the Delft University of Technology (TU Delft).

The purpose of this research is to understand how to translate regenerative medicine with ethical considerations in Japan.
This study will take you approximately 20 minutes to complete. We will be asking you about the difficulties you feel when involved with the process of translating regenerative medicine based on your answers in the previous online questionnaire. Translating in this study means that the activities required to develop treatment or products from preclinical research. The data will be used for the analysis in the study of the master’s thesis. We may quote some of your responses anonymously in research outputs.

As with any online activity, the risk of a breach is always possible. We treat your data confidentially; Your answers are treated as anonymous. Personal information, such as name and contact information, will only be collected for thesis-related purposes (e.g., organising the interview). With your permission, the interview will be recorded, and the text will be automatically transcribed using Microsoft Teams. I will manually adjust the automatic transcription to match the original interview (and translate it into English since the master's thesis is written in English). The original transcripts and recordings will be stored on a secure server within TU Delft, in the Netherlands, which is accessible only to the research team. They will not be published anywhere and will be removed after completing the research.

Your participation in this study is entirely voluntary and you can withdraw at any time. You are free to omit any questions.

If you have any questions or comments about the study, you can contact Misa Aikawa via M.Aikawa@student.tudelft.nl

この調査は「日本における責任ある再生医療技術の実現」と題した修士論文研究の一環です。この研究はオランダのデルフト工科大学（TU Delft）の修士課程学生である相川美紗が行っています。

本研究の目的は、どのようにすれば倫理的視点を踏まえた再生医療技術の実現が可能となるか分析検討・提案することです。
本調査では、オンライン調査でのあなたの回答を元に、再生医療の実現に係るプロセスにおいて、あなたが難しいと感じる点等について伺うもので、所要は 20 分程度です。本研究における「再生医療の実現に係るプロセス」とは、前臨床研究から実際の治療法や製品を開発するまでの活動を指します。いただいた回答は上述の修士論文研究における分析に使用されます。修士論文において、いただいた回答の一部を匿名で引用させていただく可能性があります。

オンラインでのやりとりには必然的に一定の情報漏洩等リスクが伴いますが、機密性を保持した上で情報を取り扱います。いただいた回答は匿名で処理され、名前や連絡先等の個人情報は本インタビューの調整のためのみに使用されます。同意をいただいた上で、インタビューは録音され、Microsoft Teams によって自動的に文字起こしがなされます。その後、私（相川）が手動で調整を行ないます。修士論文は英語で執筆されるため、インタビュー録も私（相川）が英語へ翻訳を行います。インタビュー録と録音データは、

本研究チームのみがアクセス可能な、機密性の担保された大学内サーバーに保存されます。これらのデータは公表せず、本研究終了後に破棄されます。

参加は完全に任意であり、いつでも自由に撤回が可能です。質問を無回答とすることも可能です。

御不明点等ございましたら、M.Aikawa@student.tudelft.nl まで御連絡ください。

Protocol

The interview was semi-structured and took about 20 minutes. The interviewee was asked about the backgrounds of some of the questionnaire answers. It was hosted on Microsoft Teams. It was recorded, and the transcript was automatically generated. It was conducted in Japanese. Therefore, the automatic transcript was adjusted to match the original interview and translated into English by the author.

Appendix 3. Summary of Results of the Online questionnaire and Interview

*: This means that the information was obtained from the supplementary interview.

Q1: Number of participants in each category

Online questionnaire

- Researcher or Doctor: 2
- Promoter or Regulator: 2
- Patient or Public: 1

Supplementary interview

- Promoter or Regulator: 1

Q2-1: Experiences of facing issues/difficulties in translating regenerative medicine

Participants chose 3 or 4, meaning they all have experienced ethical issues or difficulties regarding translating regenerative medicine in Japan. However, these results may be influenced by sampling bias. Namely, participants might decide to participate in the questionnaire because they already know ethical issues related to regenerative medicine. Therefore, this result was treated as a premise for answering the questions of this questionnaire.

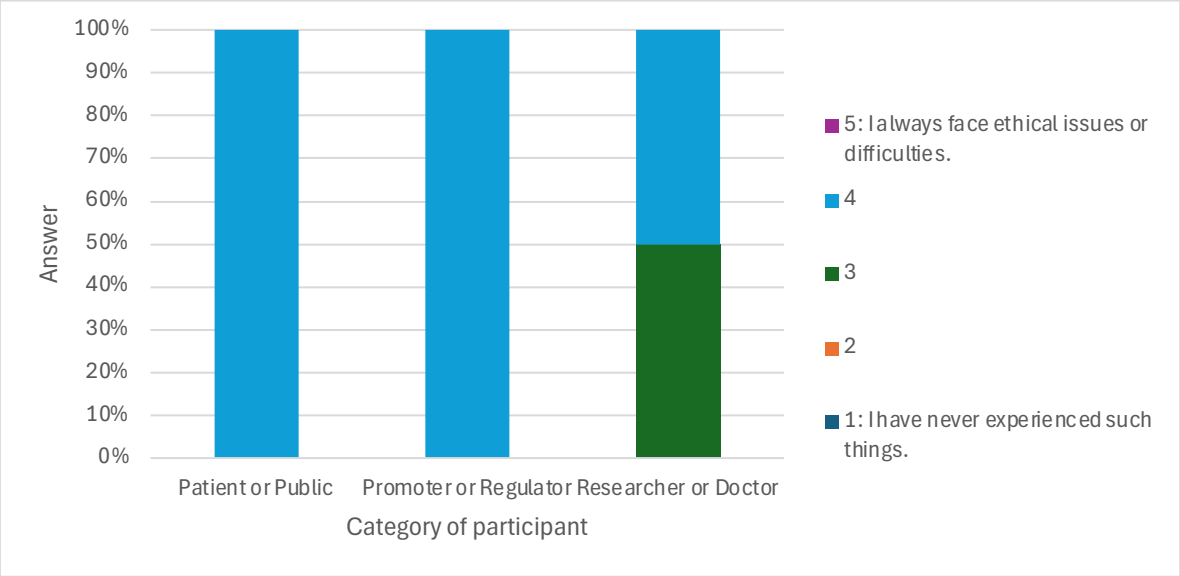


Figure A3-1. Result of Q2-1: Have you experienced any (potential) ethical issues or difficulties during your activities for translating regenerative medicine in Japan? Please choose the closest number that fits your opinion. (1: I have never experienced such things. 5: I always face ethical issues or difficulties.)

Q2-2: Examples of issues/difficulties

Researcher or Doctor

- Extreme expectations of patients and society for new treatment.
- Relations between the promotion of research development and ownership of cell donors.
- There is some evidence that safety and quality review under Law 3 is not sufficiently rigorous and that surgical elements of treatment are not evaluated.
- Like cases in the U.S., there is a practical difficulty in recalling products that have been approved conditionally and marketed under Law 4 when the evidence collected additionally shows that they are ineffective.

Promoter or Regulator

- Patient's understanding of uncertainties of regenerative medicine as an emerging technology.
- In Japan, there is a shortage of people who research ethics in this field. Also, there are few places where ethics professionals can work. These are the bottlenecks of ethical research in regenerative medicine.*

Patient or Public

- How do we deal with risks when conducting clinical research? (not only about regenerative medicine but in general medical fields)
- How do we define the acceptable extent or limitations of future research in regenerative medicine? For example, is it allowed to make brains or germ cells?

Q2-3: Ideas to address the issues/difficulties

Researcher or Doctor

- Clarify the issues based on the practical cases and then communicate with the public by collaborating with involved actors.
- Support small clinics to improve the speed and accuracy of data entry to the national database of experimental treatment and to conduct more robust long-term patient follow-ups.
- A more robust review of experimental procedures, including assessment of surgical elements and any novel delivery devices or other medical devices employed in the technique.

Promoter or Regulator

- Continuous consideration and verification from the basic research phase and conducting such research projects.
- The public discussion involves researchers, ethics professionals, patients and the public.
- Utilise mass media or SNS tools.

Patient or Public

- Careful informed consent.

Q3-1: Perception of the need to change

Answers tended to be neutral or negative against changing the current situation of regenerative medicine in Japan.

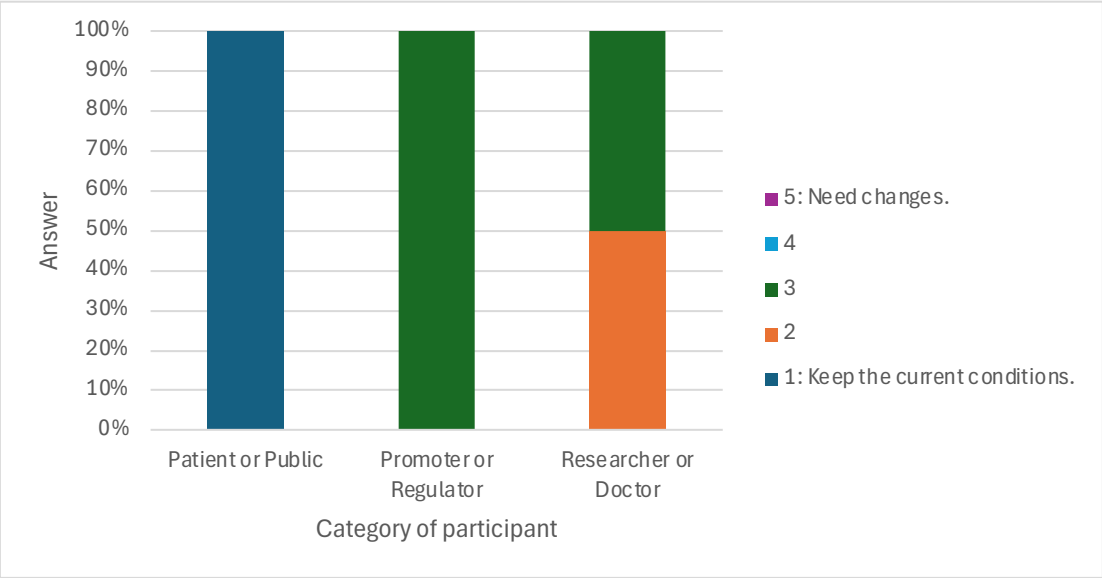
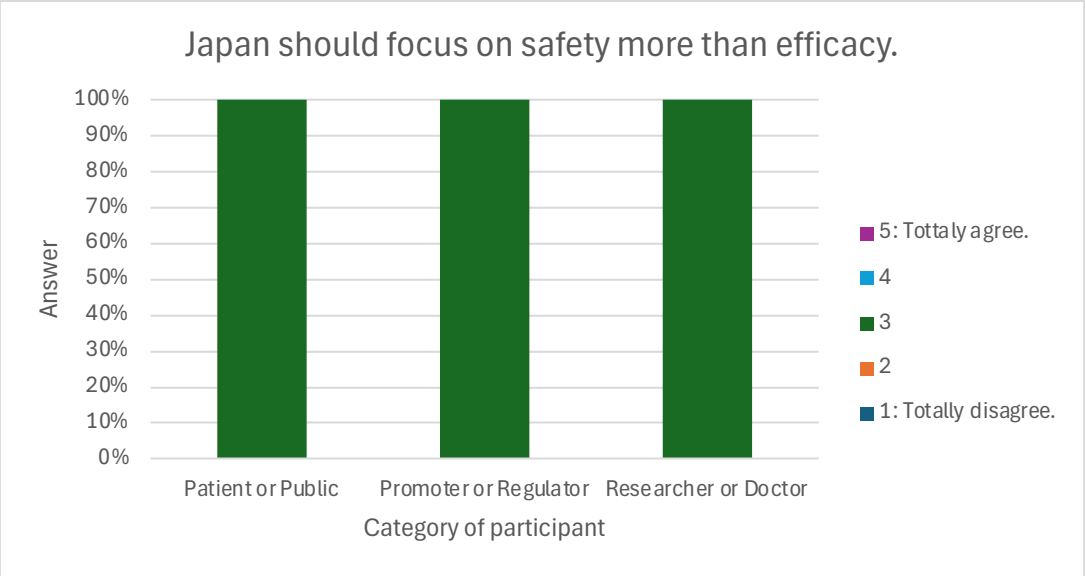
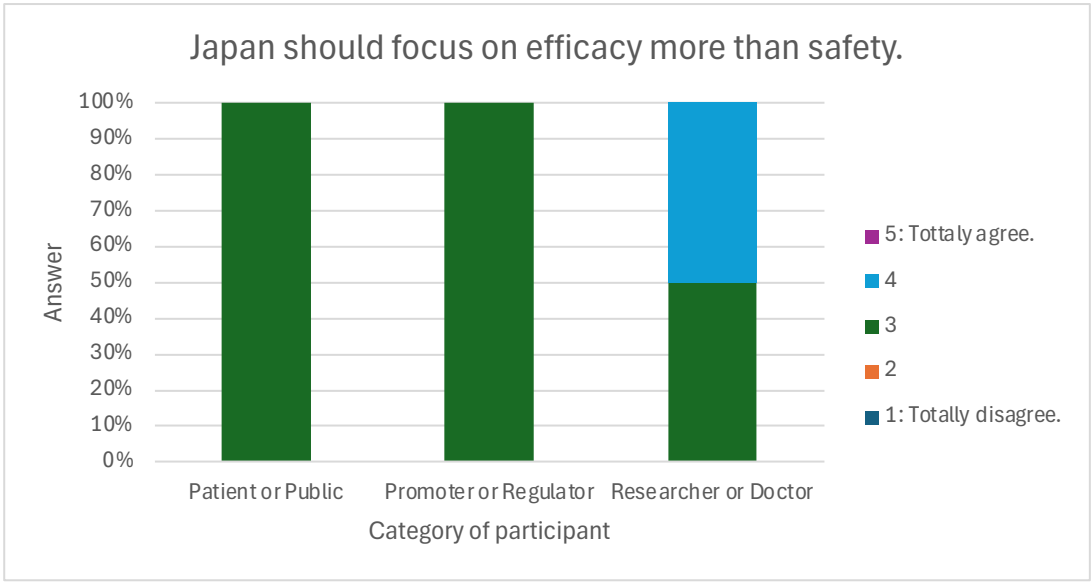


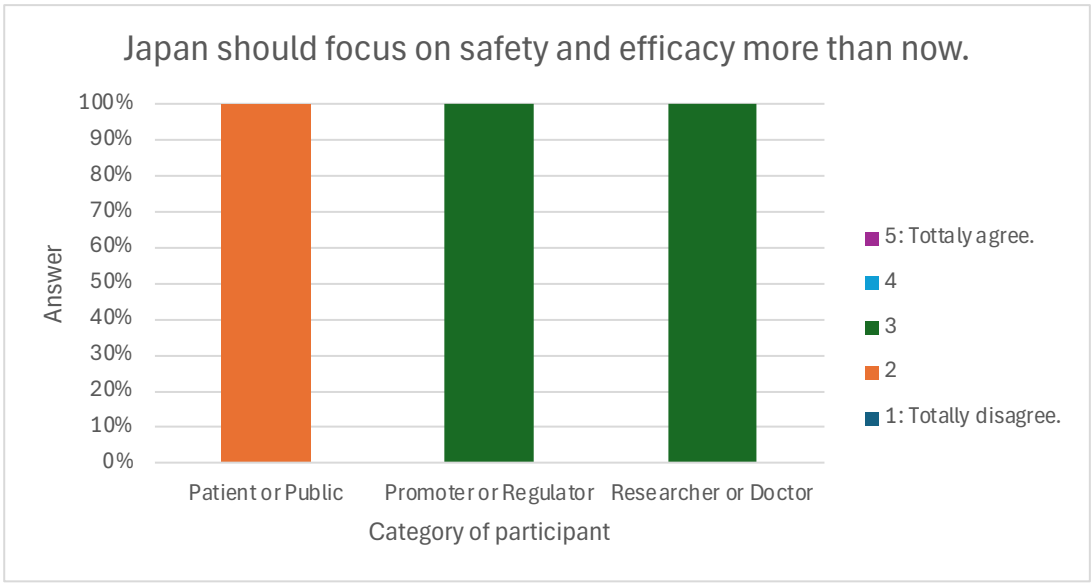
Figure A3-2. Result of Q3-1: How do you feel about the current situation as a player in translating regenerative medicine in Japan in general? Please choose the closest number that fits your opinion. (1: Keep the current conditions. 5: Need changes.)

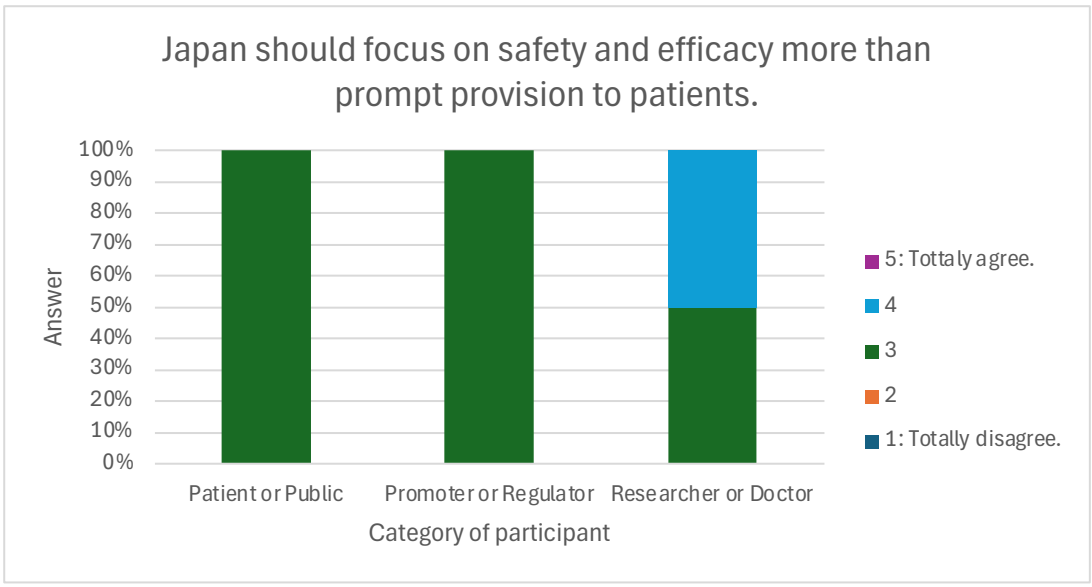
Q3-2: Priority of important aspects: safety, efficacy, prompt provision

Most participants were neutral or had no priorities when comparing critical ethical aspects. At the same time, there were relatively negative perceptions against focusing on prompt patient provision more than now. However, the background of these answers differs among participants, as shown in the answers in Q3-3.




Japan should focus on efficacy more than safety.
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Answer
Patient or Public
Promoter or Regulator
Researcher or Doctor
Category of participant
5: Tottaly agree.
4
3
2
1: Totally disagree.


Japan should focus on safety and efficacy more than now.
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Answer
Patient or Public
Promoter or Regulator
Researcher or Doctor
Category of participant
5: Tottaly agree.
4
3
2
1: Totally disagree.


Japan should focus on safety and efficacy more than prompt provision to patients.
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Answer
Patient or Public
Promoter or Regulator
Researcher or Doctor
Category of participant
5: Tottaly agree.
4
3
2
1: Totally disagree.

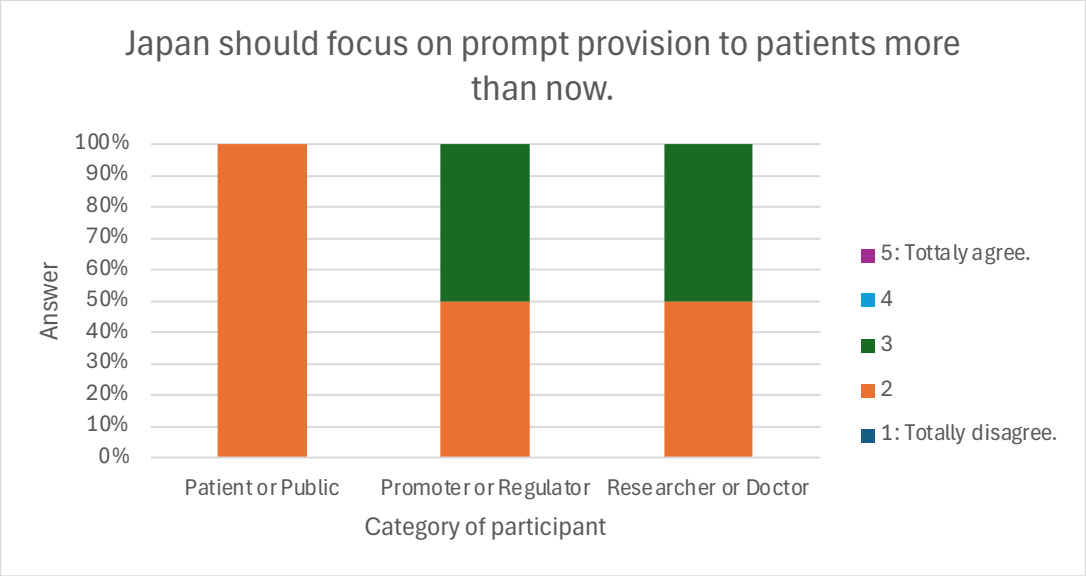


Figure A3-3. Results of Q3-2: How much do you agree with the statements? Please answer on a scale from 1 (Totally disagree) to 5 (Totally agree).

Q3-3: Comments related to Q3-2

Researcher or Doctor

- The balance (answers) depends on the more focused topic, such as clinical research, unproven treatment, or specific law in Japan.
- Japan's approach, namely creating a separate pathway for regenerative medicine under Law 3, is vital and important.

Promoter or Regulator

- It is important to consider feasibility, which enables regulations to be modified based on an objective review of the current research and development situation since new findings appear as research proceeds.
- In practice, patients should understand their conditions, i.e., how severe their disease and conditions are, possible treatments, and their risks. Practitioners must provide correct and enough information/objective evidence as much as possible to help patients understand that. Then, patients should make decisions about whether to take regenerative medicine, alternatives or nothing. Therefore, the priority of the asked aspects should depend on the case. Also, for this end, communication between practitioners and patients is crucial.

Q4: Actors' relative influences on addressing general ethical issues in translating regenerative medicine

The government and related organisations are considered to have the strongest influence. The influence of General public was considered to be lower than others. From the perspective of participants categorised as Researcher or Doctor, the influences of Researchers/Doctors and Research institutions/Hospitals and clinics are the same as that of Government and related organisations. Answers for Pharmaceutical companies and other related companies and Patients depended on the participants and were irrelevant to the participants' categories. Some participants provided reasons for their answers, as shown below.

Researcher or Doctor

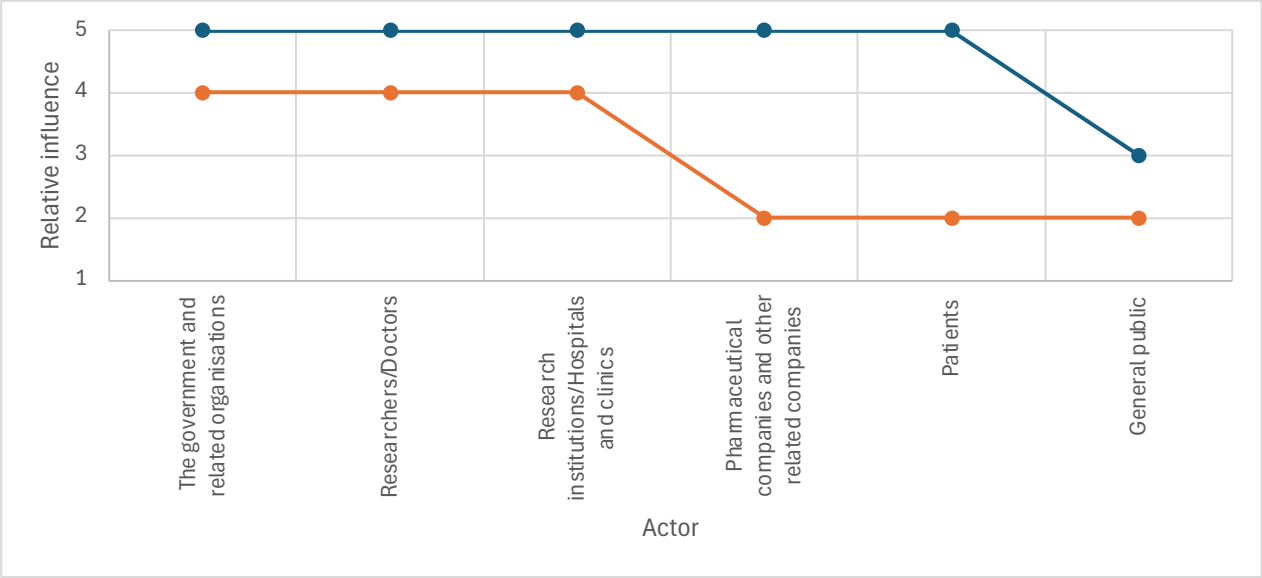


Figure A3-4. Answers to Q4 by Researcher or Doctor

Reasons for the answer shown in the orange in Figure A3-4:

- Patients and General public engagement with science and medicine have traditionally been limited in Japan. Also, there is limited evidence of patients, and even less so the public, being able to exert an influence on how medical practice, including research, is conducted or delivered. Therefore, Patients and General Public are listed as having low influence.
- Pharmaceutical companies could have a stronger influence. However, in practice, they typically view ethics as a matter of legal compliance rather than an area in which to develop innovative practices.
- The government, along with researchers, physicians and hospitals currently have the greatest potential to impact compared to the above actors.

Promoter or Regulator

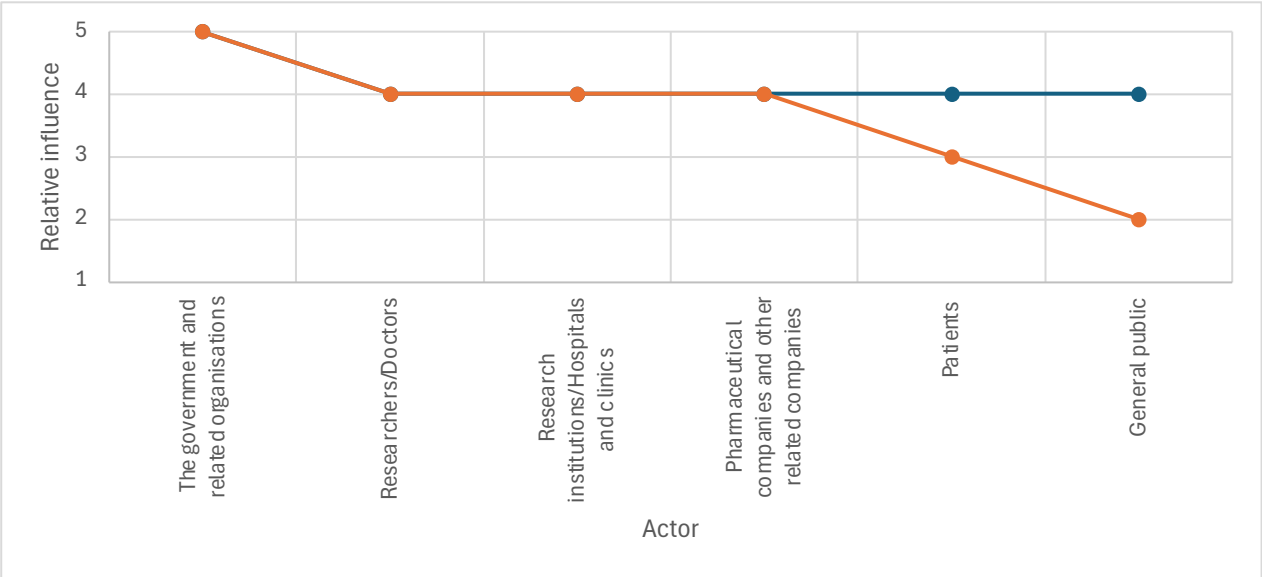


Figure A3-5. Answers to Q4 by Promoter or Regulator

Reasons for the answer shown in the navy in Figure A3-5:

- Patients can influence clinical research in regenerative medicine by their decision to participate. They can also influence the market or practical places by their decision to use regenerative medicine

products or treatments. If their decision is based on an ethical perspective, they could influence the addressing of ethical issues in the process of translating regenerative medicine.*

- Recently, it has been easier to create a big wave via SNS in Japan, and this is influential. For example, during the COVID-19 pandemic, the demerits of vaccines were distributed and partly exaggerated, and some people refused to take them. Ultimately, the percentage of people who have taken the vaccines three times is under 70 %, which might mean such a wave could move over 30 % of the population. In this way, General public could influence each other via SNS and impact the translation of regenerative medicine.*

Patient or Public

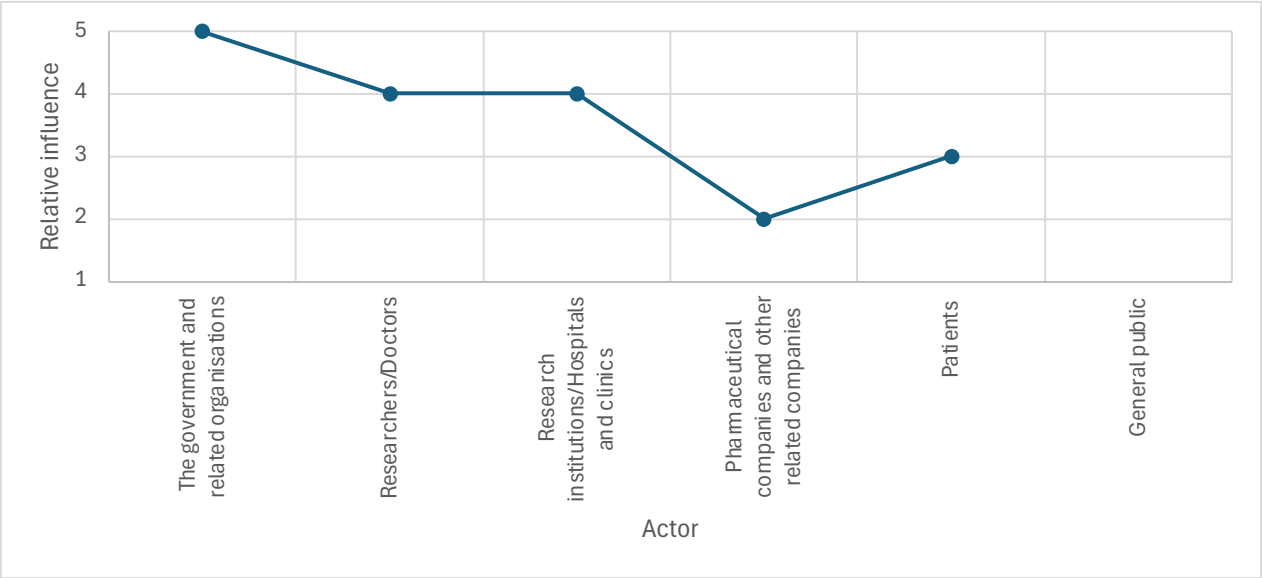


Figure A3-6. Answer to Q4 by Patient or Public. The answer of General public was blanked.

Other noted comments

- It is important to remember that even positions on acceptable standards of evidence are political: the three-phase clinical trial model is tied to the pharmaceutical industry business model, and its costs ensure that medicines remain expensive and cannot, for the most part, be delivered by the public sector.
- The ethical issues have not appeared socially, or people have not perceived their impacts enough to move to change the situation. We need to prepare before something happens, while society is usually aware of the need to change after disasters occur. Related to this, researchers and doctors of regenerative medicine perceive ethics professionals as a brake on research and development. Ethics professionals tend to research only their interests or what is in front of them and do not have the foresight to consider the societal impacts of translating regenerative medicine. Due to this gap, there are few job opportunities for ethics professionals, which leads to a shortage of them. It would be better if they could create concrete outputs in translating regenerative medicine and show their importance to society.*

Appendix 4. Overview of the Results of the Brief Literature Review to Understand Existing Studies Related to the Translations of Emerging Technologies

Table A4. Overview of the results of the brief literature review

Technology	Main questions/objectives	Methods	Main findings	Source
Non-invasive prenatal tests (NIPTs)	Review the downside of implementing NIPTs	Literature review (national policies and implementation programs)	• The fact that NIPTs require decisions about frameworks, access rights, social equity, financial support, and quality control, which are intertwined at various levels and responsibilities of multiple levels, including political and professional ones, makes it difficult to predict potential impacts • There are no control mechanisms yet available to avoid harm to the users of NIPT technology	(Baldus, 2023)
Nanotechnology	Shed light on the risk assessment for nanotechnology and identify the way to achieve it	Literature review	To avoid the technology from being used for weapons of mass destruction (WMD) : •Require joint efforts and consensus of governments, researchers and large producers •Regulating the domain at a national level •Implement new paradigms for educating scientists and engineers	(Buzdugan et al., 2022)
Civilian Unmanned Aerial Vehicle (UAV)	Explore governance challenges of emerging technology (civilian UAVs) in agriculture insurance through responsible innovation in India	• Literature survey • Interviews with possible actors and stakeholders	The RI approach, through its dimensions and steps, enables equal participation and deliberation among all the actors and stakeholders of UAV governance	(Chamuah & Singh, 2022)
Precision Medicine (PM)	Look in detail at the issues surrounding the implementation of PM for better strategy and faster processes for policymakers in Qatar	Literature review	Five keys to promote PM: •Create community awareness and PM education programs •Engage and empower patients •Communicate PM value •Develop appropriate infrastructure and information management systems •Integrate PM into standard healthcare system and ensure access to care	(Essa et al., 2020)
Public monitoring survey (case study)	Assess the legal and ethical implications of implementing policy using new technologies by looking at the case of wastewater monitoring for	Literature review	•Recommend further research to establish the sensitivity and specificity of the technique of the survey •Legal and ethical considerations must be taken into account, including appropriate limits on sample and data collection, use, and sharing, so as to prevent unduly undermining privacy and	(Gable et al., 2020)

	COVID-19 surveillance in the US		autonomy, and to reduce the potential for problematic misuse of data or coercive interventions	
AI	Analyse the misalignment of ethical AI between the governmental document and deployment in social service	Literature review based on the approach of institutional ethnography	The ethical AI discourse focuses more on adapting to a world with AI rather than questioning whether such a world is desirable, and they are disconnected from the critical public dialogue about the real-world application of AI in social welfare	(James & Whelan, 2021)
Biotechnology field	• What are the major barriers to implementing RRI in the US biotechnology innovation systems • How can policy entrepreneurs get RRI on the national policy-setting agenda	• Literature review to find barriers • Analysis to get RRI on the agenda by using three policy process theories: Multiple Streams Approach, Punctuated Equilibrium Theory, Advocacy Coalition Framework	• Three levels of barriers towards implementing RRI in biotechnology innovation systems: micro-, meso-, macro-levels • Three types of organisational barriers: cultural, structural, and interchange-related • To promote RRI in national policy-making: shifting the policy image of RRI, changing policy venues to encourage RRI, expanding the scope of RRI as a policy issue, and catalyzing focusing events to raise national awareness about RRI	(Kuzma, 2022)
Robotics and AI	Summarise ethical frameworks and regulations with a specific focus on ethical principles that have been translated into law by government bodies in the EU, the US, and Canada	Literature review (ethical principles, policies, and regulations proposed by governments and international organisations)	• Ethical questions of robotics policy: functionality, capability, autonomy • Policies are built through comprehensive analysis of ethical considerations • Governments and organizations have also implemented risk-and impact-assessment tools to facilitate policy adaptation for each case. • Current ethical frameworks are being translated into enforceable policy, where stakeholders are collaborating to create a set of regulations that would ensure sustainable innovation and human wellbeing	(Langman et al., 2021)
CRISPR (gene editing system)	Help construct more nuanced and effective ethical frameworks for public policy by unpacking the framing of CRISPR as a revolutionary technology	Identify CRISPR as a revolutionary technology and compare it with Ford Model T from the three aspects (product, process, social impact)	As CRISPR is a revolutionary technology, the ethical development, implementation, and provision requires early regulatory oversight and attention to its far-reaching global implications	(Mariscal & Petropanagos, 2016)
Neurotechnology	Review and analyse neuroethics guidance documents to envision roles and responsibilities	Literature review (guidance documents of several countries)	• Identify key ethics concerns and governance/procedural concerns • Strategies for regulatory bodies to implement ethics principles: increase regulatory attention, use healthcare provision, increase	(O'Shaughnessy et al., 2023)

	of stakeholders and suggest implementation strategies		post-market surveillance, consider more responsive strategies, utilise international and scientific advisory bodies, build and update international agreements, strengthen incentives	
Nanotechnology	Examine foresight study on the governance of the technologies by using nanotechnology as a case to facilitate responsible innovation and public acceptance when implementing new technologies in Europe	• Have dialog with stakeholders to identify uncertainties of the technology and make foresight scenarios • Hold workshops with stakeholders to test policies under the scenarios • SWOT (strengths, weakness, oppotunities, and threads) analysis	• Keys for the optimal governance: encouragement through policy adaptation or development, encouragement of and anticipatory and responsive approach, preparedness for a negative event, incentivising participation in governance, mandating demonstrations the adoption of governance approach • Also, key actions: evidence gathering, evolving existing frameworks openly, developing governance tools, incorporating international-level consensus • The interaction of stakeholders is an important component of delivering optimal governance	(Read et al., 2015)
Reproductive and genetic medicine (expanded carrier screening (ECS), non-invasive prenatal diagnosis (NIPD) and germline genome editing (GGE))	Explore how culture, structure and practice in healthcare is being shaped by innovations and changing dynamics in genetic and reproductive medicine in the Netherlands by focusing on three emerging technologies (ECS, NIPD, GGE)	• Interview with key stakeholders • Use the two theoretical frameworks for the study design and the interpretation of findings: Constellation Perspective and Network of Actors model	• Careful and step-wise implementation of new technologies is desirable for achieving social acceptance and responsible use of innovative discoveries in line with existing practice, structure and culture in the Netherlands • It is important to understand the contexts of innovation, by unravelling the culture, structure and practice	(Van Dijke et al., 2022)