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Review

Recommendations for the safe implementation of intravenous administration of mesenchymal stromal cells

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ABSTRACT

Mesenchymal stromal cells (MSCs) are immunosuppressive, inflammation-reducing, and fibrosis-modifying cells that are currently being used for a variety of diseases. In this context, the transvenous administration of MSCs must be performed correctly under controlled standards. To support clinical practitioners, the Japanese Society for Regenerative Medicine (JSRM) formed Mesenchymal Stromal Cells Infusion Working Group and developed a proposal on the management standards that should be followed by medical practitioners in the implementation of regenerative medicine regarding the transvenous administration of MSCs.

This review provides a comprehensive framework for the appropriate explanation of intravenous MSC administration to patients, including detailed discussions on the associated risks, protocols for addressing potential complications during administration, and strategies for ensuring patient safety. Particular emphasis is placed on the precautions and preparations necessary to mitigate the risk of fat embolism during MSC administration. The review outlines methods for patient monitoring to prevent such adverse events, protocols for responding effectively if a fat embolism occurs, and best practices for the handling of mesenchymal stem cells to minimize the likelihood of complications. Additionally, it includes recommendations for post-administration patient observation to enhance safety and efficacy. This review further incorporates a detailed checklist aimed at facilitating safe and effective MSC administration. It emphasizes the need for implementers to exercise the highest standards of care throughout the process. By addressing key practical and safety concerns, this review aims to serve as a valuable resource for ensuring the secure and reliable application of MSC therapies in clinical practice.

We hope that this paper will lead to the safe transvenous administration of mesenchymal stromal cells and that these recommendations will serve as a platform for the implementation of regenerative medicine in the future.

Contents

1. Introduction 172
2. Appropriate explanation to the patient 172
   2.1. Related to informed consent 172
   2.2. Points to be checked 173

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2.3. Points to be checked that should be recommended to implement the above 173
3. Precautions: risks and countermeasures for bone marrow and adipose tissue collection 174
3.1. Countermeasures against fat embolization 174
3.2. Points to be checked in advance for eligible patients 174
4. Dosage considerations 174
4.1. Prevention of embolism by administered cells and tissues 174
4.2. Other points to check 174
5. Preparation for administration 174
5.1. Precautions for administration 174
6. Observations during and after administration 175
7. Conclusion, future prospects 175
Declaration on conflict of interest 176
References 176

1. Introduction

The rapid increase in mesenchymal stromal/stem cell (MSC)-based therapies highlights their emerging significance across diverse clinical domains, including immunomodulation, tissue regeneration, and broader regenerative medicine applications. This growing interest in MSC therapies reflects their potential to address unmet medical needs; however, it simultaneously introduces critical scientific and regulatory challenges. Paramount among these challenges is the standardization of clinical protocols, the variability in MSC sourcing—ranging from bone marrow and adipose tissue to umbilical cord-derived cells—and inconsistencies in culture methodologies and quality control measures. Furthermore, the long-term safety profiles and therapeutic efficacy of MSC interventions remain areas requiring rigorous empirical investigation to ensure both clinical reliability and patient safety.

To address these challenges, Japan has established a regulatory framework under the Act on the Safety of Regenerative Medicine (ASRM). This framework mandates that all MSC-based therapeutic plans undergo stringent evaluation and commentary by accredited review committees, followed by formal notification to the Ministry of Health, Labour and Welfare (MHLW). As of December 16, 2024, over 1000 treatment plans involving MSC administration have been submitted under this framework [1].

The implementation of ASRM in Japan has significantly contributed to the transparency and regulation of stem cell therapies, particularly those performed without marketing authorization at the discretion of medical practitioners in private clinics. By mandating the submission of treatment plans and regular reports to the government, the ASRM framework has enabled the quantitative evaluation of the previously opaque expansion of stem cell treatments across the country. This system allows the government to monitor compliance, assess the safety of treatments, and gather critical data to guide policy-making and ensure patient safety. Moreover, the structured oversight discourages unethical or unproven practices, fostering an environment for responsible innovation and clinical standardization in regenerative medicine.

This substantial regulatory oversight reflects a deliberate effort to promote innovation in regenerative medicine while upholding stringent safety standards and ensuring ethical compliance in clinical practice.

While the ASRM framework represents a critical step toward the structured clinical application of MSCs, further refinement and alignment with global standards are imperative. Collaborations between academic societies and regulatory authorities such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), as well as the Japanese MHLW, will be essential for harmonizing safety protocols, addressing disparities in access and cost, and fostering consistency in therapeutic outcomes. Achieving such global harmonization will significantly enhance the scalability, reliability, and widespread adoption of MSC-based therapies, ensuring their sustained integration into clinical practice worldwide.

In clinical practice, the administration of MSCs via intravenous routes necessitates meticulous oversight. Unlike pharmacologically active substances, MSCs are significantly larger in size, which increases their likelihood of becoming trapped in capillaries during circulation. This characteristic poses a heightened risk of embolic events[i], particularly in the lungs, where the density of capillary networks is exceptionally high. In cases of adverse events, such as pulmonary embolism, myocardial infarction, or cerebral infarction caused by administered cells, prompt identification and intervention are critical to mitigate potential complications. The size-related risk underscores the importance of careful monitoring and preparation to address embolic complications during and after MSC administration.

Donor institutions are required to ensure that both the patient's condition and the donor system meet all necessary safety standards prior to treatment. Moreover, comprehensive post-administration monitoring is essential, including preparedness for hospitalization in cases of adverse reactions. Even if acute symptoms resolve, the potential for subsequent complications warrants careful patient management and institutional readiness to address emergent risks.

In the following section, we present a comprehensive checklist outlining the procedural safeguards and monitoring protocols necessary to ensure the safe intravenous administration of MSCs.

2. Appropriate explanation to the patient

2.1. Related to informed consent

When administering MSCs intravenously, the project leader or physician in charge should explain the procedure to the patient or surrogate and obtain consent using the submitted consent explanation document. When explaining consent, the following points should be checked in addition to including the mandatory items [2] specified in the Enforcement Regulations of

[i] Fat emboli are often caused by orthopedic trauma (especially fractures), but can also occur with bone marrow transplantation, liposuction, and pancreatitis. Pulmonary emboli are the most common (75 %), with other lesions in the brain, skin, eyes, and heart. Symptoms of pulmonary emboli include hypoxia, tachycardia, and fever. Cerebral lesions from fat emboli are cerebral edema due to circulatory disturbance rather than ischemia, with a variety of nonspecific symptoms including loss of energy, somnolence, disorientation, and insomnia. Skin lesions, including skin petechial hemorrhage, are present in 50 % of fat emboli, but often resolve within 24 h. Diagnostic tests are non-specific, although lipase, free fatty acids, and phospholipase A2 are elevated. Macrophage uptake of fat may be seen in BAL (bronchoalveolar lavage). The diagnosis is generally made by symptoms.

the Act on the Safety of Regenerative Medicine in the consent document[ii].

[ii] According to items 31 to 54 of the Checklist of Standards for the Provision of Regenerative Medicine (Reference 2), the following points must in principle be explained to the recipient of a regenerative medicine therapy, using as simple language as possible, and written consent must be obtained.

a) The name of the regenerative medicine therapy to be provided and a statement that the plan for the provision of the regenerative medicine therapy has been submitted to the Minister of Health, Labour and Welfare
b) The name of the medical institution providing the regenerative medicine therapy, and the names of the administrator of the medical institution, the person responsible for implementation of the regenerative medicine therapy, and the physician or dentist who will perform the regenerative medicine therapy (in the case where regenerative medicine therapy is performed as a multicenter joint research, the name of the representative administrator and the names of other medical institutions performing the regenerative medicine therapy and the administrator of the medical institutions.
c) Purpose and details of the regenerative medicine therapy to be provided
d) Information on the cells to be used for the regenerative medicine therapy
e) Reason for selection as a recipient of the regenerative medicine therapy (limited to cases where the regenerative medicine therapy is performed as research)
f) the anticipated benefits and disadvantages resulting from the provision of the regenerative medicine therapy
g) Refusal to receive the regenerative medicine therapy is voluntary.
h) Matters concerning the withdrawal of consent
i) The patient shall not be treated disadvantageously by refusing to receive the regenerative medicine therapy, or by withdrawing consent.
j) Method of disclosing information on research (limited to cases where the regenerative medicine therapy is conducted as research)
k) A statement that the research plan and other materials on the implementation of the research may be obtained or inspected upon request of the person who is to receive the regenerative medicine therapy, or the surrogate consent, and the method of obtaining or inspecting such materials (limited to cases where the regenerative medicine therapy is conducted as research).
l) Matters concerning the protection of personal information of a person who receives the regenerative medicine therapy
m) Method of storage and disposal of samples, etc.
n) Status of involvement in research prescribed in each item of Article 8-8(1) of the Enforcement Regulations of the Act on the Safety of Regenerative Medicine (limited to the case where the regenerative medicine therapy is conducted as research)
o) System for responding to complaints and inquiries
p) Matters concerning expenses for the provision of the regenerative medicine therapy
q) Availability and details of other treatment methods and comparison with the anticipated benefits and disadvantages of those treatment methods
r) Matters concerning compensation for damage to health resulting from the provision of the regenerative medicine therapy (limited to cases where regenerative medicine therapy is provided as research)
s) In cases where there is a possibility that important findings may be obtained concerning the health of a person who receives the regenerative medicine therapy, genetic characteristics that may be passed on to his/her descendants, etc., the handling of such findings (including incidental findings) pertaining to the person concerned
t) If there is a possibility that the sample, etc. obtained from a person who receives the regenerative medicine therapy will be used for future research that is not specified at the time the consent is obtained from the person or will be provided to other medical institutions, a statement to that effect and the details of such research that are assumed at the time the consent is obtained
u) Matters to be examined by an accredited committee for regenerative medicine, which conducts the business of examination, etc. of the regenerative medicine therapy and other matters concerning the accredited committee for regenerative medicine pertaining to the regenerative medicine therapy
v) The details of the contract prescribed in Article 32 of the Clinical Research Act (limited to the case where the regenerative medicine therapy is conducted as research) in the case where research is conducted with research funds, etc. provided by a manufacturer or distributor of pharmaceuticals, etc. who manufactures and sells or intends to manufacture and sell pharmaceuticals, etc. used in research or a specially related person thereof
w) Other necessary matters concerning the provision of the regenerative medicine therapy.

2.2. Points to be checked

- ☐ Is the consent explanation document submitted to the Accredited Committee for Regenerative Medicine correctly explained to the patient or donor?
- ☐ Are the risks of cell collection and administration adequately documented?
- ☐ In particular, has the possibility of embolism been explained?
- ☐ Is the explanation given to the patient recorded in the medical record?
- ☐ Has a compensation plan been considered?
- ☐ Is there a contact person listed in the description document who can be reached anytime regarding physical changes, emergencies, or complaints?
- ☐ Are appropriate responses and emergency implementation systems explained in the event of any illnesses, etc.?
- ☐ Has it been explained that the harvested cells may not be useable?

2.3. Points to be checked that should be recommended to implement the above

(1) Basic Implementation Facility Structure
- ☐ In the case of hospitals, an internal hospital committee should be established to clarify the system of responsibility
  Experienced physicians should be responsible for managing clinics with small staff.
- ☐ Is the system of responsibility for collection clearly defined?
- ☐ Is an emergency contact network in place?
- ☐ Preferably provided by physicians and facilities certified by the Japanese Society for Regenerative Medicine and the Japanese Society of Blood Transfusion and Cell Therapy

(2) Development of implementation system
- ☐ Is there adequate supervision by medical staff with sufficient experience?
- ☐ Are ECGs, oxygen saturation monitors, oxygen delivery systems, resuscitation sets, and emergency medical supplies in place in case of a sudden change in the donor's condition during collection?
- ☐ Is there a physician available to provide immediate emergency care? Or, is there a system in place for immediate transport to an emergency facility?
- ☐ Is there a manual of procedures for collection, etc.?
- ☐ Is the treatment plan clearly explained to the patient?
- ☐ Are you supposed to see the doctor for a certain period of time after administration?
- ☐ Is the administration information documented in the medical record?
- ☐ Are vital signs, physical findings, and blood tests confirmed immediately after administration?
- ☐ Is a specific explanation given for the appearance of illness, etc. (specific examples: pulmonary embolism symptoms, dyspnea, numbness in arms and legs, chest pain, cerebral infarction, loss of consciousness, speech entanglement) after the patient returns home?
- ☐ (If possible, a contact person who can be reached 24 h a day, 7 days a week, should be clearly identified in the event of the emergence of any of the above diseases, etc.)

- ☐ Are the cells tested for infections about a few months after administration in anticipation of the development of infections related to cell administration?
- ☐ Is there clear contact information for any post-administration illnesses, etc.?
- ☐ In the case of a clinic, are the facilities necessary for emergency medical care notified in the plan for providing regenerative medicine therapy, including emergency hospitalization on the same day ensured?

3. Precautions: risks and countermeasures for bone marrow and adipose tissue collection

3.1. Countermeasures against fat embolization

- Be aware of the possibility of fat embolization during bone marrow or adipose tissue collection.
- Mechanism: Fat cells (adipocytes) in the bone marrow or adipose tissue are destroyed and triglycerides enter the vein, causing pulmonary embolization. Platelets and leukocytes react locally to the embolized fat droplets, causing vascular endothelial injury and vasoconstriction.
- Countermeasures: The following measures, etc., should be taken at the discretion of the physician.
- (Monitoring) Monitor oxygen saturation with a pulse oximeter during collection.
- (Action) If oxygen saturation falls below 92 %, administer oxygen inhalation immediately and discontinue collection.
- (Examination) (If an embolus is suspected) After collection, perform chest x-ray, CT, pulmonary scintigraphy, blood flow scan, etc.
  (When implementing the plan, advance contact should be made with the facilities necessary for emergency medical care as notified in the plan for providing regenerative medicine therapy)

3.2. Points to be checked in advance for eligible patients

(1) Donor (for autologous cell administration) checklist
- ☐ No history of thrombosis?
- ☐ No evidence of active infectious disease such as infectious diseases such as HIV, tuberculosis, hepatitis virus, syphilis, etc.
- ☐ Are there any serious underlying diseases or laboratory abnormalities?
- ☐ No or uncontrolled hypertension or hyperlipidemia
- ☐ No myeloproliferative disorders such as leukocytosis, thrombocytosis, or abnormalities of the coagulation system
- ☐ Is blood to be drawn or otherwise checked for safety after the collection is complete?
- ☐ Can you come to the hospital after the collection is completed to confirm the results?

4. Dosage considerations

4.1. Prevention of embolism by administered cells and tissues

A) In cases involving adipocyte culture (passaging) (adipose tissue contamination is thought to be rare, but there are actual cases)
B) When fat cells are administered without culture (need to consider how much fat can be removed)

In the case of non-adipose cells, it is necessary to check for aggregates of mesenchymal stromal cells, leukocytes, lymphocytes, etc.

4.2. Other points to check

(1) Processing Facilities and Structure
- ☐ Are sanitary controls in place?
- ☐ Is the equipment regularly inspected?
- ☐ Are operating procedures documented and reliably recorded?
- ☐ Are procedures in place to check for abnormalities in monitoring values of safety cabinets, incubators, freezers, centrifuges, etc. during operations?

(2) Confirmation of processed products
- ☐ Is the container damaged?
- ☐ Are cell counts, cell concentrations, and dosing rates reasonable?
- ☐ Evaluate for aggregation (can be predicted by visual microscopy and cell count calculations)
- ☐ Is the concentration and dosage of Dimethyl sulfoxide: DMSO (a widely used cryoprotectant in cell preservation, plays a critical role in maintaining the viability of MSCs during storage and transport.) in the body appropriate?
- ☐ Is it necessary to remove agglomerates by filtering (mesh size 100 μm or smaller) before filling the bag?
- ☐ Has the quality of the product been checked during transportation?
- ☐ Is there a system in place for the physician to confirm that transportation and hauling are being performed properly?
- ☐ Are procedures in place to ensure that there is no risk of contamination, such as broken containers, when administering the drug?

5. Preparation for administration

During administration, use a commercially available transfusion set for red blood cells (e.g., Terufusion transfusion set) or a microaggregate removal filter (Pall transfusion filter) to remove aggregates.

5.1. Precautions for administration

The same risk considerations must be taken into account when administering the drug as they are when collecting it. It goes without saying that even if the frequency of risk is very low, the risk may be life-threatening, and therefore, all possible preparations and responses are necessary.

In particular, cell administration should always be performed under the supervision of medical personnel experienced in regenerative medicine from start to finish, always taking into account the possibility of embolism due to cell aggregation or contamination with fatty tissue or other substances, allergic reactions, adverse reactions due to residual reagents or other substances, and infections caused by biologically derived products.

(1) Pre-check of patients to be administered
- ☐ Any history of thrombosis such as pulmonary embolism, myocardial infarction, or cerebral infarction
- ☐ Are there any problems with coagulation tests (PT, APTT, FDP, D-dimer, Protein C, S, AT-III)?
- ☐ No thrombosis (deep vein thrombosis, pulmonary embolism, etc.) at this time?

- ☐ No coronary, cardiac, pulmonary, hepatic, or neurological disease?
- ☐ Cardiac, respiratory, and hepatic function problems prior to administration?
- ☐ No history of allergies to chemicals or other substances used?
- ☐ Is there an anastomosis between venous arteries that would cause cells to enter the arterial system (e.g., septal defects in the heart)?
- ☐ No hypertension or hyperlipidemia?
- ☐ No myeloproliferative disorders such as leukocytosis, thrombocytosis, or abnormalities of the coagulation system?
- ☐ Has the patient developed an acute infection other than the one being treated at the time of administration?
- ☐ Is the safety of the patient to be confirmed by blood sampling or other means after the administration is completed?
- ☐ Can it be checked by visiting the hospital after the administration is completed?

(2) System at the time of implementation at the time of administration

- ☐ Is the doctor familiar with regenerative medicine (e.g., a doctor certified in regenerative medicine by the Japanese Society for Regenerative Medicine) in charge?
- ☐ Is the doctor familiar with the target disease?
- ☐ Is there adequate supervision by medical staff with sufficient experience?
- ☐ Are ECGs, oxygen saturation monitors, oxygen delivery systems, resuscitation sets, and emergency medical supplies (including boosters and steroids) in place in case of a sudden change in the patient's condition during administration?
- ☐ Is there a firm set amount of time for watching and observation by the medical staff at the time of administration?
- ☐ Is there a physician available who can quickly provide emergency care? Or, is there a system in place for immediate transport to an emergency facility (it is advisable to request emergency assistance in advance from the ICU, emergency department, or nearby emergency facility)?
- ☐ Are there written procedures and other manuals for administration?
- ☐ Do you provide regular training on risks and procedures for the medical care you provide?

6. Observations during and after administration

(1) time of administration

- ☐ Are there any abnormalities in vital signs?
- ☐ Are there any abnormalities in the EKG?
- ☐ Are there any abnormalities in cardiopulmonary function?
- ☐ No fever?

(2) Post-administration checks

- ☐ The physician in charge and several related personnel will confirm the patient's safe status with regard to the above. If any adverse event is predicted to occur, the patient should be admitted to an institution that can respond to the emergency.

(3) Next day onwards

- ☐ In addition to the absence of abnormalities in cardiopulmonary and physiologic parameters, the following tests are performed: urinalysis, chest X-ray, general blood tests (white blood cell count, red blood cell count, platelet count, white blood cell fraction), blood chemistry tests (total protein, albumin, total bilirubin, direct bilirubin, AST, ALT, gamma-GTP, alkaline phosphatase, cholinesterase, LDH, uric acid, BUN, ammonia, serum creatinine, sodium, potassium, C-reactive protein), and blood coagulation system tests (PT (%), PT-INR, APTT, FDP, D-dimer, antithrombin III) are checked for abnormalities, and initial observation is completed.

Even if no disease or other problems occur after cell administration, an appropriate schedule of reexamination within one week should be established and implemented, considering the development of late complications.

7. Conclusion, future prospects

The adoption and clinical application of MSCs continue to grow globally, driven by their potential to address a wide range of unmet medical needs. Ensuring the safe and effective implementation of MSC therapies is paramount to maximizing their clinical utility while minimizing associated risks. To this end, JSRM has developed the first comprehensive procedural manual, incorporating a detailed checklist tailored for the intravenous administration of MSCs. This checklist not only provides a practical framework for medical practitioners but also establishes a benchmark for standardizing MSC administration procedures in Japan.

The significance of this checklist lies in its capacity to address critical safety concerns, such as the risk of embolic events, adverse immune responses, and infections. By mandating thorough patient monitoring, proper handling of cells, and rigorous adherence to protocols, the checklist ensures a higher standard of care in MSC therapies. Furthermore, its systematic approach facilitates better training and preparedness among medical personnel, ultimately contributing to the reliability and scalability of MSC treatments.

Japan, with its robust regulatory framework under ASRM, has positioned itself as a leader in the safe implementation of regenerative medicine. The ASRM framework mandates transparency through the submission of treatment plans and regular reporting to the Ministry of Health, Labour and Welfare (MHLW), enabling the government to quantitatively evaluate the widespread use of stem cell therapies in private clinics. This transparency has not only enhanced regulatory oversight but has also allowed Japan to identify key considerations in the clinical application of MSC therapies. These insights, drawn from extensive practical experience, are poised to serve as a valuable resource for shaping international guidelines.

Looking forward, the procedural manual and checklist developed by JSRM have the potential to make a profound global impact. By disseminating these best practices internationally, Japan can contribute to the harmonization of MSC administration protocols and foster consensus on safety and efficacy standards. Such efforts will be instrumental in mitigating risks and building trust among patients and stakeholders worldwide. Additionally, the checklist can serve as a foundational tool for collaborative efforts with international regulatory authorities, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), to develop globally unified standards for MSC-based therapies.

In conclusion, this initiative represents a significant milestone in the field of regenerative medicine. The procedural manual and checklist are not only pivotal for ensuring safe MSC administration in Japan but also hold the promise of advancing international efforts

toward safer and more effective cell therapies. As MSC treatments continue to expand, these resources will play a critical role in achieving global alignment on best practices, thereby enhancing patient safety and clinical outcomes across diverse healthcare systems.

Declaration on conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The Japanese Society for Regenerative Medicine has received declarations of conflict of interest regarding the following items from each member involved in the Working Group for Recommendations for the Safe Implementation of Intravenous Administration of Mesenchymal Stromal Cells regarding financial relationships with specific companies.

Name	Items to declare A	Items to declare B
Shuji Terai	Not applicable	1. ROHTO Pharmaceutical Co., Ltd.AbbVie Inc.Sumitomo Dainippon Pharma Co., Ltd. Otsuka Pharmaceutical Co., Ltd.Mochida Pharmaceutical Co., Ltd.Asahi Kasei CorporationNippon Kayaku Co., Ltd.FUJIFILM WAKO PURE CHEMICAL CORPORATIONStemRIM Inc.Abbott LaboratoriesJapan Biological Products (JBP) Kowa Co., Ltd.Shionogi & Co., Ltd,Cuorips Inc. 3. Chiome Bioscience Inc. 4. Otsuka Pharmaceutical Co., Ltd. AbbVie Inc.ASKA Pharmaceutical Co., Ltd.Chiome Bioscience Inc.Sumitomo Dainippon Pharma Co., Ltd.Takeda Pharmaceutical Co., Ltd.Gilead Sciences, Inc.Janssen Pharmaceutical K.K. * 2, 5, 6, 7, 8, 9, 10, 11, 12 not applicable
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3. Consulting fees
4. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events
5. Payment for expert testimony
6. Support for attending meetings and/or trave
7. Patents planned, issued or pending
8. Participation on a Data Safety Monitoring Board or Advisory Board
9. Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid
10. Stock or stock options
11. Receipt of equipment, materials, drugs, medical writing, gifts or other services
12. Other financial or non-financial interests

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[2] Research and Development Division, Medical Policy Bureau, Ministry of Health, Labour and Welfare. Checklist of standards for the provision of regenerative medicine. Annex 4 of the Administrative Notice (issued on 21st November 2014 and last updated on 20th February 2023 in Japanese). https://www.mhlw.go.jp/content/001060328.pdf [Last Accessed 2 January 2025][ii].