The 24th JSRM Congress
March 20, 2025, Yokohama

シンポジウム01「日本の再生医療を支える基盤形成の現状と課題」

NRMD & REAP: Databases for the Collection of Real-World Clinical Data in Regenerative Medicine

NRMD & REAP: 再生医療のリアルワールドデータの蓄積を目指した臨床データベース

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DISCLAMER

NRMD & REAP: 再生医療のリアルワールドデータの蓄積を目指した臨床データベース

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薬品部

筆頭演者は、過去1年間（1月～12z月）において、本演題の発表に関して開示すべきCOIはありません。

本発表で述べられた見解・意見は発表者のものであり、必ずしも国立医薬品食品衛生研究所、厚生労働省、日本再生医療学会の公式な方針や見解を示すものではありません。

NRMD & REAP: Databases for the Collection of Real-World Clinical Data in Regenerative Medicine

Yoji Sato, Ph.D.,
Division of Drugs,
National Institute of Health Sciences

For the past year (January-December), 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.

NRMD and REAP

JSRM

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

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

JSRM

Name	Patient Data Registration Systems for Regenerative Medicine		
	REAP (RM Evidence Accumulation Platform)	**NRMD** (National Regenerative Medicine Database)	
Main Purpose	Explorative Study 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	**REAP** [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	NRMD/CR [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	

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Two Major Regulatory Challenges for the Development of Regenerative Medical Products

NRMD/PMS

JSRM

☐ Conventional approval process

Real world data are quite important!

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

☐ New 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

Challenge

NRMD/CR

- 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.

Background of NRMD Construction

厚生労働省
Ministry of Health, Labour and Welfar

「再生医療製品患者登録システムの在り方に関する検討会・体内埋植型医療機器患者登録システムの在り方に関する検討会報告書」（厚生労働省, 2014.7.4）

“再生医療等製品や体内埋植型医療機器については、多種多様な製品が想定され、さらに製品毎の使用患者の数が必ずとも多数ではないこと等を踏まえると、製造販売業者が製品毎に患者登録システムを構築するのではなく、医療機関、学会、製造販売業者及び行政が協力して、横断的な患者登録システムを構築し、利活用することが効率的である”

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 ｚ 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

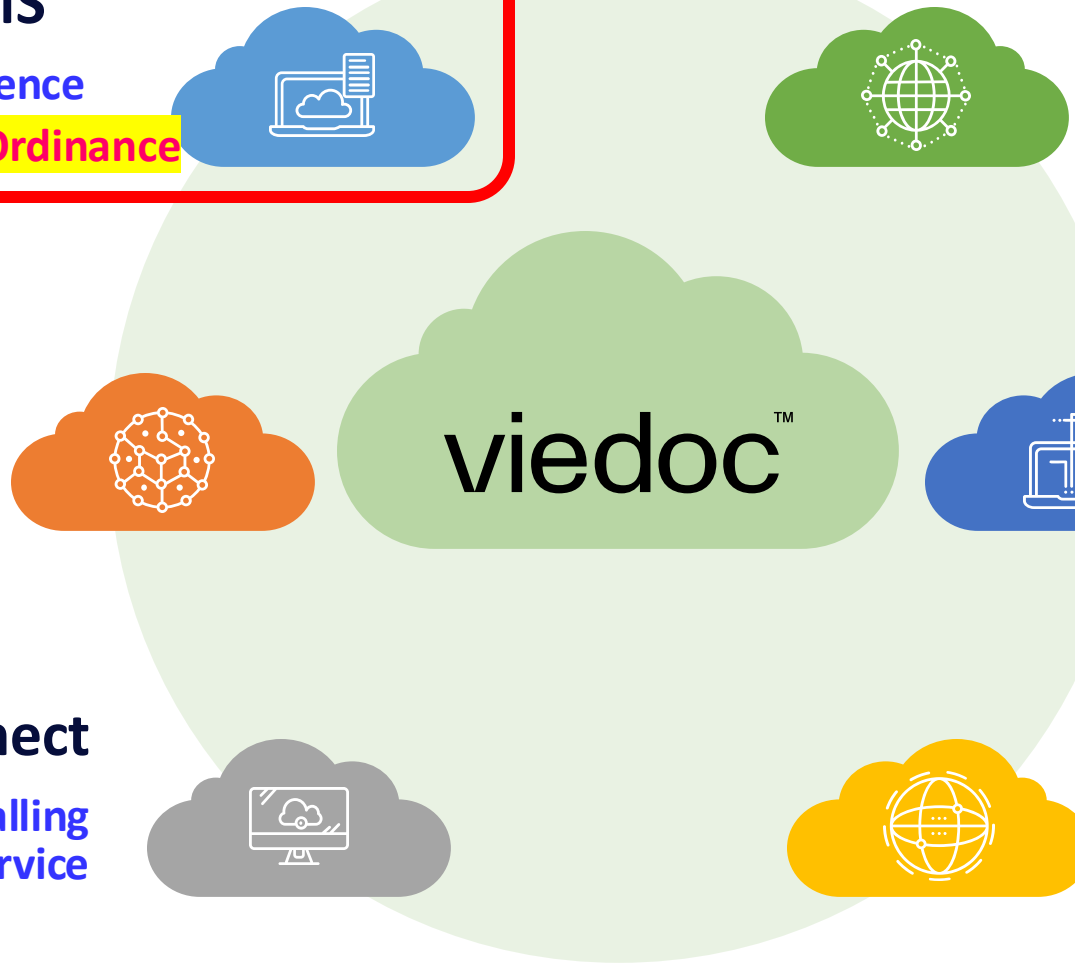
Clinic/PMS

Study Registration and Reference

Compliant with MHLW's GPSP Ordinance

Reports

Diverse reporting services



Me

ePRO/eCOA Services

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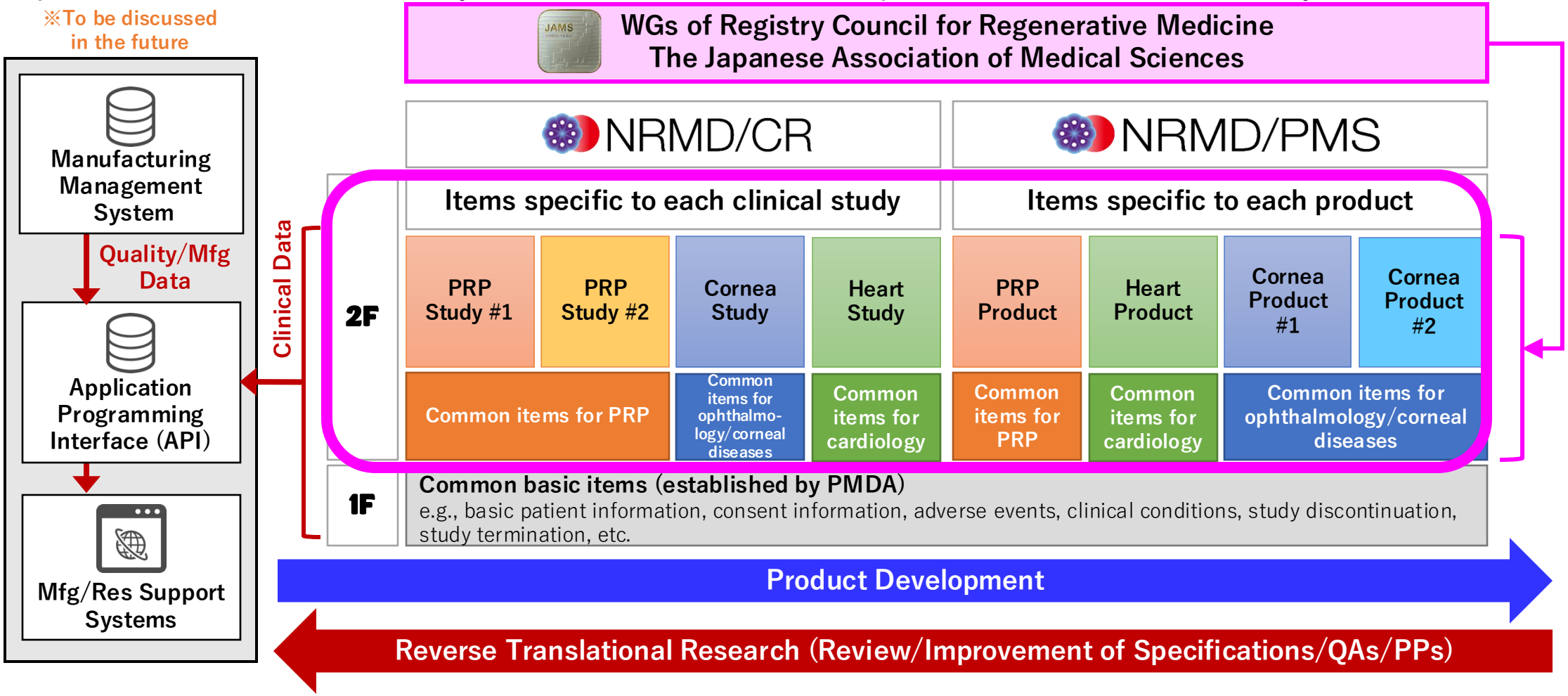
1F: Common basic items (general items determined in consultation with PMDA)

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

Outline of NRMD



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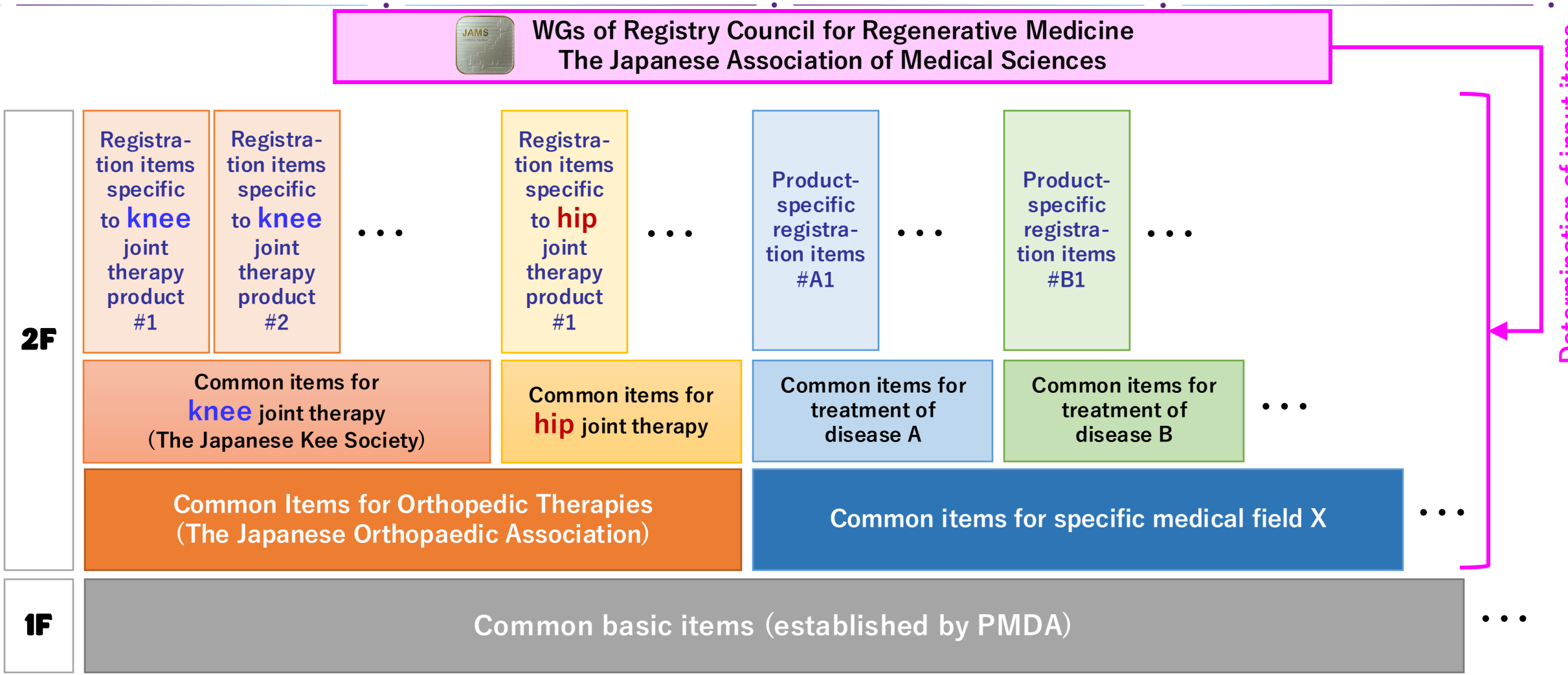
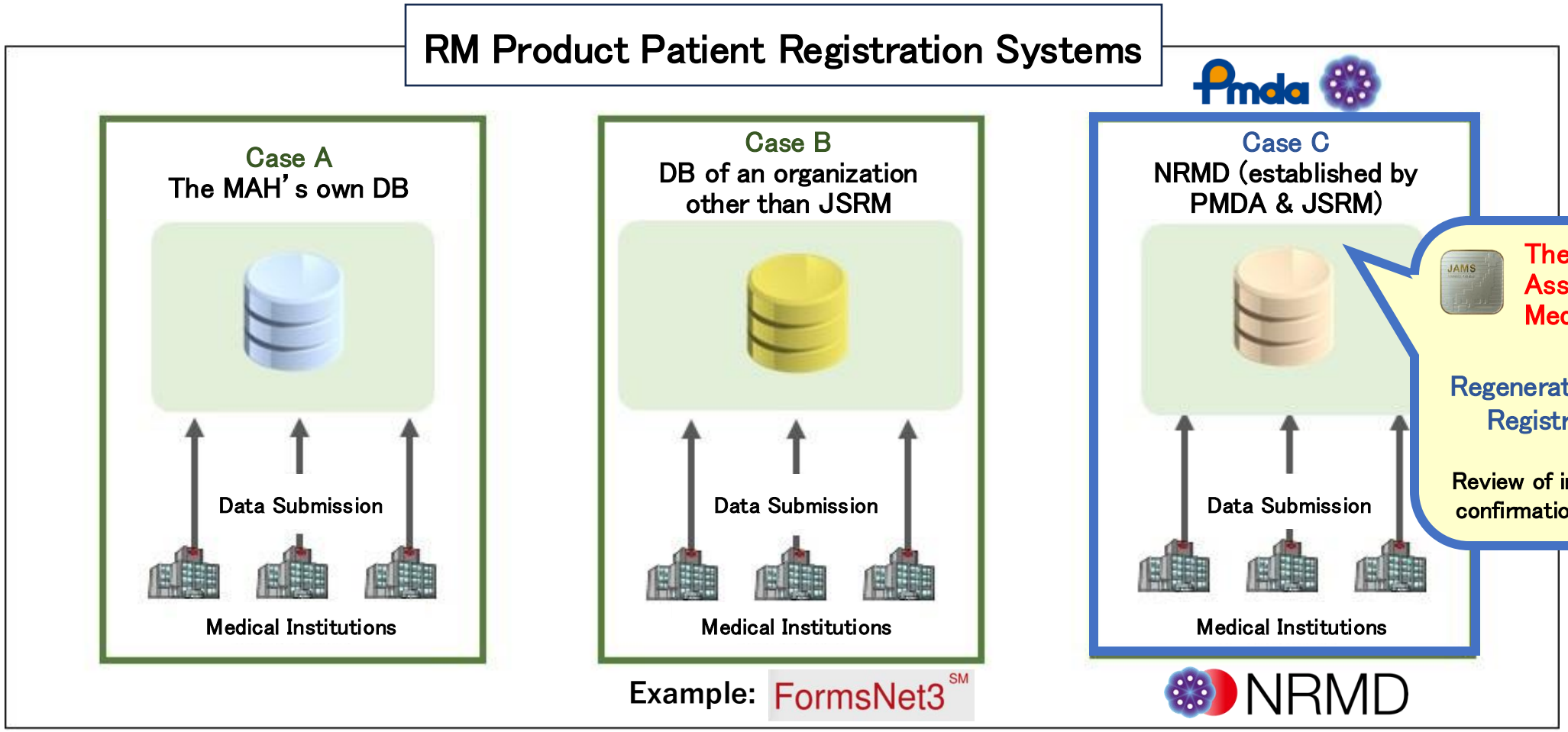
2F: Hierarchy of product/disease-specific items (examples)

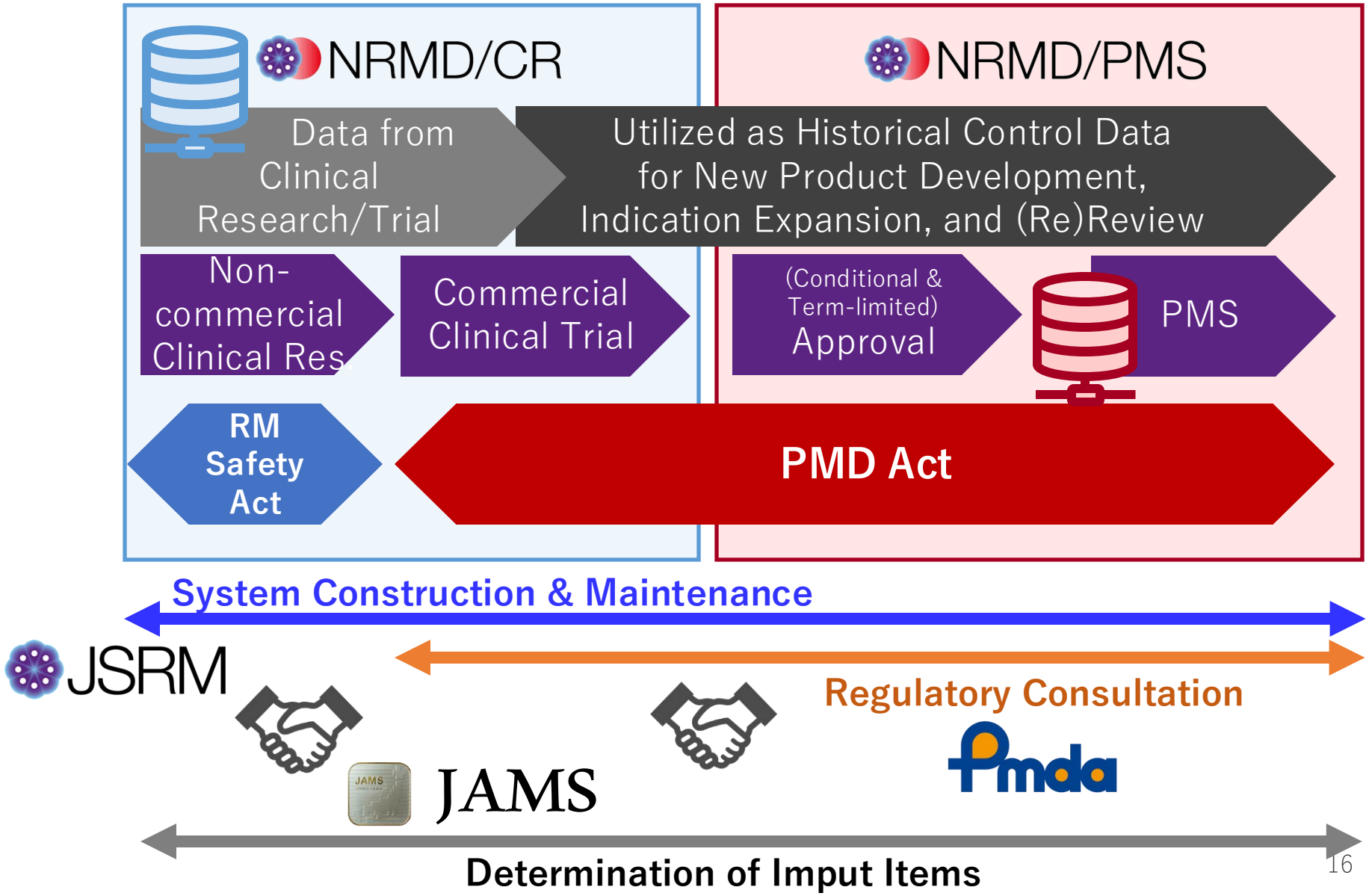


Three Types of Patient Registration Systems for Regenerative Medical Products (CTPs/GTPs)



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.

Integrated use of NRMD/CR, and NRMD/PMS



Challenges in Achieving the Original Objectives of the NRMD

◆ ヒストリカルコントロールとしての利用可能性

これまでに蓄積されたデータは、評価期間中又は論文執筆中のため、当面は第三者と共有できない。ヒストリカルコントロールデータとして**外部の者が利用できるようになるまで、まだ時間がかかる。**

- **ヒストリカルコントロールとして汎用できるデータを如何に効率的・大量に収集するか？**

◆ リアルワールドデータをエビデンスとする方法論

- **リアルワールドデータ**（条件・期限付承認後）を**どのように収集し、どのように用いればどの程度の有効性評価ができるのか**、という**方法論に関するコンセンサス**が必要。

◆ 価格・サービスの課題

- NRMD/PMSを**利用するか否かは企業の判断次第**
- **JSRMは非営利団体**なので、借入金を使った顧客獲得キャンペーンなど（例：お試しディスカウント価格等）が出来ず、**経済的メリットをアピールできない。**
- 欧米のような慈善家による寄付も期待できない。
- JSRMは**DM・統計解析サービスを提供していない。**従って、CRO等に別途委託する手間がかかる。

◆Availability as historical control

The data accumulated so far cannot be shared with third parties for the time being because the evaluation period or the paper is still being written. **It will take some time before the data can be used as historical control data by outsiders.**

- **How to collect data efficiently and in large quantities that can be used as historical control data?**

◆Methodology to use real-world data as evidence

- **Consensus is needed on the methodology** of **how to collect real-world data** (after the conditional & term-limited approval) **and how to analyze them to show the product effectiveness**.

◆Pricing and service issues

- The decision to use NRMD/PMS is **up to the companies and not obligatory**.
- Since **JSRM is a non-profit organization**, it **cannot** conduct customer acquisition campaigns using loans (*e.g.*, trial discount pricing) to **promote economical benefits**.
- Donations by philanthropists, as in the West, cannot be expected.
- **JSRM does not provide DM/statistical analysis services**, which requires the extra effort of outsourcing separately to a CRO, *etc.*

NRMD and REAP

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The Establishment of REAP (2023)

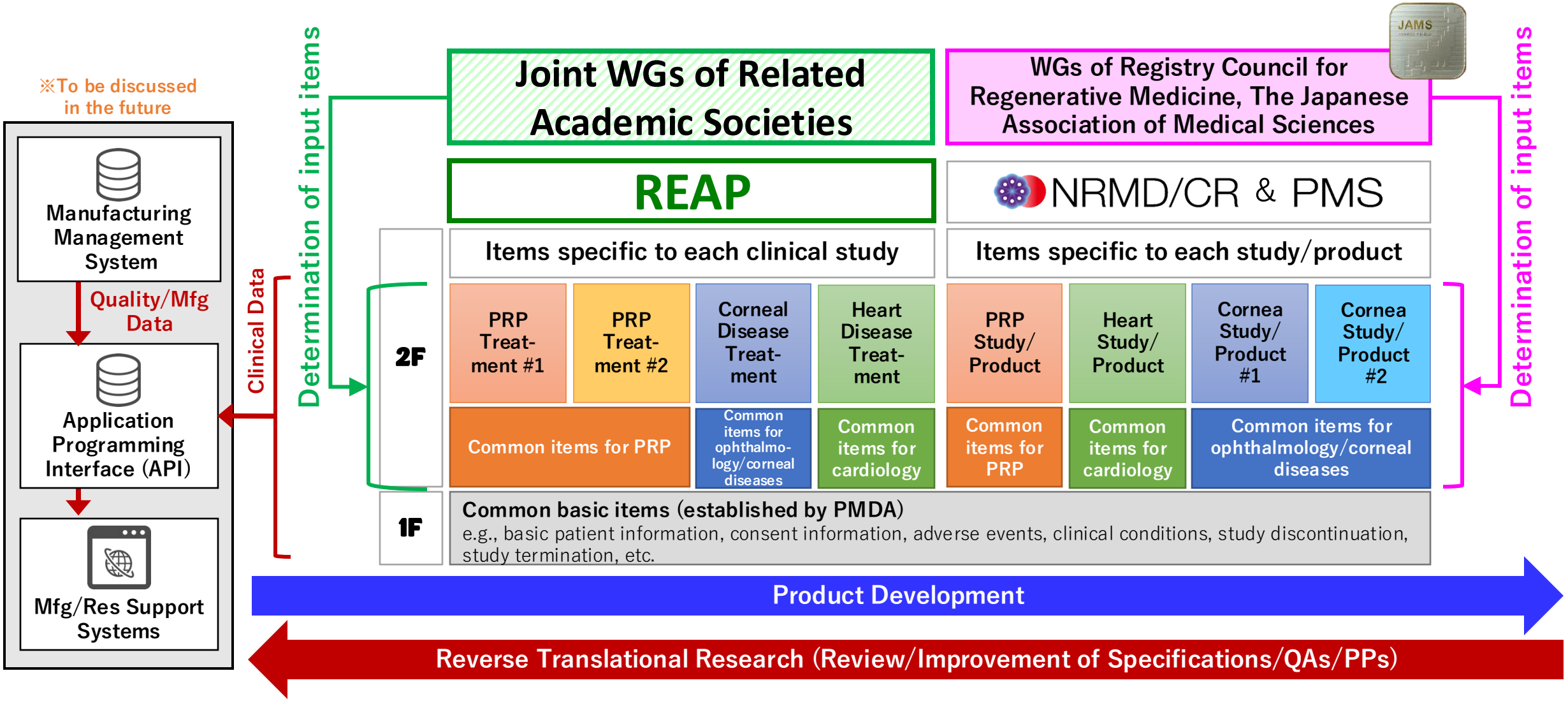
Background

- 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**.

Solution

- **REAP (Regenerative medicine Evidence Accumulation Platform)** was established in 2023 as a registry service for such treatments, independent of NRMD.
-

Outlines of NRMD & REAP



EDC employed for NRMD/CR and NRMD/PMS and REAP

JSRM

Clinic/PMS

Study Registration and Reference

Compliant with MHLW's GPSP Ordinance

Reports

Diverse reporting services

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ePRO/eCOA Services

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Document management of related documents

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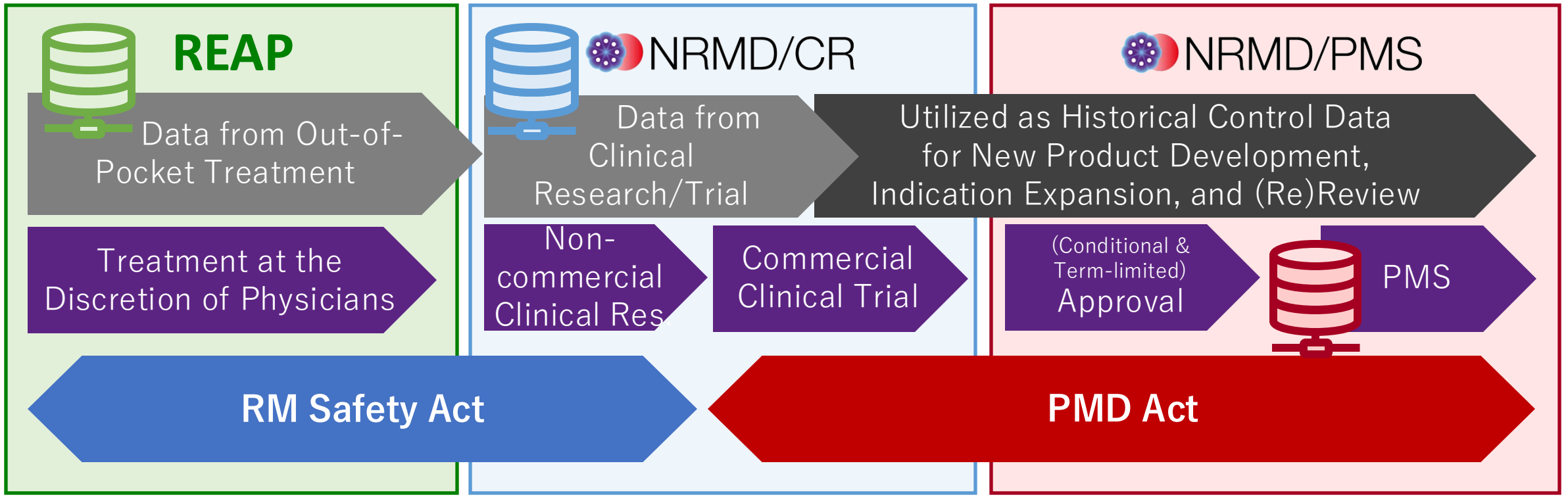
Common Management System for Regenerative Medicine Product

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

Integrated use of REAP, NRMD/CR, and NRMD/PMS



System Construction & Maintenance

JSRM

Regulatory Consultation

Pmda

Challenges in the Operation of REAP

REAP

◆ ヒストリカルコントロールとしての利用可能性

- ヒストリカルコントロールとして汎用できるデータを如何に効率的・大量に収集するか？

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- リアルワールドデータ（条件・期限付承認後）をどのように収集し、どのように用いればどの程度の有効性評価ができるのか、という方法論に関するコンセンサスが必要。

◆ 価格・サービスの課題

- GPSP準拠のCSVを実施するREAPの維持・管理費用は高額となりやすく、薬事承認製品を持つ企業や公的研究費を得ている臨床研究実施機関とは比べ、検証型の自由診療を実施する医療機関にとってはデータ登録時の資金的・労力的コストがより大きな課題。
- 検証型診療として提供される再生医療等技術は、必ずしも薬事承認や製薬企業への技術移転を直接目指すものではないので、現行のNRMD/REAPのシステムはオーバースペックとの意見もある。

⇒ REAPの廉価版の可能性とその信頼性保証レベルのあり方はJSRM内で現在検討中。

◆ Availability as historical control

- How to collect data efficiently and in large quantities that can be used as historical control data?

◆ Methodology to use real-world data as evidence

- Consensus is needed on the methodology of how to collect real-world data (after the conditional & term-limited approval) and how to analyze them to show the product effectiveness.

◆ Pricing and service issues

- The cost of maintaining and managing REAP that implements GPSP-compliant CSV tends to be high. So, compared to companies with regulatory-approved products or non-commercial clinical research institutions with public research funds, the cost of funds and input labor at data registration is a bigger challenge for medical institutions providing explorative regenerative medicine therapy.
- Some argue that the current NRMD/REAP system is too heavily equipped, because regenerative medicine technologies provided as explorative therapies do not necessarily aim directly for regulatory approval or technology transfer to pharmaceutical companies.

→ The construction of a low-cost edition of REAP and its reliability assurance level are under discussion within JSRM.

The ISSCR Encourages Japanese Policymakers to Increase Oversight of Regenerative Medicine Interventions (Feb 22, 2025) [Excerpt]
ISSCR、日本政府に再生医療等に対する監視強化を提言（2025年2月22日）[抜粋]

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

多数実施されている第二種再生医療等への対応

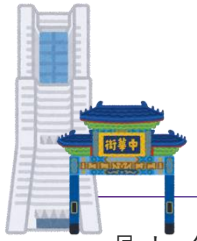
「安確法の枠組みは現在、認定された委員会により 提供計画が審査・承認されれば、正式な臨床試験以外での第二種再生医療等の提供を認めています。 しかし、この仕組みは、『幹細胞研究と臨床応用のための ISSCRガイドライン』を含む国際的な規範とは異なるものです。 **実証されていない再生医療等を、特に研究の場以外でも広く受けることが可能である点については、患者の安全性と科学的厳密性が懸念されるところです**。

2014年に再生医療等安全性確保法が施行されて以来、**第二種再生医療等の提供計画が1000件以上**承認され、その結果、毎年1万人以上の患者が治療を受けています。これだけ件数が多いということは、**リスクと潜在的ベネフィットの十分な評価がなされないまま承認される提供計画があることを示唆しています。**また、昨年報告された脂肪由来間葉系幹細胞の静脈内注入後に患者が視力障害を起こした東京の事例を含め、有害事象も記録されています。同様の有害事象は日本のみならず世界中で報告されており、実証されていな治療が重大なリスクをもたらすことを示しています。私たちは、厚生労働省が第二種再生医療等提供計画を拒否する裁量権を持たないことを理解していますが、これらの計画の承認が慎重に行われ、国際的に認知された科学的・倫理的基準により近い形で行われるよう、厚生労働省にお願い申し上げたく存じます。」

Address the high volume of Class II RM approvals

The ASRM framework currently permits the administration of Class II RM interventions outside of formal clinical trials, provided the provision plans are reviewed and approved by a certified committee. However, this structure differs from international best practices, including the ISSCR Guidelines for Stem Cell Research and Clinical Translation. **The widespread availability of unproven RM interventions, particularly outside the scope of research settings, raises concerns about patient safety and scientific rigor.**

Since the ASRM's implementation in 2014, **more than a thousand Class II RM provision plans** have been approved, resulting in over ten thousand patients receiving interventions each year. This volume suggests that **some plans may be approved without adequate assessment of risks and potential benefits.** There have also been documented adverse events, including a case in Tokyo reported last year where patients experienced vision impairment following an intravenous infusion of adipose-derived mesenchymal stem cells. Similar instances of adverse events have been reported in Japan and worldwide, demonstrating that unproven RM interventions pose a significant risk. While we understand that the Ministry does not have discretionary authority to deny Class II RM provision plans, we encourage the Ministry to explore ways to ensure that approvals for these plans are granted cautiously and align more closely with internationally recognized scientific and ethical standards.



YOKOHAMA Declaration 2025 (Mar 19, 2025) [Excerpt]

YOKOHAMA 2025（2025年3月19日）［抜粋］

『本会は、医薬品医療機器等法（薬機法）下の薬事開発を引き続き支援するのみならず、**再生医療等安全性確保法（安確法）下の臨床研究および治療等の科学的評価に基づいた信頼性獲得に向け**、次の行動目標により研究・開発・規制の全方位を対象に活動を強化していく。

1. 患者・市民との対話を重ね、薬事承認（薬機法に基づいた製造販売承認）に基づく治療、ならびに**安確法下で自由診療として提供される薬事未承認の医療技術のうち安全性および有効性の「検証」を伴う「検証型診療」*およびそれらの検証を伴わない「無検証診療」についての正確な理解が醸成されるよう、積極的な社会との対話、臨床に携わる会員との意見交換を行う**。<後略>』

JSRM's Strategic Vision for the Future

In alignment with its commitment to scientific rigor and patient-centric innovation, JSRM will intensify its efforts to support regulatory advancements and fortify interdisciplinary collaborations across research, development, and policy domains. **These initiatives will ensure that clinical trials and therapeutic applications uphold the highest standards of credibility and efficacy under the framework of the Act on the Safety of Regenerative Medicine (ASRM).**

Key actions:

Public Engagement and Education:

JSRM actively engages in ongoing dialogue with patients and the public as well as society at large, and facilitates exchange of views with clinically engaged members, **aiming to foster an accurate understanding of medical treatments under the Pharmaceuticals and Medical Devices Act (PMD Act), as well as two categories of medical treatments under ASRM: "Explorative Therapies" which involve "Explorative Studies,"* and "Uninvestigated Therapies," which do not involve Explorative Studies.** <Omission>

***検証型診療：薬事承認が得られていない細胞加工物または核酸等を用いた再生医療等の治療のうち、その臨床データが第三者的レジストリに蓄積され、治療の事前および事後に安全性と有効性について科学的な検証が実施されるもの**

*** Explorative Therapy: Therapy using processed cells or nucleic acids, etc. for which a manufacturing and marketing approval has not been obtained under PMD Act, and for which clinical data are accumulated in an independent third-party registry and an Explorative Study is conducted both prior to and following the treatment**

For more information about NRMD & REAP

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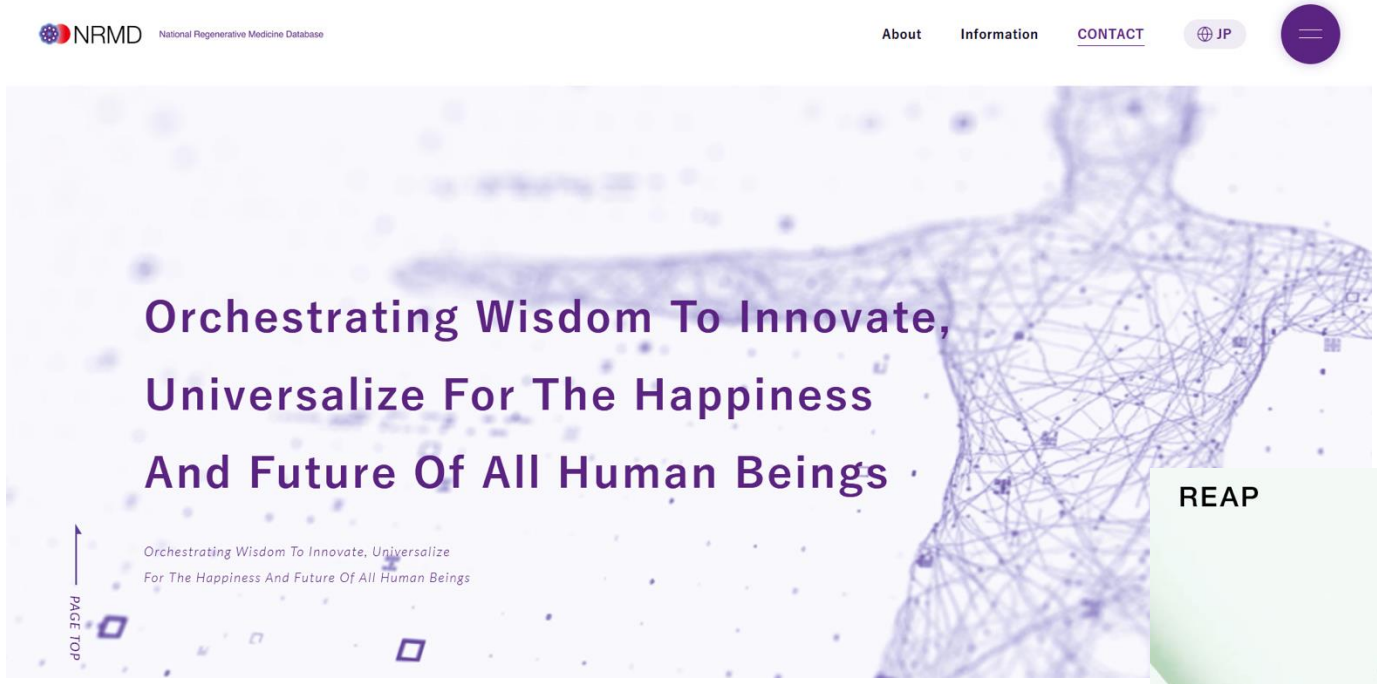

Thank you for your attention!

Visit

https://www.nrmd.jp

https://www.reap.jp