The current situation and future direction of utilization of real-world clinical evidence for regulatory decision-making

Pharmaceuticals and Medical Devices Agency
Office of Medical Devices I
Takeshi Shiba

Outline

1. Guidance on RWD utilization
2. Examples of RWD use in approval review
3. PMDA's consultation process

2018	MHLW revised the Ministerial Ordinance to utilize RWD in post-marketing surveillance(PMS).
2019	PMDA has launched registry consultation's menu.
2021	MHLW has issued guidance for the utilization of registry.

PMDA/MHLW RWD guidance on the use of RWD for medical devices

1. Points to consider for ensuring the reliability in utilization of registry data for applications (March 23, 2021) https://www.pmda.go.jp/files/000240811.pdf

2. Basic principles on utilization of registry for applications (March 23, 2021) https://www.pmda.go.jp/files/000240810.pdf

3. Q&A regarding the considerations for reliability when utilizing registries for medical device approval applications (May 29, 2024) https://www.pmda.go.jp/files/000271519.pdf ［in Japanese］

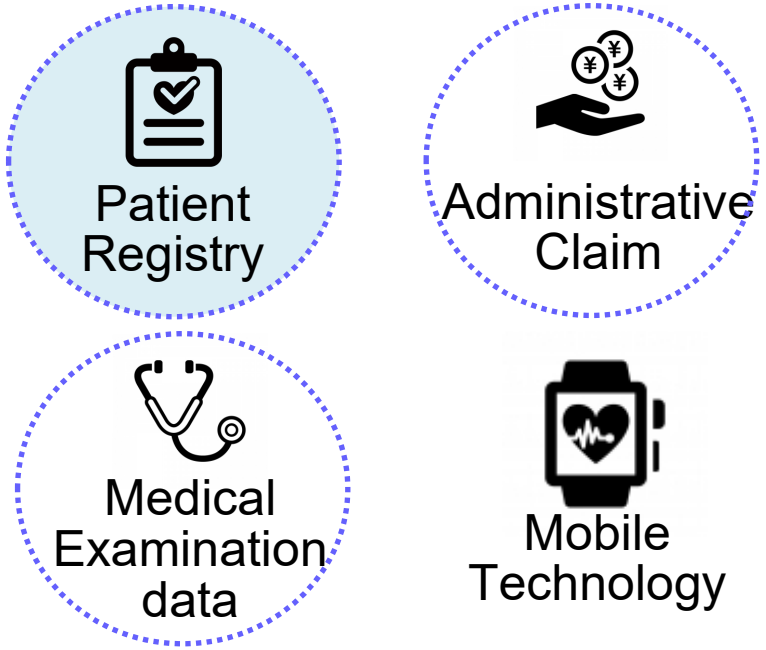
4. Points to consider for externally controlled trials (Early Consideration) (March 24, 2025) https://www.pmda.go.jp/files/000275337.pdf

NEW

Utilization of RWE to Evaluate Clinical Outcomes of Medical Devices

Source of RWD

- National / International
- Academic / Sponsor
- Procedure / Medical Device



Purpose of Utilization in regulatory use

1. External control of clinical trials
2. Primary data or complement of clinical trials
3. Efficacy and/or safety evaluation of conditionally approved items
4. Post-marketing surveillance for safety measures

Utilization of registry data as an *external control* of clinical study

Product	Product summary（indications）	Registry
EXCOR Pediatric (Cardio)	Extracorporeal Ventricular Assis Device (Circulatory support until heart transplantation (BTT) for pediatric patients with severe heart failure)	ELSO-DB（US）
Najuta. Thoracic Stent Graft System (SB Kawasumi)	Stent graft (Thoracic aortic aneurysm treatment)	JACVSD（Japan）
HVAD (Medtronic)	Implantable Ventricular Assist Device (Circulatory support until heart transplantation (BTT) for patients with severe heart failure)	INTERMACS（US）
daVinci surgical system (Intuitive)	Surgical robotic unit (Endoscopic surgery in general digestive surgery, thoracic surgery, cardiac surgery, urology, and gynecology)	STS-DB（US）
MitraClip NT system (Abbott)	Mitral TEER（for the patient at high risk for open-heart surgery ）	Duke University-DB（US）
SATAKE･HotBalloon catheter (TORAY)	Percutaneous radiofrequency ablation (Paroxysmal atrial fibrillation)	J-CARAF DB（Japan）
Heart Mate 3 (NIPRO/Abbott)	Implantable Ventricular Assist Device (Long-term circulatory support (DT indication) for patients with severe heart failure who are not suitable for heart transplantation)	INTERMACS（US） J-MACS（Japan）

Ishii K. PMDRS, 52(5),318-324(2021)(in Japanese)

Utilization of registry data as *complement* for clinical study

Product	Product summary（indications）	Registry
Paxman Scalp Cooling System Orbit and Cap (CMI)	Head cooling device（Reducing hair loss in patients receiving drug therapy for solid tumors）	Netherlands Cancer Registry（Netherlands） : Treatment outcomes by cancer type
Edwards SAPIEN 3 (Edwards)	Transcatheter Heart Valve（for TAV in SAV）	TVT Registry (US) : Outcomes for all sizes, including sizes not included in the clinical trial
Edwards SAPIEN 3 (Edwards)	Transcatheter Heart Valve（for Low risk patients）	TVT Registry (US) : Outcomes of subclavian/axillary approach and transapical/transaortic approach
CoreValve Evolut R (Medtronic)	Transcatheter Heart Valve（for Low risk patients）	TVT Registry (US) : Pacemaker implantation rate

Ishii K. PMDRS, 52(5),318-324(2021)(in Japanese)

Utilization of registry data as *substitute* for clinical study

	Product	Product summary（indications）	Registry
	Edwards SAPIEN 3 (Edwards)	Transcatheter Heart Valve （for TAV in TAV in 2022）	TVT Registry (US)
NEW	SelectSecure Lead (Medtronic)	Pacing lead (for LBBAP(left bundle branch area pacing) in 2024)	Product Surveillance Registry (Company-led international collaborative registry)
NEW	COMBO Plus Coronary Stent (OrbusNeich)	Coronary stent (for additional stent size in 2024)	MASCOT registry (Multinational Abluminal Sirolimus Coated Bio-engineered stent) (Company-sponsored international collaborative registry)

Overview of the Consultation Process for Utilization of RWE

Review team

General consultation/ Consultation pre-meetings
(Sharing the information to be discussed in the following formal consultation, such as the overview of device and registry, discussion items)

Consultation of the necessity of conducting clinical trails.
(Suggestion on matters, such as appropriateness of registry's data usage and adequacy of endpoints.)

Compliance team

General consultation
(Sharing the information to be discussed in the following formal consultation, such as the overview of registry, discussion items)

Consultation for development of registry data
Suggestion on ***general consideration*** of development strategies for registry

Consultation for compliance assessment of registries
Checking and specifying the status of data reliability of registry for marketing approval corresponding to the individual device.

Consultation on the necessity of conducting clinical trails

<Propose of the consultation>

- Suggestion on matters, such as appropriateness of registry's data usage and adequacy of endpoints, when utilizing a registry data for the approval application of individual product.

<*Target Consulter*> Applicant (Medical device company)

<Flow of the consultation>

- <Applicant>Submission of consultation documents, 3 weeks prior to meeting.
- <PMDA>Reviewing the contents internally and send inquiries to the applicant about the items that need to be explained in more detail or resolved prior to the consultation
- Face-to-face and/or web meeting are held for 2 hours in Japanese.
- Meeting minutes summarizing PMDA's advice will be issued by PMDA.

<Points to consider for the efficient consultation>

- Applicants should explain that the concerned registry data appropriate for the purpose of utilizing the data including the following items.
  - Specification of appropriate population according to the purpose of utilizing the concerned data.
  - Adequacy of endpoints and evaluation period for evaluation of the device etc.

Consultation for Development of Registry

<Propose of the consultation>

- ***General consideration*** of development strategies for registry.
- ***Methods of ensuring the data reliability of registry*** for marketing approval/PMS applications.

<Target Consulter> Registry holder (mainly academic society)

<Flow of the consultation>

- ***Applicant***: Submission of consultation documents, ***4 weeks prior to meeting***.
- ***PMDA***: Reviewing the contents internally and send inquiries to the applicant about the items that need to be explained in more detail or resolved prior to the consultation.
- Face-to-face and/or web meeting are held in Japanese.
- Meeting minutes summarizing PMDA's advice will be issued by PMDA.

<Points to consider for the consultation>

- The consultation can be provided ***regardless of whether the registry is in the planning stage or has already been established***.
- It’s necessary to explain the procedures for managing the registry based on the procedure manual and ***capability of obtaining the consent of a patient*** who provides data to registry based on Japanese Act on the Protection of Personal Information and so on.

Consultation for Compliance Assessment of Registry

<Propose of the consultation>

- Checking and specifying the status of data reliability of registry for marketing approval corresponding to the individual device.

<Target Consulter> Applicant (Medical device company)

<Flow of the consultation>

- ***Applicant***: Submission of consultation documents, ***8 weeks prior to meeting***.
- ***PMDA***: Reviewing the contents internally and send inquiries to the applicant about the items that need to be explained in more detail or resolved prior to the consultation
- Face-to-face and/or web meeting are held in Japanese.
- Meeting minutes summarizing PMDA's advice will be issued by PMDA.

<Points to consider for the efficient consultation>

- The consultation menu is ***intended to investigate the reliability of registry data*** before the application.
- By gathering the necessary documents for the actual investigation during the application process, it’s possible to ***clarify concerns and matters that require action***.
- It’s necessary to explain the capability of obtaining the consent of a patient who provides data to registry based on Japanese Act on the Protection of Personal Information and so on.

Summary

- Successful cases utilizing the RWD are gradually accumulating in Japan. PMDA is actively offering various consultation services to promote the utilization of registry data for regulatory decision-making.
- The collaboration between academia, industry and regulator is important to accelerate the utilization of RWD.
- We need to continue discussing for more effective RWD utilization in regulatory decision making.

We would like to consider what we can do in HBD activities to promote the use of RWD.
(potential new POC projects with RWD)

Thank you/Questions