October 28, 2024
Seoul, Korea

JSRM

2024 Advanced Regenerative Medicine Forum

Session 2: The Status of RM and Data Management System by Country

NRMD & REAP

The Clinical Databases for Regenerative Medicine in Japan

Yoji Sato, Ph.D.

Head, Division of Drugs, National Institute of Health Sciences

Database Committee, Japanese Society for Regenerative Medicine

DISCLAIMER

NRMD & REAP: the Clinical Databases for Regenerative Medicine in Japan

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For the past year, the speaker has no COI to disclose for this presentation

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 Ministry of Health, Labour & Welfare, or the Japanese Society for Regenerative Medicine.

1. What are NRMD and REAP?

2. Overview of NRMD

3. Overview of REAP

4. Operation and utilization of NRMD/REAP

NRMD and REAP: Features of the two databases

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Regenerative Medicine Patient Data Registration Systems Established and Operated by the Japanese Society for Regenerative Medicine

NRMD *(National Regenerative Medicine Database)*

NRMD/CR Platform for registering
non-commercial clinical research on specified processed cells,
certified advanced medical care using specified processed cells, and
commercial clinical trials of regenerative medical products (CTPs/GTPs)

NRMD/PMS Platform for registering
post-marketing surveillance of regenerative medical products

REAP *(Regenerative Medicine Evidence Accumulation Platform)*

Platform for registering
therapies based on physician's discretion using specified processed cells

There is no particular difference in the electronic data capture (EDC) system used.

NRMD and REAP: Features of the two databases

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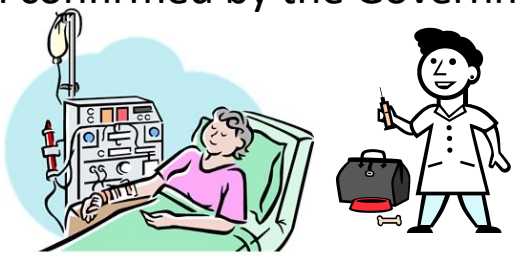
Name	Patient Data Registration System for Regenerative Medicine (RM)		
	REAP (RM Evidence Accumulation Platform)	NRMD (National Regenerative Medicine Database)	
Main Purpose	Validation of RM	Development & Evaluation of RM	Commercial Development of Regenerative Medical Products
Relevant Law	Act on the Safety of RM (RM Safety Act)		Pharmaceuticals & Medical Devices Act (PMD Act)
Target	[RM Safety Act] Therapies based on physician's discretion using specified processed cells (= cell processed products not yet approved by the MHLW)	NRMD/CR [RM Safety Act]: Non-commercial clinical research on specified processed cells or certified advanced medical care using them [PMD Act]: Commercial clinical trials for regenerative medical products	NRMD/PMS [PMD Act] Post-marketing surveillance (PMS) for regenerative medical products (= cell processed products or gene therapeutics)
Determination of Input Items	Joint WG of Regenerative Medicine-Related Societies	WG of the Registry Committee of the Japanese Association of Medical Sciences	

Two Acts Regulating RM/CT

Regenerative Medicine (RM)
Cell Therapy (CT)

Medical practices using processed cells, whose safety and efficacy have not yet been confirmed by the Government



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)

- Clinical trials of RMPs (commercial)
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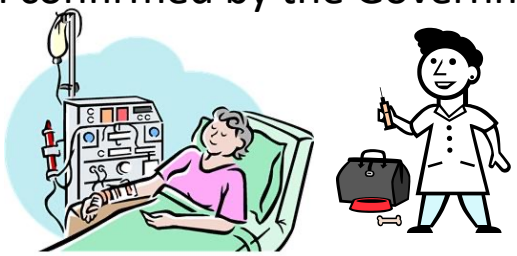

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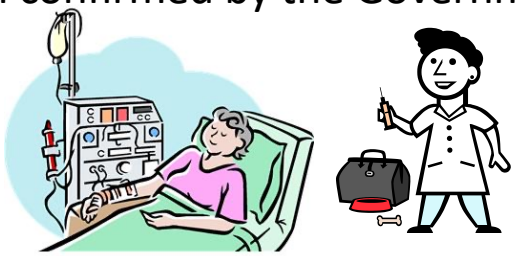

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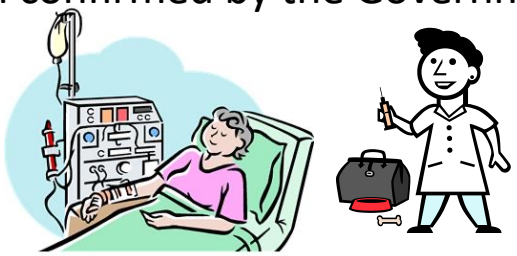

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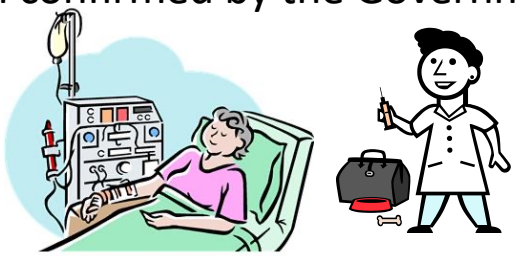

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Two Major Regulatory Challenges for the Development of Regenerative Medical Products

JSRM

☐ Conventional approval process

☐ New approval process that accommodates early practical application of RM products

- 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.

Two Major Regulatory Challenges for the Development of Regenerative Medical Products

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☐ Conventional approval process

Real world data are quite important!

☐ New approval process that accommodates early practical application of RM products

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Background of NRMD Construction

Report of the Study Group on the Ideal Patient Registration System for Regenerative Medical Products and the Study Group on the Ideal Patient Registration System for *In-Vitro* Implantable Medical Devices (MHLW, July 4, 2014)

"Considering that a wide variety of products are expected for regenerative medical products and implantable medical devices and that the number of patients using each product is not necessarily large, it is efficient for medical institutions, academic societies, manufacturing/marketing authorization holders, and the government to cooperate to establish and utilize a cross-sectional patient registration system, rather than for manufacturing/marketing authorization holders to establish a patient registration system for each product."

History of NRMD

PMDA

Constructed a post-marketing surveillance EDC (with the reliability assured by CSV)

2015

AMED

Outsourced the development of RMed-Japan (mainly for non-commercial clinical research) to JSRM as a contract R&D project

The RM National Consortium

2016

JSRM

Integrated PMDA-built EDC and RMeD-Japan services, adopted Viedoc as platform, and renamed NRMD.

2016
2017

NRMD

NRMD operation started **by JSRM**

2017

EDC employed for NRMD/CR and NRMD/PMS

JSRM

Clinic/PMS

Study Registration and Reference

Compliant with MHLW's GPSP Ordinance

Reports

Diverse reporting services

Me

ePRO/eCOA Services

viedoc™

TMF

Document management of related documents

Connect

Video Calling Service

Logistics

Common Management System for Regenerative Medicine Product

In addition to Viedoc EDC, there are several other services available.

Outline of NRMD

JSRM

※To be discussed in the future

Manufacturing Management System

Quality/Mfg Data

Application Programming Interface (API)

Mfg/Res Support Systems

Clinical Data

WGs of Registry Council for Regenerative Medicine
The Japanese Association of Medical Sciences

Determination of input items

	NRMD/CR				NRMD/PMS			
	Items specific to each clinical study				Items specific to each product			
2F	PRP Study #1	PRP Study #2	Cornea Study	Heart Study	PRP Product	Heart Product	Cornea Product #1	Cornea Product #2
	Common items for PRP		Common items for ophthalmo-logy/corneal diseases	Common items for cardiology	Common items for PRP	Common items for cardiology	Common items for ophthalmology/corneal diseases	
1F	Common basic items (established by PMDA) e.g., basic patient information, consent information, adverse events, clinical conditions, study discontinuation, study termination, etc.							

Product Development

Reverse Translational Research (Review/Improvement of Specifications/QAs/PPs)

CSV (Computerized System Validation) is applied to the clinical research database to ensure the data quality and to realize seamless utilization of real-world data for product development and reverse translational research. (CR has been operational since October 2017, and PMS since March 2018)

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1F: Common basic items (general items determined in consultation with PMDA)

Category	Items
General Information	consent, date of consent, post-marketing survey flag, date of birth, and gender, date of use or start of use, time of use or start of use, height, weight, primary disease, disease history, complications, allergies, specific allergies
Periodic Survey	survey conducted or not, date of observation
Adverse Events /Defects Information	whether or not an adverse event occurred, type of the adverse event, date of onset, severity, treatment or other measures for the adverse event, specific details, date of outcome, outcome, detailed status, causal evaluation, opinion on the adverse event, whether or not a defect occurred, type of the defect, date of occurrence
Survey Completion	Date of survey completion, reason for survey completion, detailed status

https://www.pmda.go.jp/safety/surveillance-analysis/0036.html

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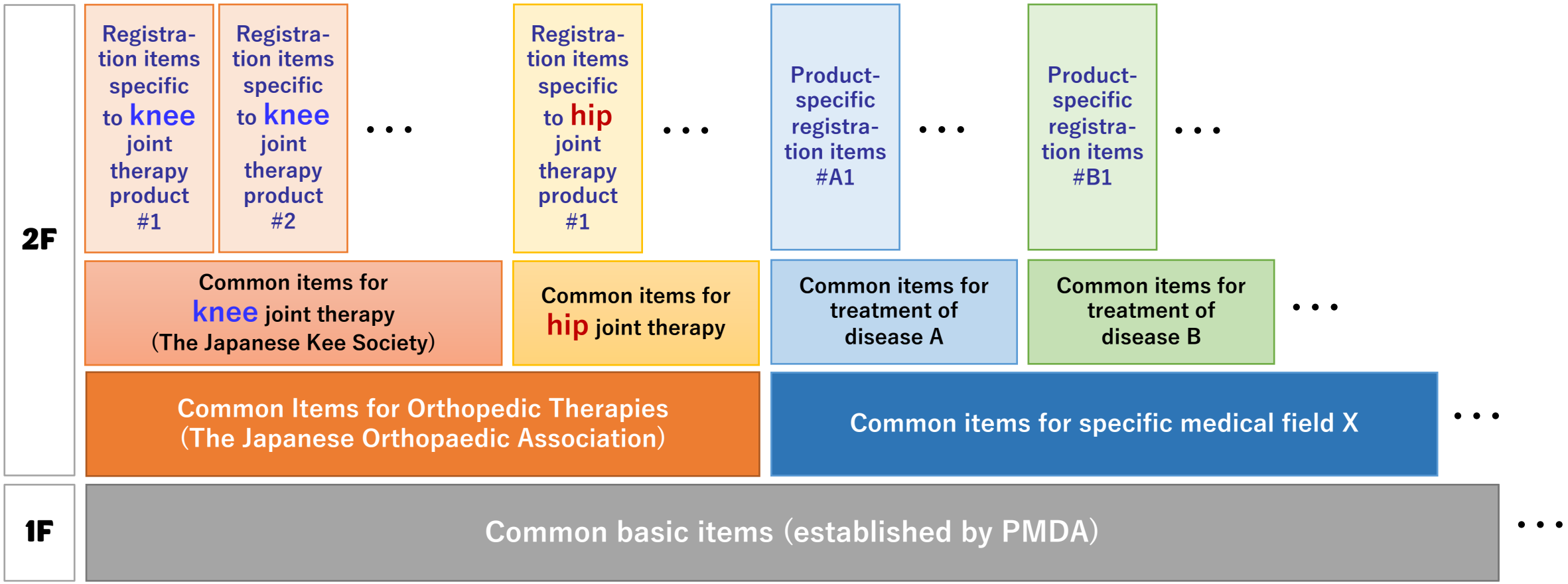
2F: Hierarchy of product/disease-specific items (examples)



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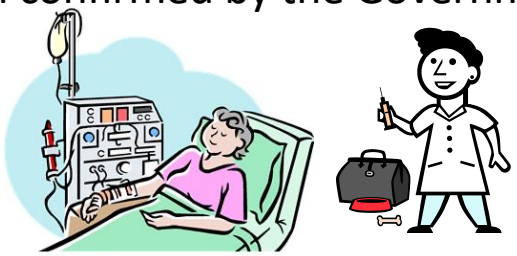

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REAP

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NRMD/CR

Clinical researches using processed cells (non-commercial)

Pharmaceuticals & Medical Devices Act (PMD

Clinical trials of RMPs (commercial)

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Regenerative medical products (RMPs=CTPs/GTPs)

The Establishment of REAP

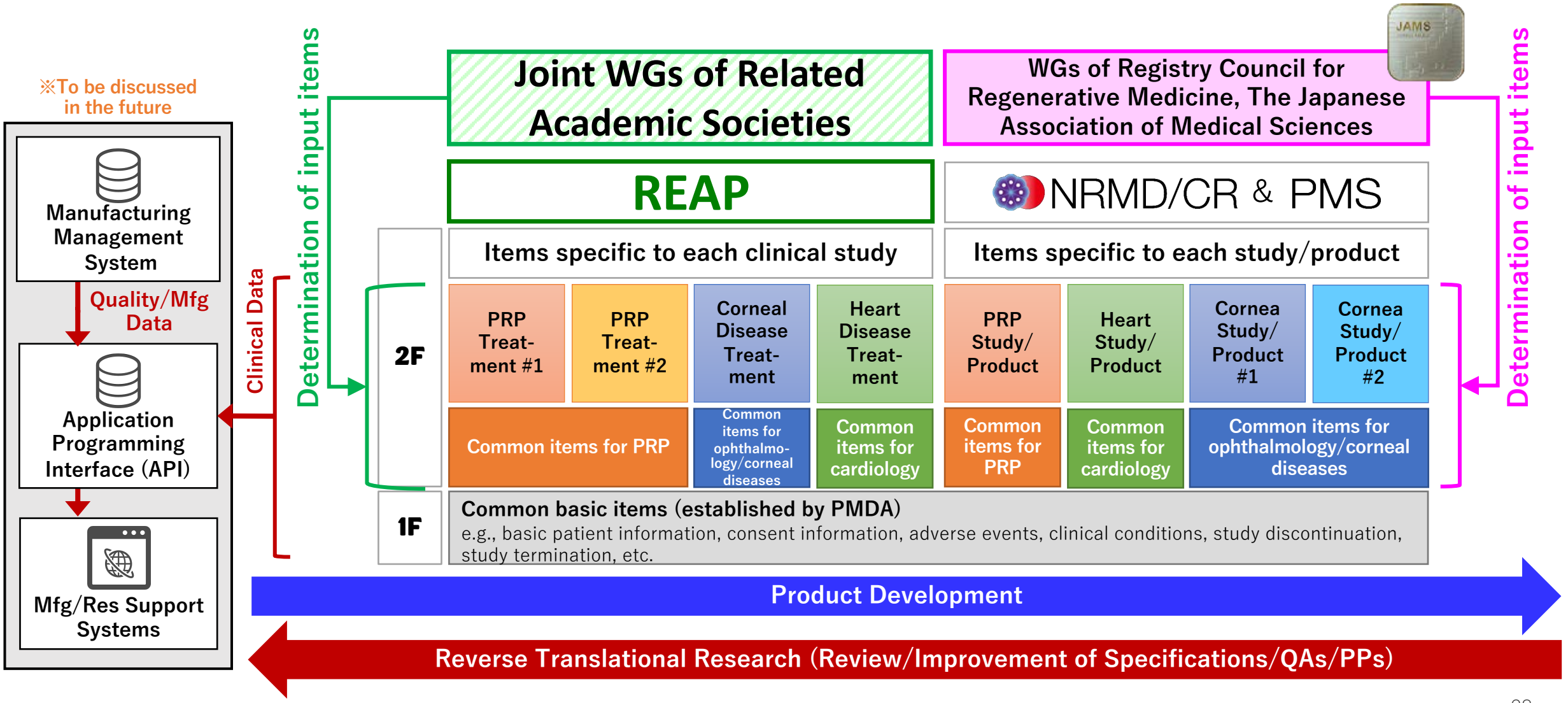
Background

- From the viewpoints of public health and new product development, **a registry should be established for therapies using unapproved cell processed products**, which is legal in Japan **as medical practices at the discretion of physicians**, and **information on their safety and validity (efficacy) should be accumulated**.
- Asking for cooperation of the Japanese Association of Medical Sciences in the development of input items for their clinical outcomes may give rise to the misunderstanding that the JAMS is promoting unproven medical treatment.

Solution

- **REAP (Regenerative medicine Evidence Accumulation Platform)** was established in 2023 as a registry service for such treatments, independent of NRMD.
- Related academic societies other than the Japan Medical Association are in charge of input items.

Outlines of NRMD & REAP



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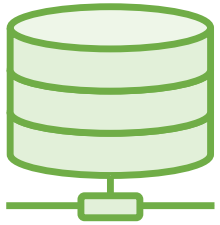
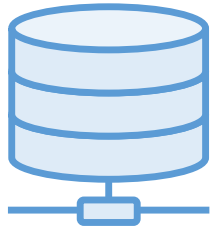
Utilization of registration data

REAP



NRMD/CR



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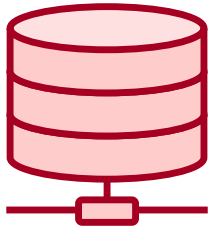


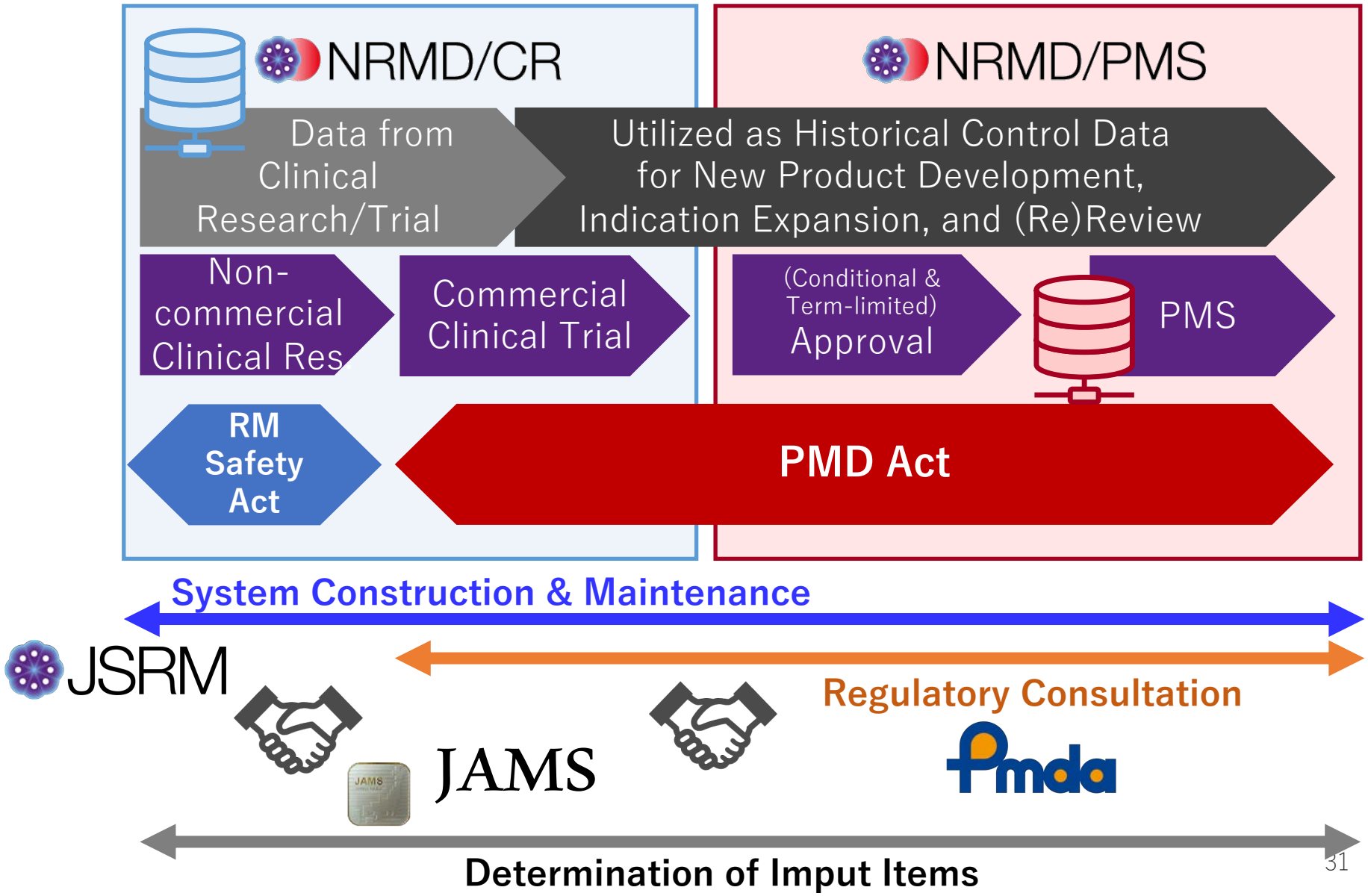
1. Data quality is assured for **REAP** and **NRMD/CR** by using CSV (Computerized System Validation), which conforms to **the Good Post-marketing Study Practice (GPSP) under the Pharmaceuticals and Medical Devices Act**.
(→ **Certified Advanced Medical Care, Tech Transfer to Industry, *etc.***)

1. For **non-commercial clinical research** that allows for a control group, **data from the control group can be registered with the same quality**.

2. **Data from previous control groups may be used as historical controls** in subsequent non-commercial clinical research or post-marketing studies (PMS).

3. For products for which it is difficult to establish a control group, **a PMS-focused R&D design** could support smooth commercialization without reliance on randomized controlled trials (RCTs).

Integrated use of NRMD/CR, and NRMD/PMS



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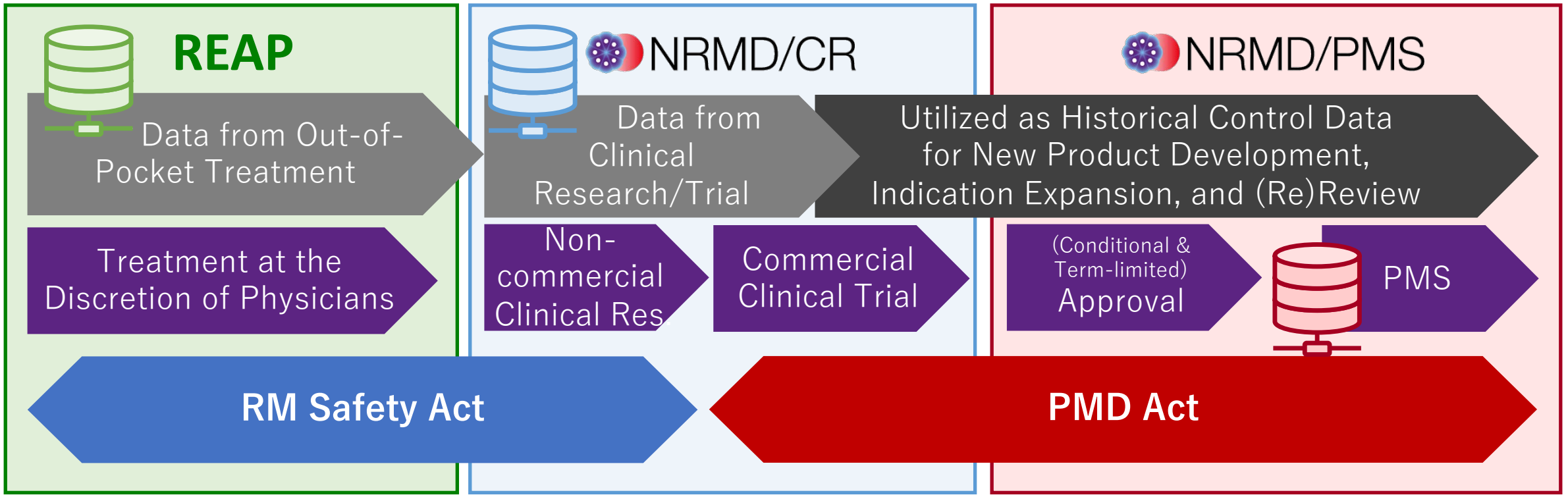
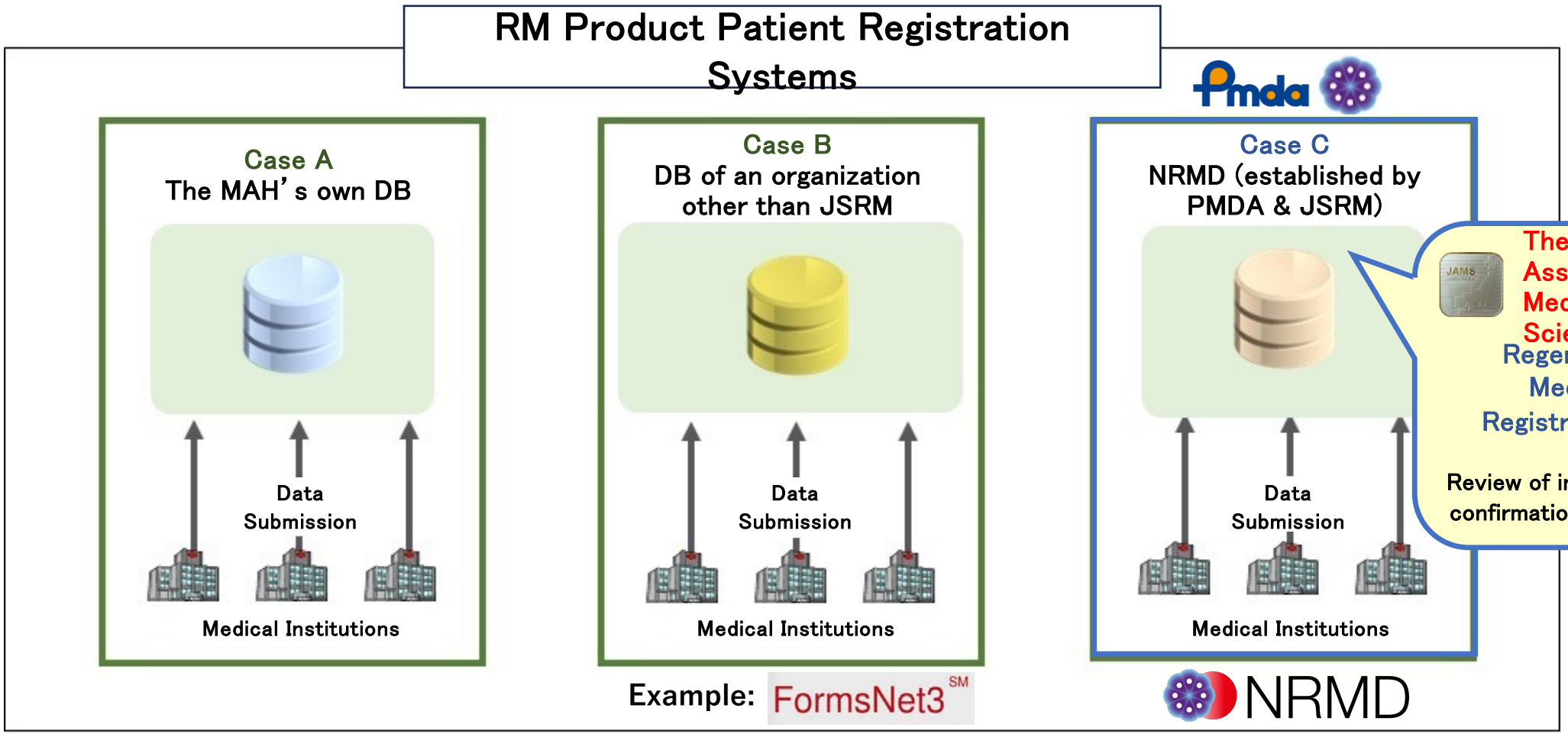


Three Types of Patient Registration Systems for Regenerative Medical Products (CTPs/GTPs)

https://www.pmda.go.jp/safety/surveillance-analysis/0036.html



The Japanese regulatory authorities (MHLW/PMDA) recommend the use of NRMD/PMS for MAHs of CTPs/GTPs, but it is not mandatory. In contrast, the Japanese funding agency (AMED) requires the use of NRMD/CR for non-commercial clinical research using specified processed cells.

For more information about NRMD

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For more information about REAP

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Visit
https://www.reap.jp

… & use Google Chrome's translate function

Thank you for your attention!

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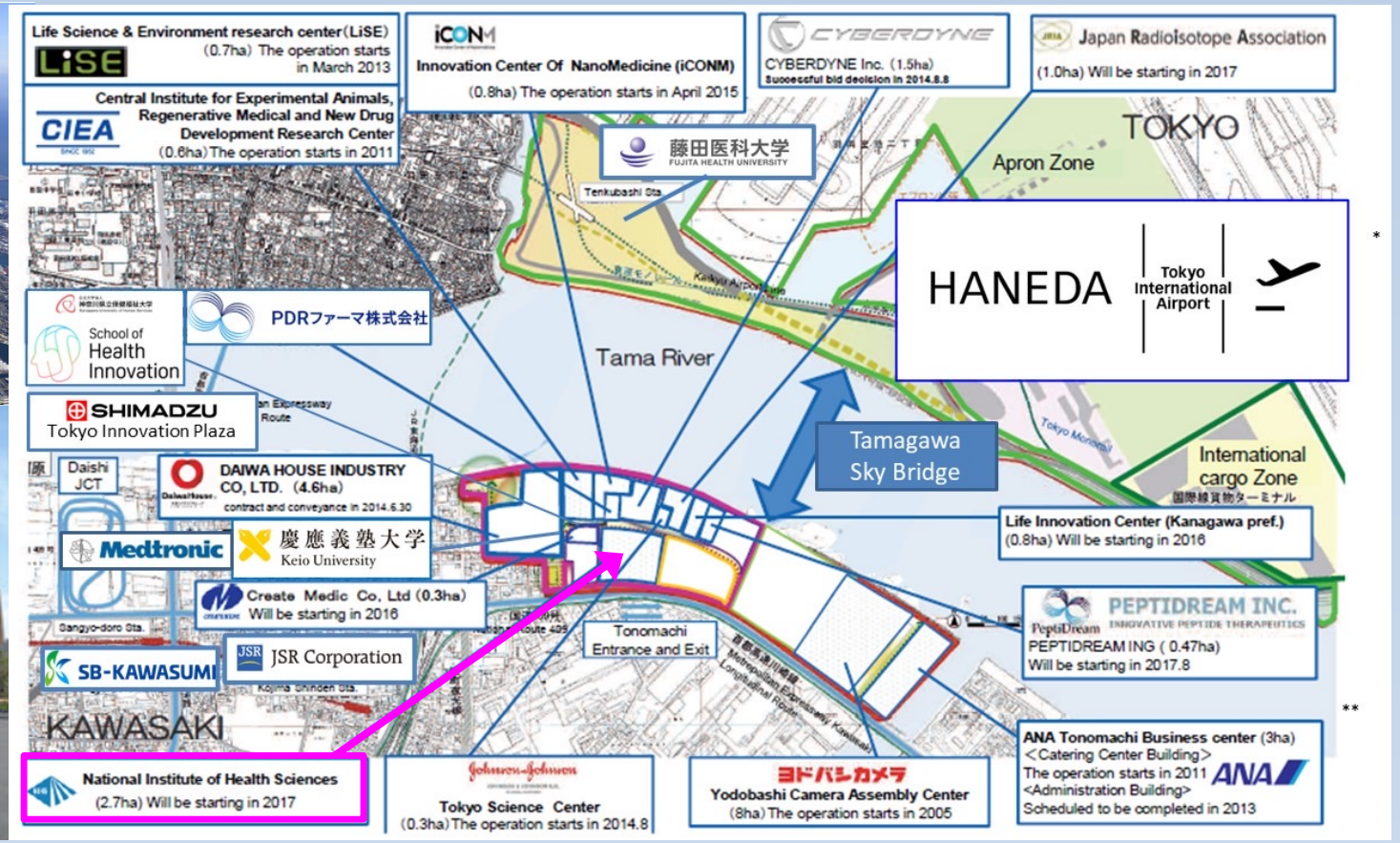

* https://www.oag.com/hubfs/air-canada-787.jpg

** http://www.city.kawasaki.jp/en/page/0000038680.html

Supplements

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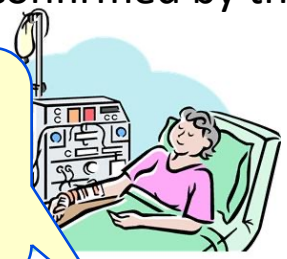
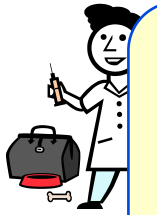
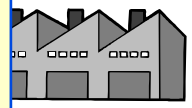
A more correct indication of REAP's coverage





Clinical studies on regenerative/cellular therapies, which are funded by AMED (a national funding agency) are required to register clinical data in the NRMD/CR



Act on the Safety of Regenerative Me… (RM… ty Act)

REAP

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NRMD/CR

Pharmaceuticals & … Medical Devices Act (PM…

Clinical trials of RMPs (commercial)

NRMD/PMS

Regenerative medical products (RMPs=CTPs/GTPs)

Regulation of cell-based therapeutic products in the United States, the European Union (and the United Kingdom), and Japan

	US	EU (and UK)	Japan
Classification of PSC-derived CTPs	351 HCT/P	Advanced Therapy Medicinal Product (ATMP)	Cell-Processed Product
Product type	Biologics or Medical Devices	Medicinal Products	Regenerative Medical Products
Regulatory authority	FDA	EMA (MHRA in UK)	MHLW and PMDA
Compliance with GCP in clinical trials	essential	essential	essential in commercial clinical trials
Good Practice(s) for Quality and Manufacturing Controls	cGMP (for biologics) or QSR (for medical devices)	GMP for ATMPs	GCTP
Conditional Marketing Authorization with Putative Efficacy	RMAT/HDE	Hospital Exemption (Article 28 of Regulation 1394/2007/EC)	Conditional and Term-limited Approval
Use of unlicensed products	Federal regulations prohibit manufacturers from introducing unapproved 351 HCT/Ps into interstate commerce.	Specials (Article 5 (1) of Directive 2001/83/EC)	Specified Processed Cells under the RM Safety Act

Hirai T, *et al., Stem Cell Reports.* 2023;**18:**1573-1591.

Q: Is there any risk of medical treatment being carried out at the discretion of medical practitioners only with the consent of the patient and hospital and without prior review ?

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.

Medical practitioners who conduct **cell therapy without notifying the authorities can be arrested** by the Government **in order to prevent future adverse events.**

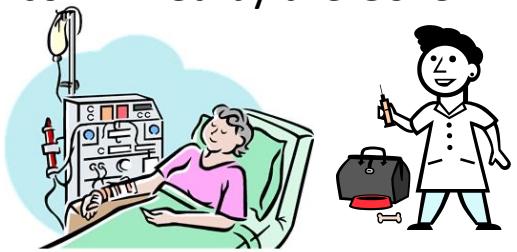
https://english.kyodonews.net/news/2017/08/5d0a5ee3cba3-update1-6-arrested-over-unauthorized-stem-cell-therapy-using-cord-blood.html

Q: How much do patients pay for regenerative medicine as a medical treatment, clinical research, or advanced medical treatment? (Percentage of insurance coverage, percentage of patient contribution, *etc.*)

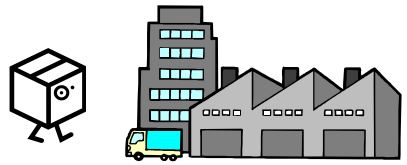
Two Acts Regulating RM/CT

Regenerative Medicine (RM)
Cell Therapy (CT)

Medical practices using processed cells, whose safety and efficacy have not yet been confirmed by the Government



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)

- Clinical trials of RMPs (commercial)
- Regenerative medical products (RMPs=CTP/GTPs)

Public insurance NOT applied

Funded by research grant

Self- (or research grant-) funded

Public insurance fully applied

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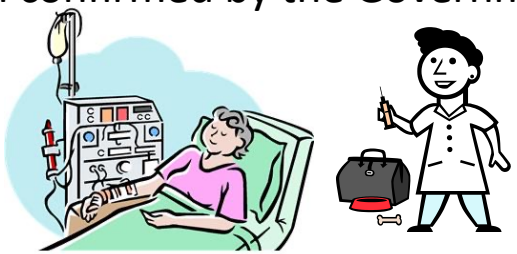

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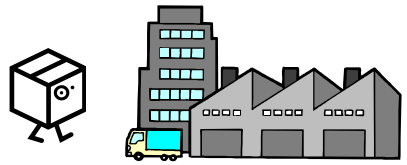

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Public insurance NOT applied → **Exception**

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→ Exception

“Advanced Medical Treatment”

- In Japan, medical treatment that is not covered by public medical insurance is not allowed to be combined with medical treatment covered by public medical insurance, and the patient must pay the full amount for both treatments when conducted at the same time.

- However, for new treatments and surgeries for intractable diseases, etc., which are studied and developed at specific university hospitals, etc., once information on efficacy and safety is accumulated, certain institutional criteria are set for each medical treatment.

- Medical treatment at an insured medical institution that meets the criteria is designated as “Advanced Medical Treatment" by the Ministry of Health, Labor and Welfare, and is allowed to be combined with medical treatment covered by public medical insurance.

- Advanced medical treatment is considered to be a treatment or surgery that is still in the process of being evaluated to be covered by public medical insurance.

“Advanced Medical Treatment”

Example:

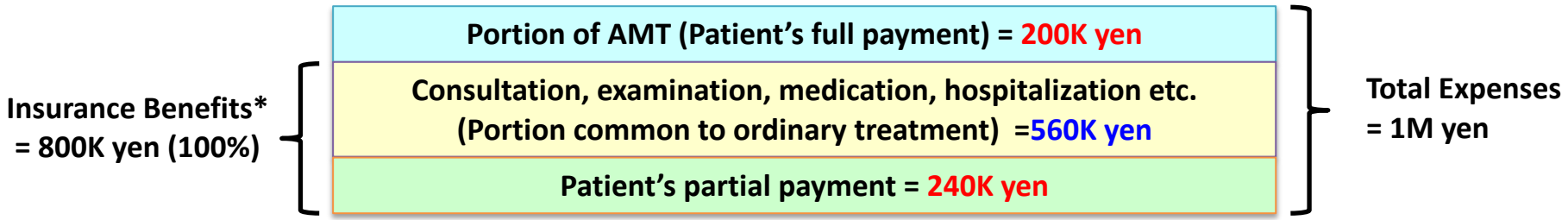
Total medical expenses are 1 million yen, of which 200,000 yen is for advanced medical treatment.

1. The patient is responsible for the entire 200,000 yen for the advanced medical treatment.
2. The portion common to ordinary treatment (consultation, examination, medication, hospitalization fee*) is the portion that is covered by public medical insurance.

Insurance benefits* = 800,000 yen (100%)

70% (560,000 yen) is paid by public medical insurance.

30% (240,000 yen) is the patient’s partial payment.



* **The high-cost medical care system** can be applied to the patient’s partial payment, which is the difference between the insurance benefits and the actual payment by public medical insurance.

Q. In the case of medical practices that are not covered by insurance (treatment at the discretion of the physician, treatment not covered by insurance), the fairness of the patient's approach to medical care for high-cost regenerative medicine procedures may be an issue. Is there any support for these through, for example, public interest funds, private funding, or any other means?

“Advanced Medical Treatment Rider”

provided by **private insurance companies**

1. There is **NO** private insurance **for medical care not covered by public insurance**, because no authority guarantees its safety and efficacy.

2. There is **NO** private insurance **that ONLY covers advanced medical treatment.**

3. **Advanced medical treatment rider** can be added **to private medical insurance and cancer insurance**.

4. Advanced medical care rider cannot be added to the other kinds of life insurance such as death benefits and individual annuities.

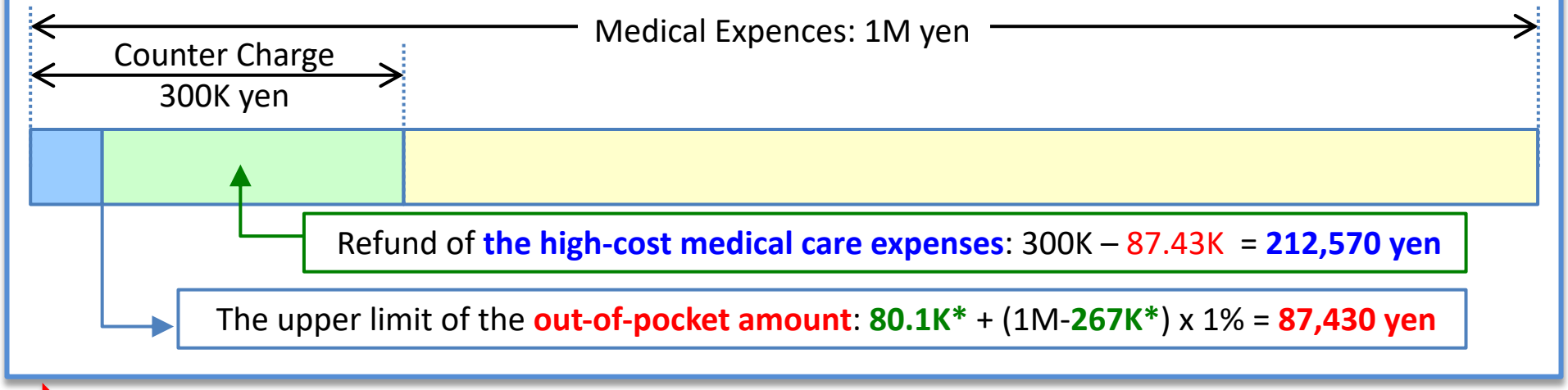
“High-Cost Medical Care System”

for medical care covered by public insurance

The high-cost medical care system is a system for paying the amount of money paid at the counter of a medical institution or pharmacy that exceeds the maximum amount for a month (from the beginning to the end of the month). This does not include the cost of food and other expenses incurred during hospitalization.

Example: 70 years old or older, annual income of approximately 3.7M-7.7M yen (→ 30% payment*)

In the case of a medical expense of 1M yen, the counter charge (30%) would be 300K yen.



212,570 yen will be paid as high-cost medical care expenses, and **the out-of-pocket amount will be 87,430 yen**. *** The amount (10-30%) depends on age and income.**