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PMDA activities for RWD

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Office of New Drug I, Pharmaceuticals and Medical Devices Agency (PMDA)

Meet the Speaker

Daisuke Iwata, PhD

Title: Deputy Review Director

Organization: Pharmaceuticals and Medical Devices Agency

He started his career as a Reviewer at PMDA in 2008 and currently he works in Office of New Drug I. He is also a member of Real World Data (RWD) Working Group that is one of projects across multi-offices in PMDA.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC or PMDA.*

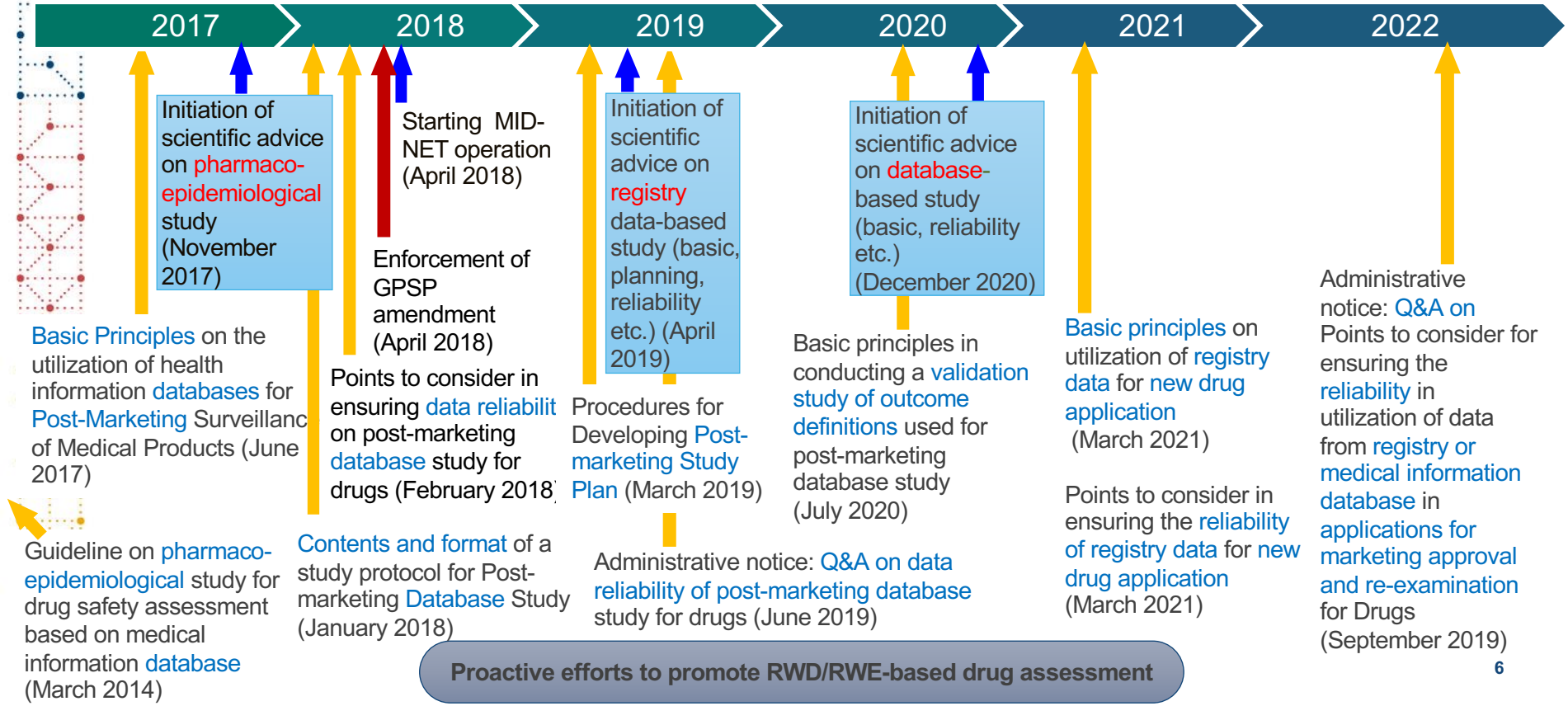
- *The author has no real or apparent conflicts of interest to report.*

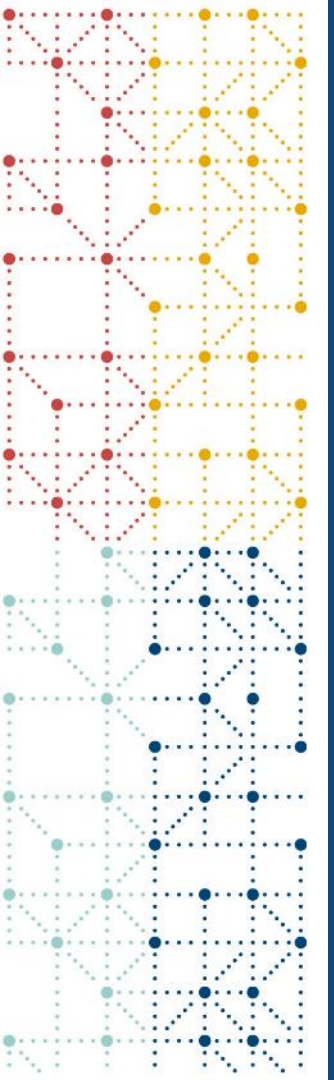
Agenda

1. Japanese regulatory initiatives/guidelines on RWD
2. Utilization of RWD for Post-marketing
3. Utilization of RWD for New drug application

Japanese regulatory initiatives/guidelines on RWD

Japanese regulatory initiatives/guidelines on RWD/RWE





Utilization of RWD for Post-marketing

Japanese regulatory initiatives/guidelines on RWD/RWE mainly for post-marketing

Guideline on pharmaco-epidemiological study for drug safety assessment based on medical information database (March 2014)

Basic Principles on the utilization of health information databases for Post-Marketing Surveillanc of Medical Products (June 2017)

Initiation of scientific advice on pharmaco-epidemiological study (November 2017)

Contents and format of a study protocol for Post-marketing Database Study (January 2018)

Points to consider in ensuring data reliabilit on post-marketing database study for drugs (February 2018)

Starting MID-NET operation (April 2018)

Enforcement of GPSP amendment (April 2018)

Procedures for Developing Post-marketing Study Plan (March 2019)

Initiation of scientific advice on registry data-based study (basic, planning, reliability etc.) (April 2019)

Administrative notice: Q&A on data reliability of post-marketing database study for drugs (June 2019)

Basic principles in conducting a validation study of outcome definitions used for post-marketing database study (July 2020)

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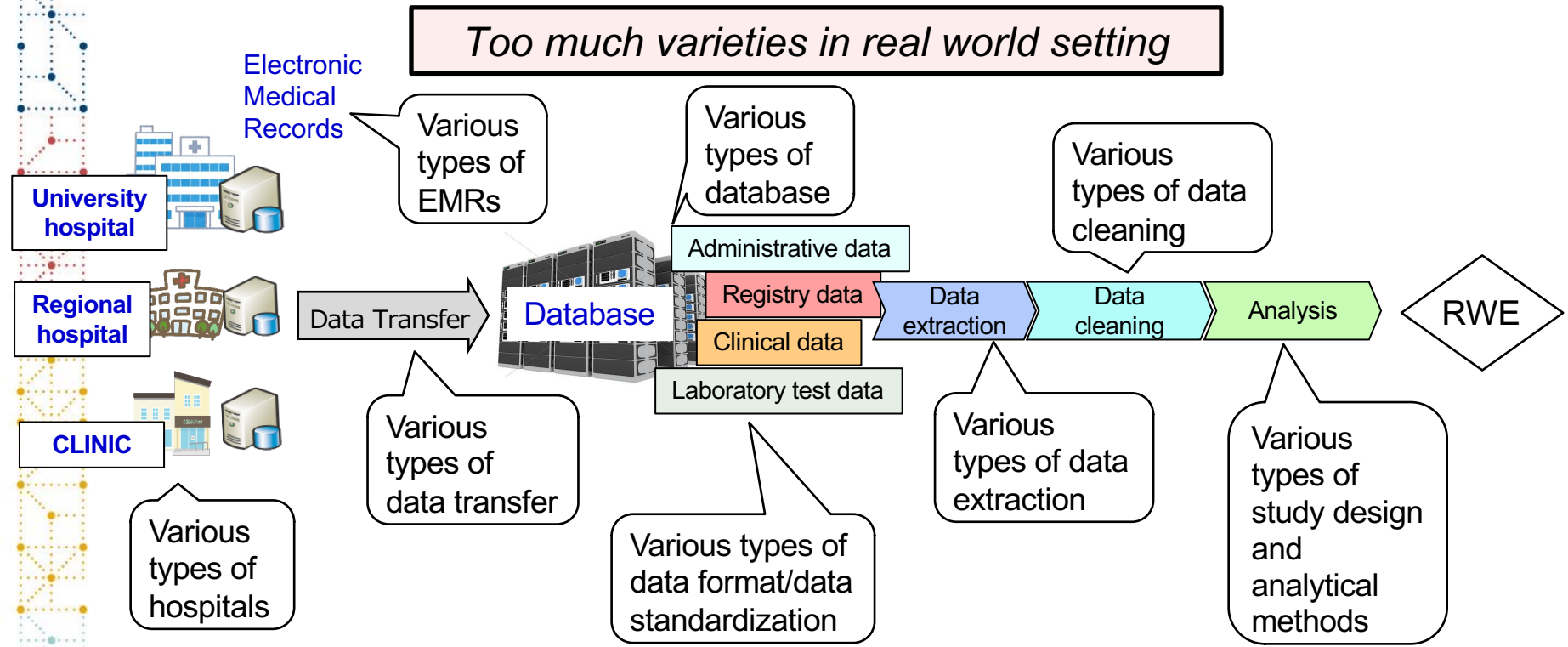
Basic principles on utilization of registry data for new drug application (March 2021)

Points to consider in ensuring the reliability of registry data for new drug application (March 2021)

Administrative notice: Q&A on Points to consider for ensuring the reliability in utilization of data from registry or medical information database in applications for marketing approval and re-examination for Drugs (September 2019)

Proactive efforts to promote RWD/RWE-based drug assessment

Many processes to create RWE

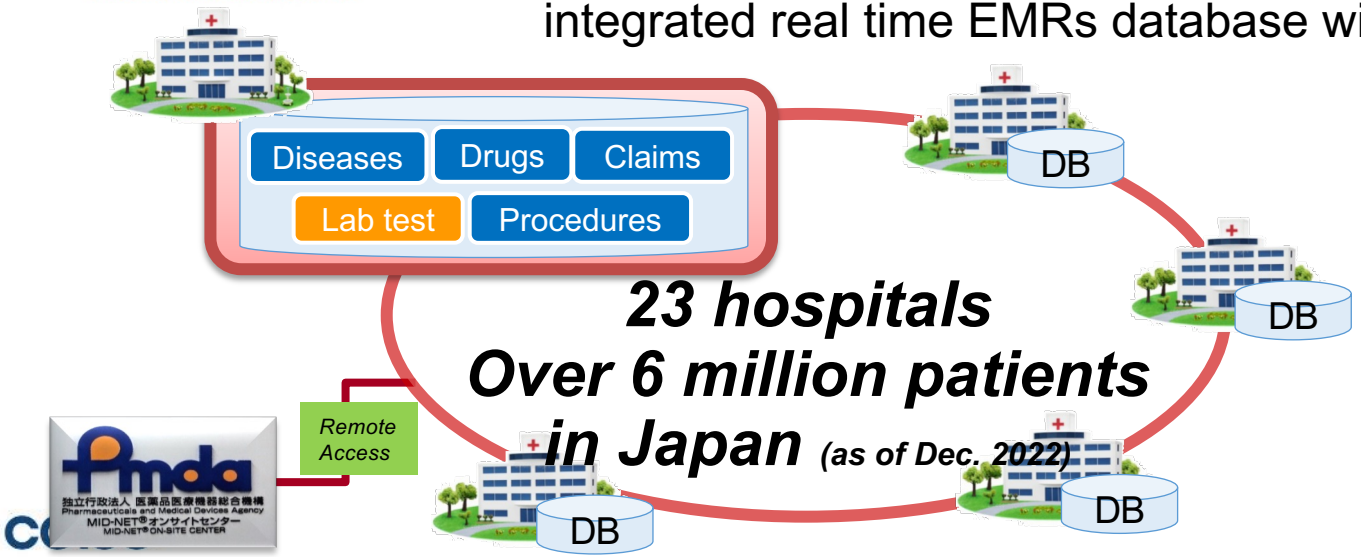


A long journey to obtain reliable and useful real world evidence

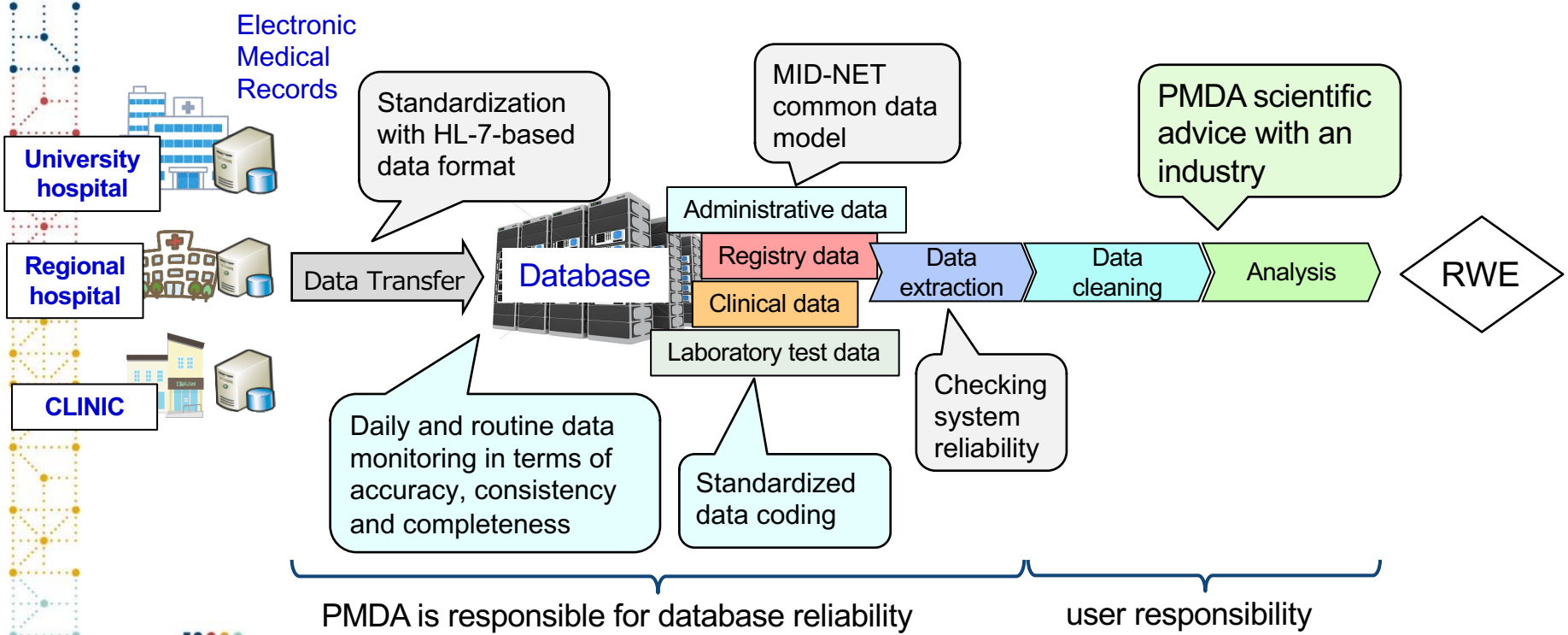
PMDA-Qualified Real World Data
Medical Information Database Network (MID-NET®)

MID-NET®
Medical Information Database Network

- The Medical Information Database Network in Japan for a real-time assessment of drug safety
  - Full operation started in April 2018
- PMDA has led the project for establishing an integrated real time EMRs database with high quality



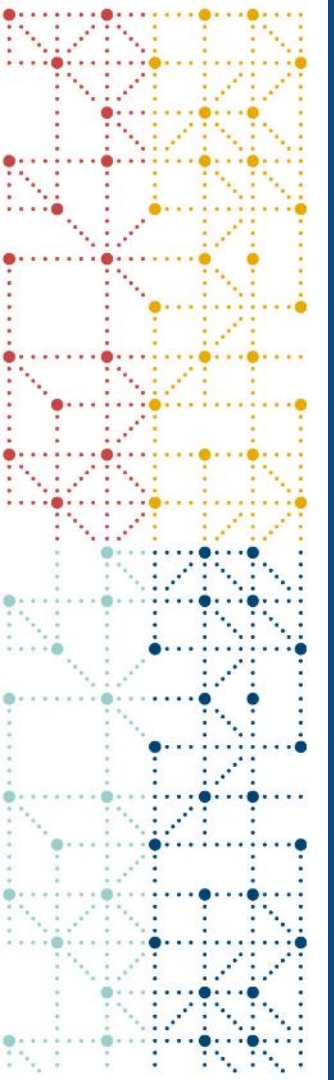
Experiences on utilization of MID-NET® for post-marketing study



Yamaguchi, M et al. Pharmacoepidemiol Drug Saf 28: 1395-1404, 2019

RWD-based pharmacoepidemiological studies

Research purpose (target events)	Target drugs	Summary of results & Regulatory actions (decisions)
Blood coagulability	Direct-acting antivirals against hepatitis C (DAAs) Therapeutic Innovation & Regulatory Science 2021 55: 539-544 DOI: 10.1007s43441-020-00247-8	• Improvement of the liver function by DAAs might be related to the fluctuation in blood coagulability in patients receiving both DAA and warfarin • Used as a reference for revising the package insert with more precautions
Thrombocytopenia	G-CSF Clinical Pharmacology & Therapeutics 2021 110: 473-479 DOI: 10.1002/cpt.2263	• Increased risk of thrombocytopenia by pegfilgrastim • Used as the major evidence for revising the package insert with more precautions
Renal dysfunction	DAAs	• Observed different risks of renal dysfunction among DAAs • Confirmed that the current warning on the package insert was appropriate and no new additional safety measures were required



Utilization of RWD for New drug application

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Proactive efforts to promote RWD/RWE-based drug assessment

Utilization of Patient Historical control in New drug Applications

Product	Approval	Indication	Usage of disease registry
Alglucosidase alfa	Apr. 2007	Pompe disease (type II glycogen storage disease)	Use of the survival rate from retrospective cohort study in US as comparator
Argartroban hydrate	May 2011	Heparin induced thrombocytopenia type II	Selected historical controls in the same trial site by the same selection criteria with subjects
Tacrolimus hydrate	Jun. 2013	Interstitial pneumonia in patients with PM/DM	Use of the survival rate from retrospective cohort study as comparator
Asfotase alfa	Aug. 2015	Hypophosphatasia	Use of the survival rate from retrospective cohort study in US as comparator

Activities for utilization of Registry

- Consultations for registry utilization (from April 2019)
  - ➢Consultation for development of registry
  - ➢Consultation for Pre-inspection on registry data reliability
  - ➢Consultation for registry utilization
- Issuance of notifications (guideline) (in Mar 2021)
  - ➢"Basic Principles on Utilization of Registry for Applications" (PSEHB/PED Notification No.0323-1, Mar. 23, 2021)
    https://www.pmda.go.jp/files/000240806.pdf
  - ➢"Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications" (PSEHB/PED Notification No.0323-2, Mar. 23, 2021)
    https://www.pmda.go.jp/files/000240807.pdf

Consultation for development and reliability

Consultation for development of registry

- Consulter:
  - Registry holder (mainly academic organization/society), possibly with the sponsor
- Content:
  - Advise appropriateness of development plan of utilizing registry data
  - Advise method of ensuring the data integrity and reliability of registry data for approval/re-examination applications
- Consultation on the issues of individual new drug/medical device application will not be provided in this consultation

Consultation for Pre-Inspection on registry data reliability

- Consulter:
  - Sponsor, possibly with the registry holder
- Content:
  - Check and advice the data integrity of registry data for approval/re-examination
  - applications corresponding to the individual new Drug/Medical Device

Consultation for actual utilization

Consultation for registry utilization

- Consulter:
  - Sponsor, possibly with the registry holder
- Content:
  - Consultation for appropriateness of utilization and/or sufficiency of data of the registry in accordance with the purpose, in case the utilization of registry for the evaluation of efficacy and safety of individual drug is expected for approval/re-examination.
  - This consultation is basically conducted before the consultation for Pre-Inspection on registry data reliability.

<Examples>

- In case of a rare disease where conducting a randomized controlled trial is not feasible, appropriateness of the utilization and sufficiency of the data items of the registry as external control for efficacy evaluation may be discussed.
- In case of special population which had small number of patients investigated before approval, appropriateness of the utilization and sufficiency of the data items of the registry for efficacy and safety evaluation as application of re-examination may be discussed.

Implementation status of consultations

As of March 31, 2023

Consultation	Number of Consultation
Consultation for development of registry	13
Consultation for Pre-Inspection on registry data reliability	13
Consultation for registry utilization*	3

* The same contents are discussed also in other clinical trial consultation meetings
  - Medical devices: 26
  - Drugs: 34

Basic Principles on Utilization of Registry for Applications

The GL was developed on the utilization of registry data for the following cases

1. Utilization of registry data as an external control of clinical studies for efficacy and/or safety evaluation in applications
2. Utilization of registry data as complement or substitute of clinical study for efficacy and/or safety evaluation in applications
3. Utilization of registry data in evaluation of drugs and medical devices with conditional approval and of regenerative medical products with conditional time-limited approval
4. Utilization of registry data in post-marketing efficacy and/or safety evaluation

The GL also provides points to consider on the following items when utilizing registry data as an external control of clinical studies for efficacy and/or safety evaluation in applications

- Registry Patient Population
- Endpoints
- Evaluation Period
- Statistical Method
- Type of observational study for natural history (prospective or retrospective)

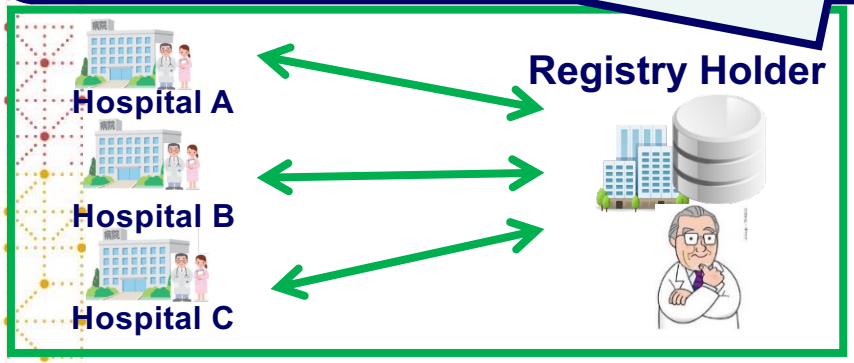
Points to consider on utilization of registry data as an external control

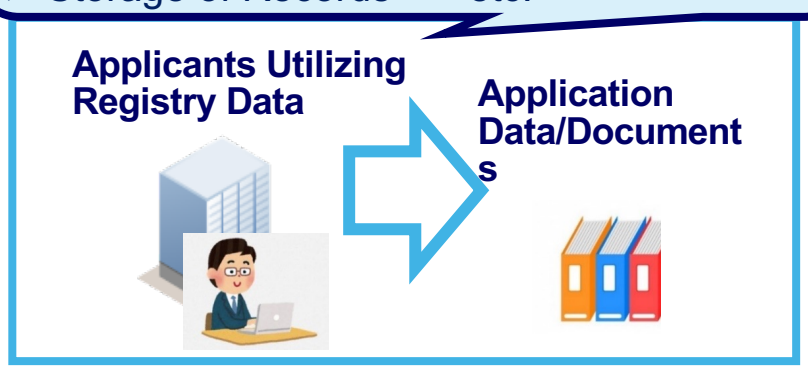
- **Registry patient population**
  - Population covered by the registry, and similarity of population characteristics between registry and clinical study
  - Pre-specification of statistical analysis plan including extraction conditions of patients from the registry to justify the comparison
  - Potential issues of difference of the enrollment condition between the registry and clinical study
  - Explanation whether registry is representative of the target population of the clinical study
  - Difficulty when registry data are collected in greatly different timing from that when clinical study is conducted
  - Potential concern of comparability when registry data are collected simultaneously with clinical study
  - Possibility of pooling data from placebo group in clinical study and natural history data
- **Endpoints**
  - Clear definition and standardized evaluation methods of endpoints in registry, and justification of comparability with the study
  - Careful examination of appropriateness of utilization, particularly for subjective endpoints
- **Evaluation period**
  - Appropriate data collection period for the purpose of utilization
  - Issues of differences in evaluation timing of individual patients and inconsistent quality of data collection
- **Statistical method**
  - Importance of characterization of data and selection of appropriate methods
  - Pre-specification of analysis methods including handling of missing data
  - Investigation of potential bias which affects the results and subsequent efficacy evaluation
- **Type of observational study for natural history (prospective or retrospective)**
  - Viewpoints which should be taken into account for utilization of registry with prospectively collected data
  - Situations which can affect efficacy and/or safety evaluation with retrospective usage of the data

Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications

- Governance by Registry Holders
- Quality Management (QM) and Security of Computerized System
- Consideration for Protection of Personal Information
- QM and QA of Registry Data etc.

- Contracts with Registry Holders
- Confirmation of Data QM Implemented by Registry Holders
- Preparation of Application Data/Documents
- Storage of Records etc.





- The scope of this notification includes not only the registries to be newly constructed but also the registries that have been constructed with accumulated data
- As the level of reliability required for the registry data may vary depending on the purpose of utilization, **an applicant is encouraged to consult PMDA** in the case of utilization of registry data as Application Data/Documents, etc.

Two important factors when utilizing RWD for regulatory purpose

Reliable Data	X	Inappropriate analysis	=	Uninterpretable results
Unreliable Data	X	Appropriate analysis	=	Uninterpretable results
Reliable Data	X	Appropriate analysis	=	Interpretable results

RWE only contributes to regulatory decision-making when both factors are fulfilled.

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Nishioka K., et al. *Clin Pharmacol Ther.* 2021 doi:10.1002/cpt.2410

Submission of electronic study data of registry data

<FAQs on Electronic Study Data Submission>

- Q1-35: When registry data are utilized in documents of clinical data for a new drug application, what are the contents of electronic study data to be submitted?

- A: Even if registry data are utilized in document of clinical data, it is still important, as with the case of clinical studies, to submit data that provide the major evidence for the efficacy, safety, and dosage and administration for a new drug application in a format conforming to the CDISC standards basically.
- On the other hand, the scope, contents and format of registry data to be submitted may require individual judgment, depending on the contents and purpose of registry data. Therefore, please consult with the PMDA in advance at an applicable consultation.
- Regarding the submission format of data, if registry data are used at least for an evaluation of efficacy as an external control in a clinical study* and an analysis that uses registry data corresponds to analyses subject to submission of analysis datasets as described in Section 4.1.1.3 of the technical conformance guide, please submit datasets used for the analysis in the ADaM format as part of the analysis datasets of the clinical study. If submission in the ADaM format is difficult because of the method of analysis or other technical reasons, please consult with the PMDA at a consultation on preparation of submission of electronic study data.

* Reference: Basic principles on Utilization of Registry for Applications (PSEHB/PED Notification No. 0323-1, PSEHB/MDED Notification No. 0323-1, dated Mar. 23, 2021）

Recent example of RWD utilization for new drug application

- Product: Trastuzumab and Pertuzumab
- Indication: Unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy
- Approval: March, 2022

Data category	Study ID	Number of subject enrolled	Overall response rate [95% confidence interval] (%)
Evaluation	TRIUMPH study (Phase II)	<Tratuzumab/Pertuzumab arm> 30 ①TBx*1 population: 27 ②LBx*2 population: 25	①29.6 [13.8, 50.2] (8/27) ②28.0 [12.1, 49.4] (7/25)
		<SCRUM-Japan registry> External control arm 6	0%(0/5*3)

*1: HER2 positive tested by tissue biopsy, *2:HER2 positive tested by liquid biopsy, *3: Best overall response evaluable population

SCRUM-Japan:

- Industry-Academia collaborative cancer genome screening project for individualized medicine in Japan.

Projects Across Multi-Offices in PMDA Newly Established RWD WG (in April 2021)

CIN WG → **Reorganization** → **RWD WG**

- Coordination of scientific Consultations on patient registries
- Preparing guidelines on utilization of patient registries for new drug application, including data reliability

- Implementation of the guidelines on patient registries
- Sharing experiences and knowledge on patient registries

For further advancement on RWD utilization

- Discuss all subjects on RWD comprehensively
  - ➢ General principles on RWD utilization and data reliability in regulatory setting

CIN: Clinical Innovation Network
RWD: Real World Data

Data reliability SWG
- Discuss reliability standards on RWD utilization in clinical development etc.

Utilization SWG
- Discuss general principles on RWD utilization for efficacy and safety assessment

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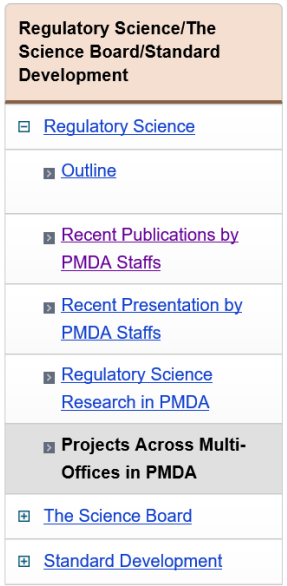
Related information will be provided on PMDA RWD WG website



RWD WG

Activities

The purpose of this WG is to deal with regulatory issues related to Real World Data (RWD) such as utilization of patient registry data and medical information databases. The WG contributes to clarify general principles on RWD utilization and data reliability ranging from development through post-marketing surveillance of drugs and medical devices, etc.

- Publicize the MHLW notifications on RWD utilization in Japan and overseas.
- Extract potential issues with implementing the notifications.
- Announce results of the WG's activity (e.g., organizing examples of regulatory use of RWD, or facilitating RWD utilization) in Japan and overseas.

Established

April, 2021

Members

Office of New Drug I-V
Office of Cellular and Tissue-based Products
Office of Vaccines and Blood Products
Office of Medical Devices I-II
Office of Standards and Compliance for Medical Devices

https://www.pmda.go.jp/english/rs-sb-std/rs/0023.html

Conclusion

- PMDA has been actively working on the utilization of RWD for post-marketing surveillance and also for new drug/device application.
- Assuring data reliability and using appropriate analysis methods are critical in utilizing RWD.
- PMDA has started to discuss all subjects on RWD comprehensively, and to apply general principles on RWD utilization and data reliability to actual regulatory settings.
- The experiences of the consultation meetings and of reviewing applications with RWD are still limited.
- We would like to continue to actively participate in discussions for the utilization of RWD.