*June 14-18, 2021*
*Virtual Summit*

## THE 2021 WORLD STEM CELL SUMMIT

# NRMD, National Regenerative Medicine Database
## A Bridge between Two Legislation Systems in Japan


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**National Institute of Health Sciences, Japan**

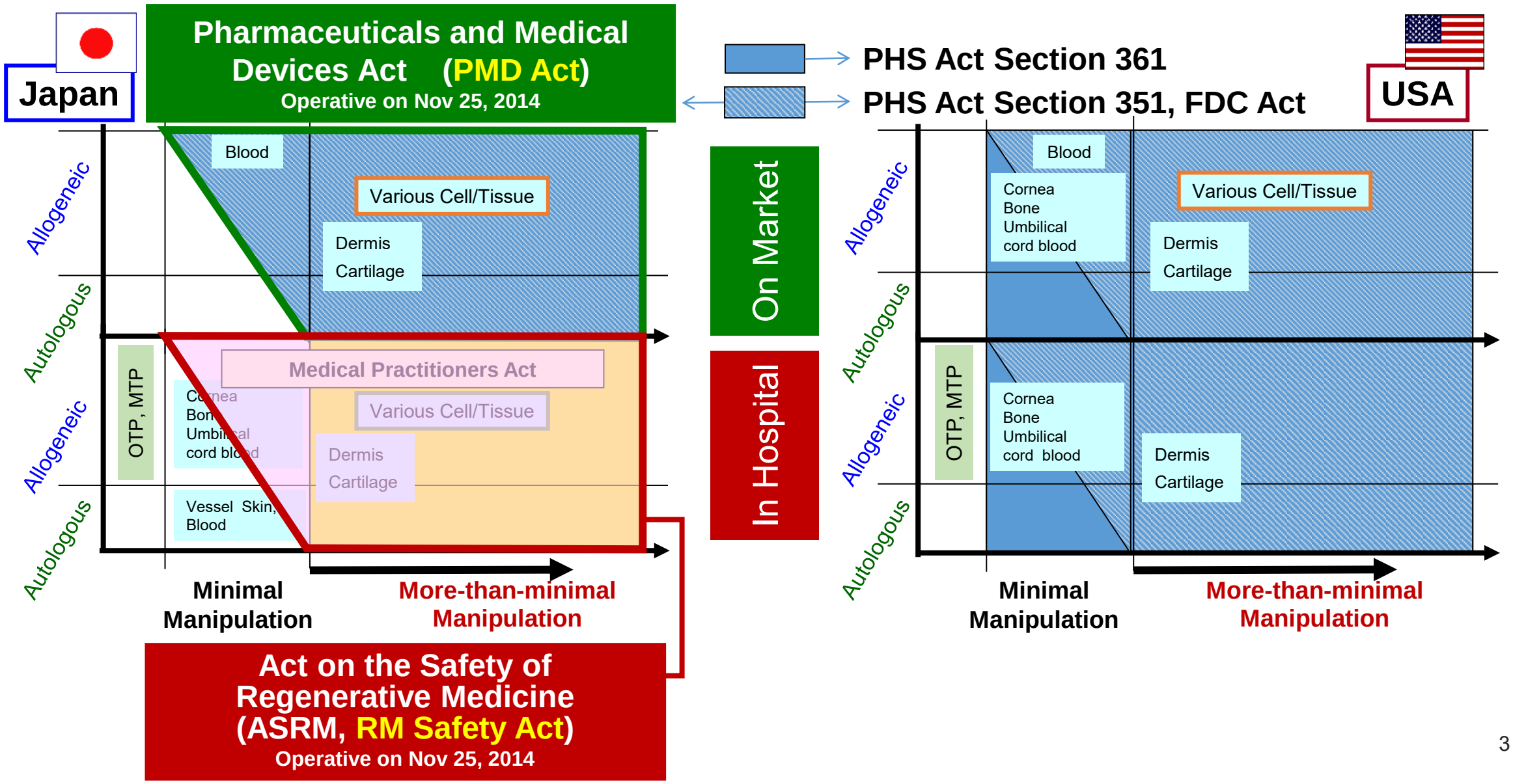
**Vice Chair of The Database Committee,**

**The Japanese Society for Regenerative Medicine**

**DISCLAIMER:**

The views and opinions expressed in this presentation are those of the presenter and do not necessarily represent official policy or position of the National Institute of Health Sciences, the Japan Ministry of Health, Labour & Welfare. Also, the presenter has no COI to disclose in connection with this presentation.

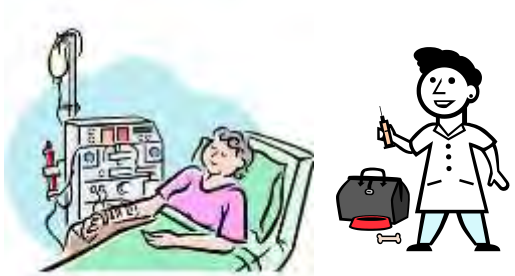
# Regulations for RM/CT



# Two Acts Regulating RM/CT

Regenerative Medicine (RM)
Cell Therapy (CT)

**Medical practices using specified processed cells**
without marketing authorization



Manufacturing and marketing of
**products for RM/CT** by firms

**Act on the Safety of Regenerative Medicine (RM Safety Act)**

- Medical treatments using processed cells
- Clinical researches using processed cells (non-commercial)

**Pharmaceuticals & Medical Devices Act (PMD Act)**

- Regenerative medical products (RMPs=CTP/GTPs)
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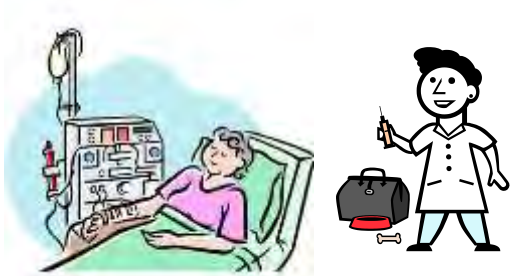

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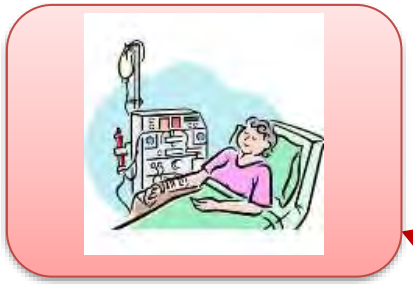
# Overview of the RM Safety Act



RM/CT as medical practices

Hospitals / Clinics

Plan

Review

Certified Committee for Regenerative Medicine

Approval

**II. Enable commissioning cell processing to licensed enterprises**

**I. Obligate hospitals and clinics to submit plans**

Cell processing

Certification

Cell processors

**III. Obligate CPFs to notify or obtain license**

Minister of Health

Notification (Hospitals / Clinics) or License (Firms in Japan)
Accreditation (Firms outside Japan)

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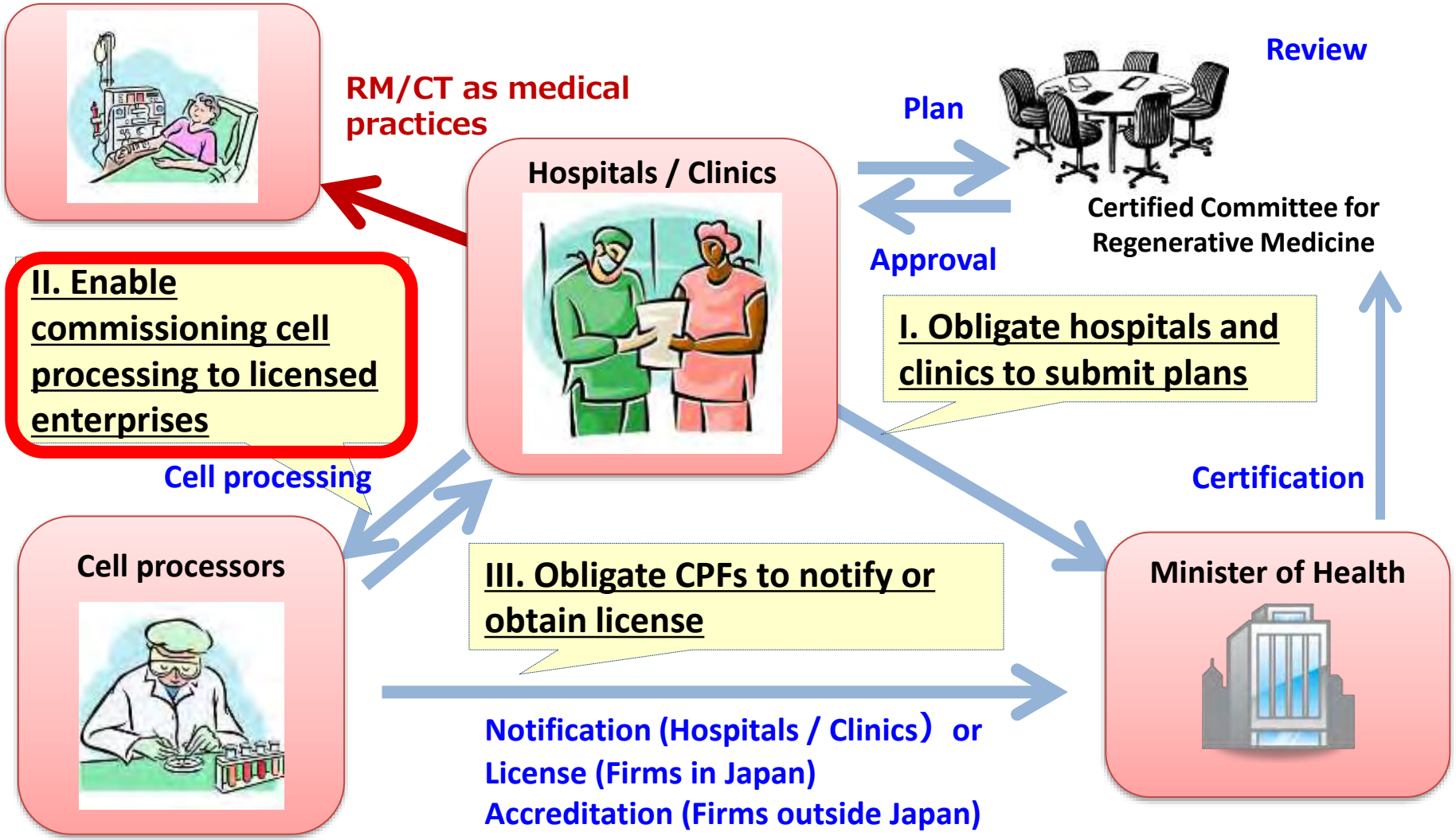


# The two legislations share common good practices for the quality/manufacturing control of manipulated cells

Out-of-pocket medical treatments
& non-commercial clinical researches
using specified processed cells without MA

Commercial distributions of
regenerative medical products
& their clinical trials

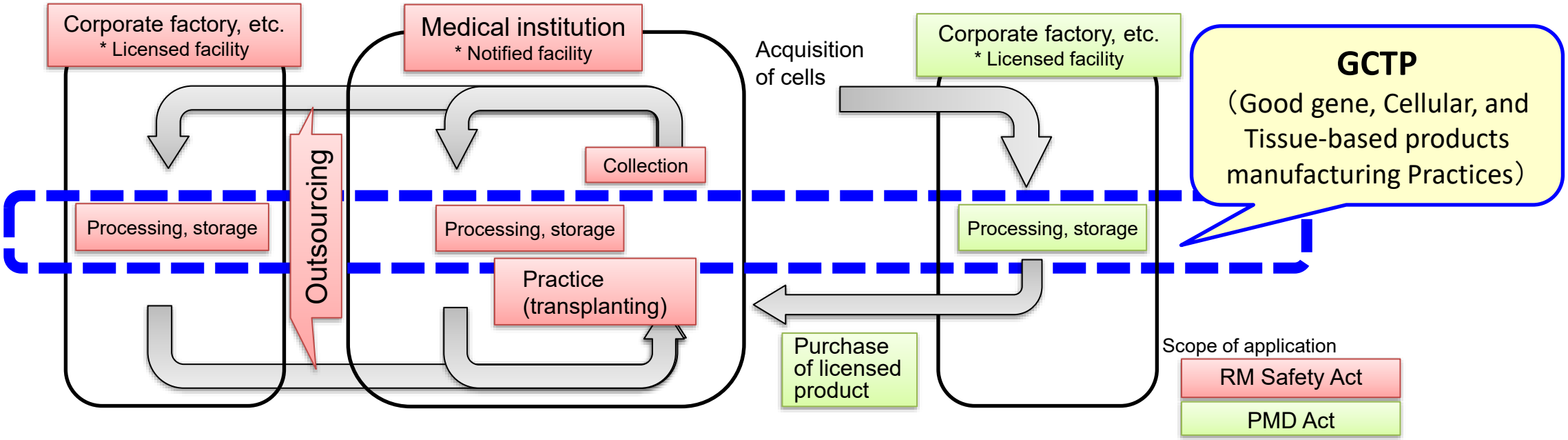
## RM Safety Act

The safety, etc., of regenerative medicine provided as a medical service is ensured by stipulating the practical procedures of, for instance, sampling, standards for medical institutions that provide regenerative medicine and standards for facilities that culture and process cells.

## PMD Act

The efficacy and safety of regenerative medical products are ensured by stipulating standards for manufactory of regenerative medical products.

* Outsourcing of cell culturing and processing carried out under the responsibility of physicians based on the Regenerative Medicine Safety Assurance Act is exempt from the application of the Pharmaceutical and Medical Device Act.



# Specials & Hospital Exemption

| | Specials | Hospital Exemption |
|---|---|---|
| **Legal basis** | Art. 5 (1) of Directive 2001/83/EC (Compassionate use on a named patient basis) | Art. 28 (2) ATMP regulation amending art. 3 of Dir. 2001/83/EC |
| **Authorisation** | No product licence but manufacturer licence | |
| **Qualified Person** | NO | |
| **Scope** | Any medicinal product including ATMPs | ATMPs only |
| **Purpose** | For special (clinical) needs of an individual patient | For an individual patient |
| **Use** | No restriction | Hospital |
| **Movement** | YES, possible export/import | NO, preparation and use within the same Member State |
| **Evolution** | Stopped once marketing authorisation obtained | *Nothing is said* |

Evidence for the efficacy is NOT required.

https://www.eurostemcell.org/regenerative-medicine-special-report/access-to-regenerative-medicine/full-article

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# Protection of the Public Health through the RM Safety Act (since 2014)

## 6 arrested over unauthorized stem cell therapy using cord blood

KYODO NEWS August 27, 2017

MATSUYAMA, Japan – Police on Sunday arrested a doctor and five others suspected of involvement in unauthorized stem cell therapies using blood from umbilical cords and placenta after childbirth.

The doctor who heads a clinic in Tokyo and people involved in cord blood sales are suspected to have administered cord blood to seven patients to treat cancer and as a beauty treatment. Each treatment is said to have cost 3 million to 4 million yen ($27,400-$36,600).

While hopes are high over the use of cord blood in the field of regenerative medicine to treat a number of diseases as it contains stem cells, the health ministry is concerned over the spread of costly medical services provided without clear scientific evidence and without ensuring sufficient safety.

The arrests were the first of anyone suspected of violating a law on regenerative medicine that came into force in 2014. The transplantation of cells could involve the risk of graft rejection and infection.

Medical institutions using stem cells are required to submit treatment plans beforehand for review by the health ministry, except for treating designated diseases such as leukemia.

The six suspects allegedly conducted the treatments without notifying the authorities.

**In order to prevent future adverse events, the Government can arrest medical practitioners** who conduct **cell therapy without notifying the authorities.**

https://english.kyodonews.net/news/2017/08/5d0a5ee3cba3-update1-6-arrested-over-unauthorized-stem-cell-therapy-using-cord-blood.html

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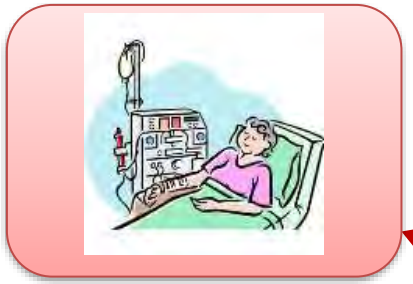

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NEWS FEATURE | 25 September 2019 | Correction 10 October 2019

# The potent effects of Japan's stem-cell policies

A five-year regulatory free-for-all in regenerative medicine has given the industry a boost. But patients might be paying the price.

David Cyranoski


"In addition to the questions about evidence and efficacy, **there are also concerns about the qualifications and independence of the committees that approve such treatments** for inclusion in the registry. The health ministry requires that these committees comprise five to eight people, and include specialists in cell biology, regenerative medicine, clinical research and cell culture. It also requires input from lawyers, bioethicists and biostatisticians. But **rules about conflicts of interest on the committee have been lax**.

…The ministry instituted policies in April to prevent such conflicts. But **even with fully independent committees, clinics can shop around for the answer they want**.

…**The government is considering extra fixes, such as requiring training to make the committee system better**."

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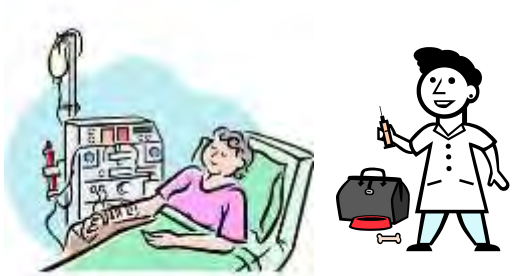

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# Unique Approval Pathway for RM products in the PMD Act

## ☐ Conventional approval process

Non-commercial Clinical Research → Clinical Trial (confirmation of efficacy and safety) → Approval → Marketing

## ☐ Approval process that accommodates early practical application of RM products

Non-commercial Clinical Research → Clinical Trial (likely to predict efficacy, and confirming safety) → Conditional/ Term-limited Approval → Marketing Further confirmation of efficacy and safety → Approval (or Revocation) → Marketing Continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients

RM Safety Act

PMD Act

- If data from the clinical trial are **likely predict efficacy and confirming safety**, **conditional/term-limited marketing authorization** for RM products might be granted to timely provide the products to patients.
- The PMD Act requires **further confirmation of safety and efficacy during the post-marketing phase**.

# RM Products Approved for Manufacturing & Marketing in Japan

[as of June 1, 2021]

**11 RM products** have been approved under PMD Act
(including **2 products for in vivo gene therapy**)

- autologous epidermis
- autologous cartilage
- allogeneic MSCs (for GVHD)
- autologous myoblast sheet (for heart failure)*
- autologous MSCs (for spinal cord injury) *
- autologous CAR-T cells
- autologous cultured corneal epithelium
- autologous CAR-T cells
- autologous CAR-T cells
- plasmid vector (for chronic arterial occlusion)*
- AAV vector (for spinal muscular atrophy)

The Japan Ministry of Health, Labour and Welfare (MHLW) is expected to approve the marketing of

- autologous cultured oral mucosal epithelial cell sheet (for extensive damage to the cornea of both eyes) &
- oncolytic virus*

within the next few months.

*conditional & term-limited approval

# Unique Approval Pathway for RM products in the PMD Act

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Real world data are quite important!

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RM Safety Act

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Challenge

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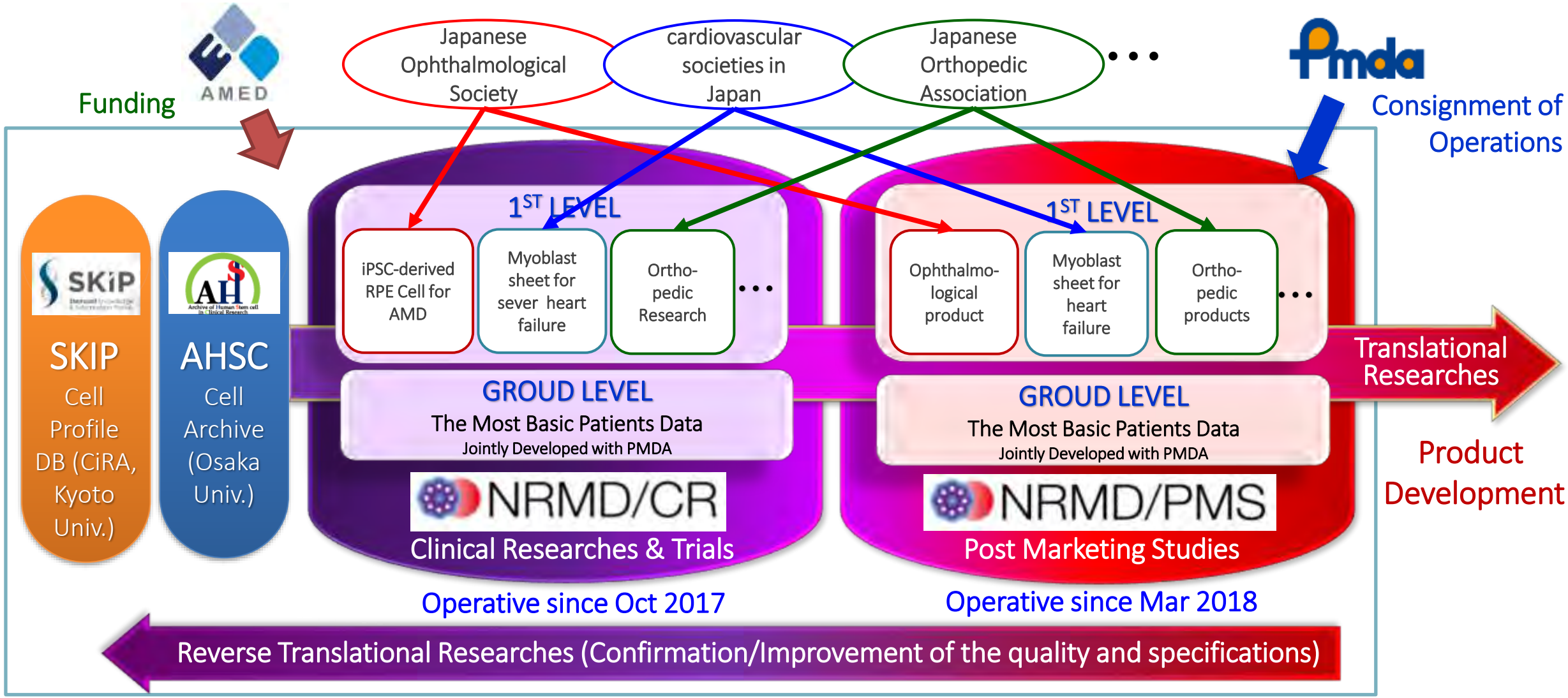
https://www.youtube.com/watch?v=LVCLVkPzrNQ

Introduction of NRMD

# Development of Nation-wide Clinical Research Data Systems (NRMD)




These Databases enables seamless translational/reverse translational researches from clinical investigation to PMS, by acquiring real world data of all clinical cases into the systems with common data quality assurance.

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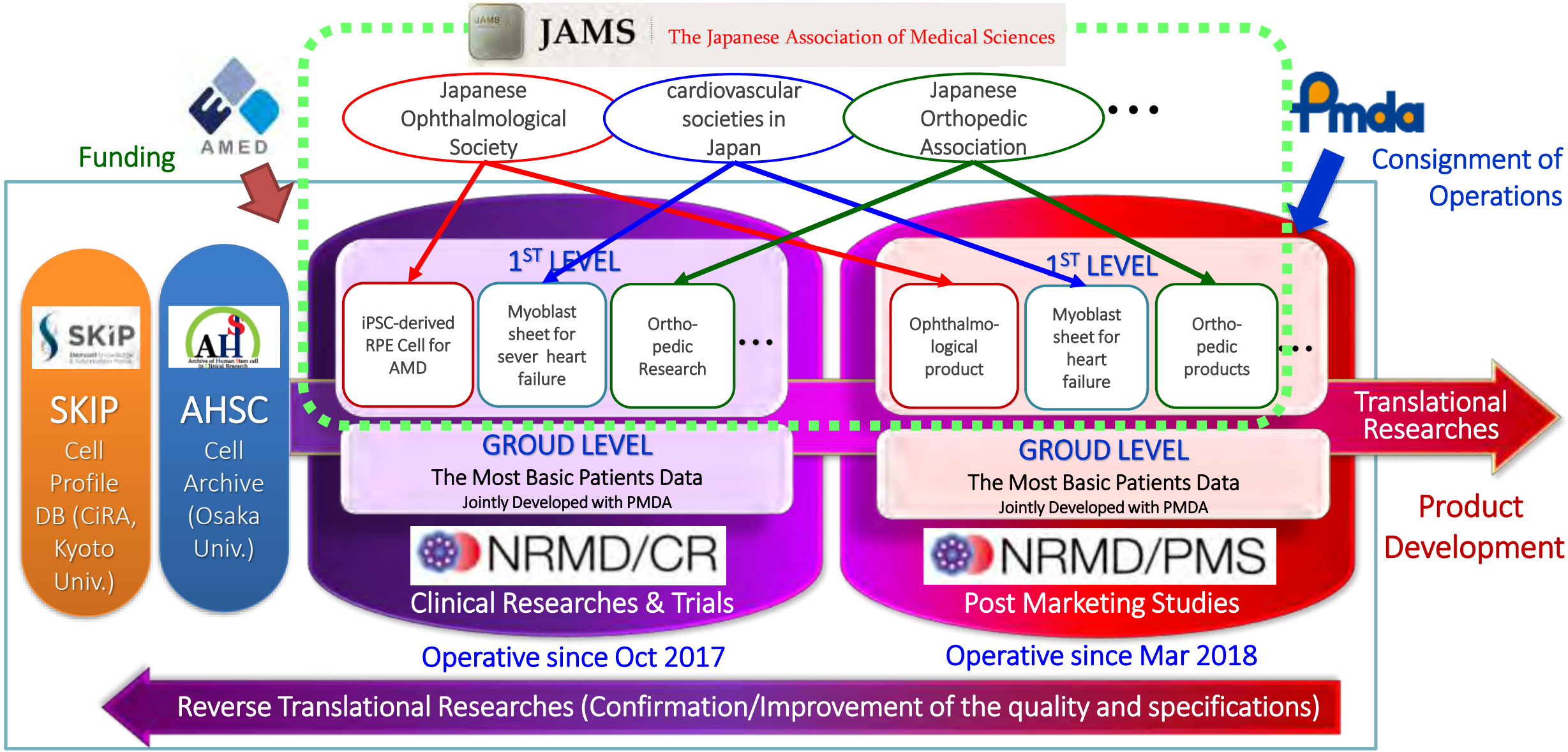


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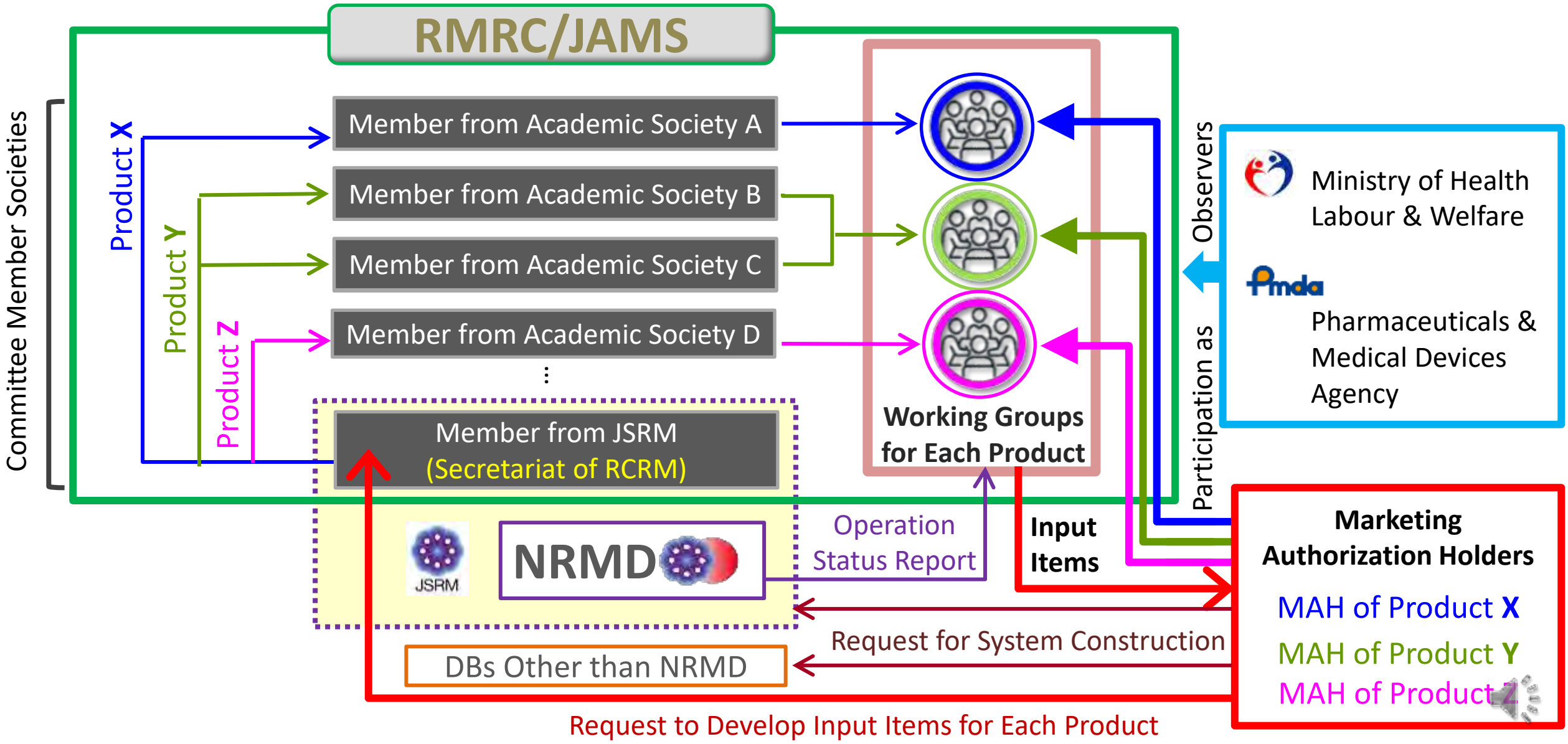
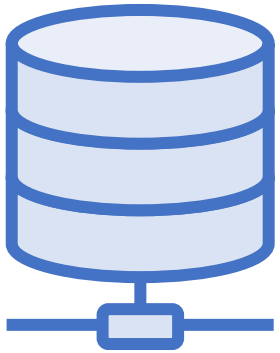
# The Regenerative Medicine Registry Committee (RMRC), The Japanese Association of Medical Sciences (JAMS)

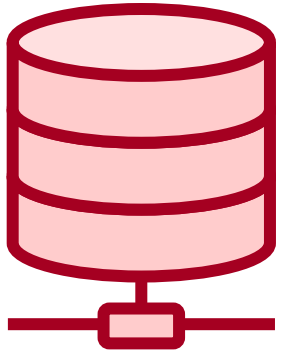


# Utilization of Registered Data

NRMD/CR



NRMD/PMS



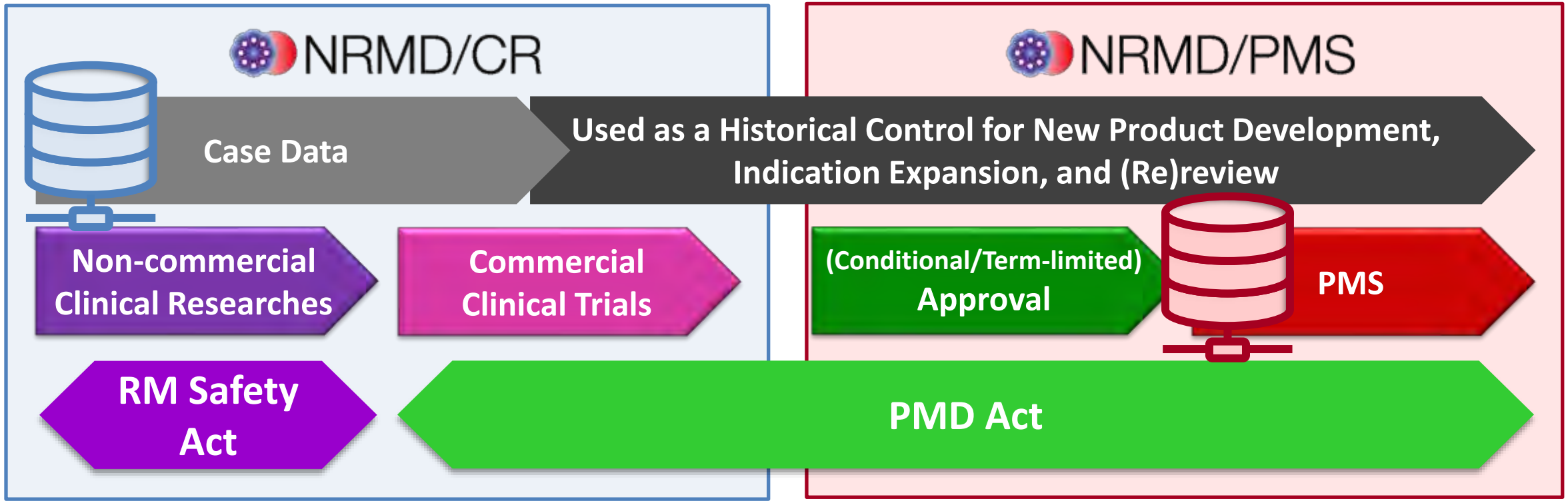
1. For NRMD/CR for non-commercial clinical researches, data quality is assured by performing Computerized System Validation (CSV) in compliance with Good Post-marketing Study Practices (GPSP).

2. For non-commercial clinical researches that allow for a control group, data from the control group can be registered with the same quality.

3. Data from previous control groups can be used as historical controls in subsequent non-commercial clinical researches or post-marketing surveillance (PMS).

4. In cases of products for which it is difficult to have a control group, smooth product commercialization without relying on randomized controlled trials (RCTs) can be supported by setting up a PMS-focused R&D design.

# NRMD/CR → Commercial Clinical Trials → Utilization of PMS Data



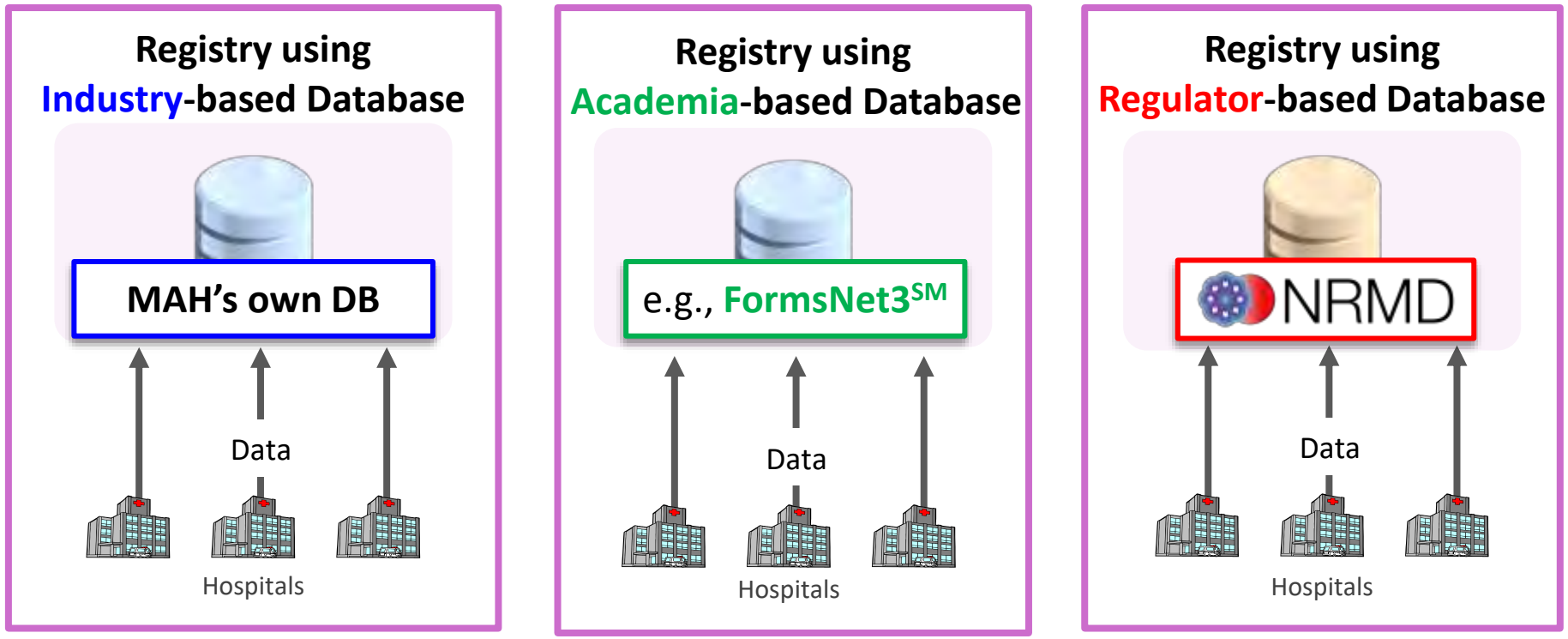

JAMS JSRM

Infrastructure Development

Pharmaceutical Affairs Consultation

# Patient Registries of RM Products in Japan

## Clinical Databases Available for Patient Registries of RM Products




MAHs utilize the patients' data collected through registry to report the malfunction (adverse events) by regenerative medical products and conduct post-marketing surveillance.

**It is up to MAHs to decide which type of database to use,
but the MHLW recommends using NRMD, considering the accumulation of data for future development of RM products.**

MENU

NRMD National Regenerative Medicine Database

For More Information
https://nrmd.jp/en/

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日本医学会

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# Thank you for your attention!

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