EFSPI regulatory statistics workshop 2021
Sep 15, 2021

Activities for utilization of RWD in PMDA

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Japanese regulatory initiatives/guidelines on RWD/RWE

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

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

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

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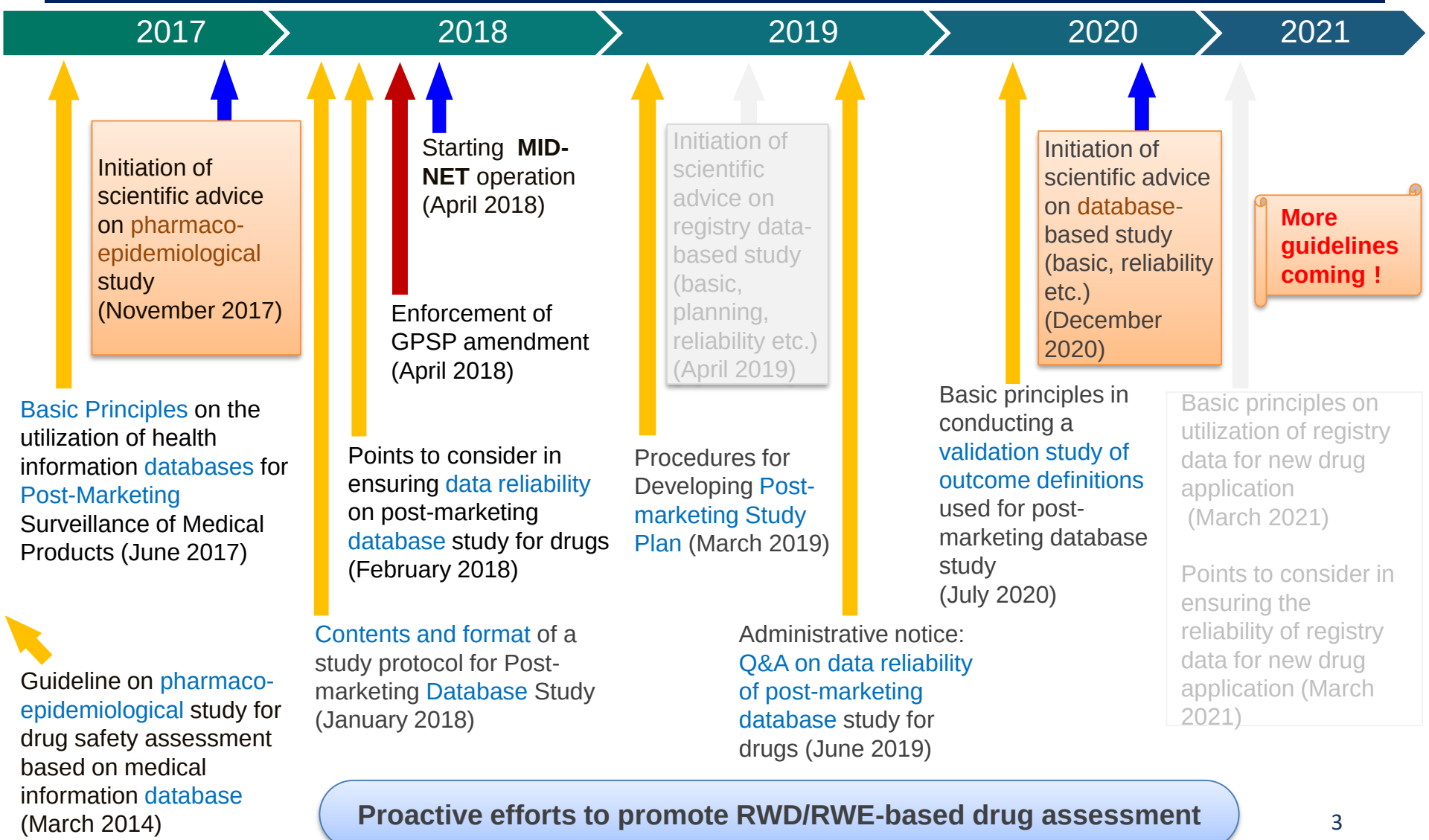
Basic principles on utilization of registry data for new drug application (March 2021)

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

More guidelines coming !

Proactive efforts to promote RWD/RWE-based drug assessment

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



Proactive efforts to promote RWD/RWE-based drug assessment

Many processes to create RWE

Too much varieties in real world setting

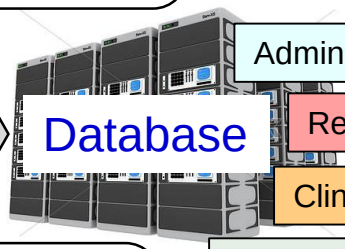
Various types of hospitals

Electronic Medical Records

Various types of EMRs

Data Transfer

Various types of data transfer



Various types of database

Administrative data

Registry data

Clinical data

Laboratory test data

Various types of data format/data standardization

Various types of data cleaning

Data extraction

Data cleaning

Analysis

RWE

Various types of data extraction

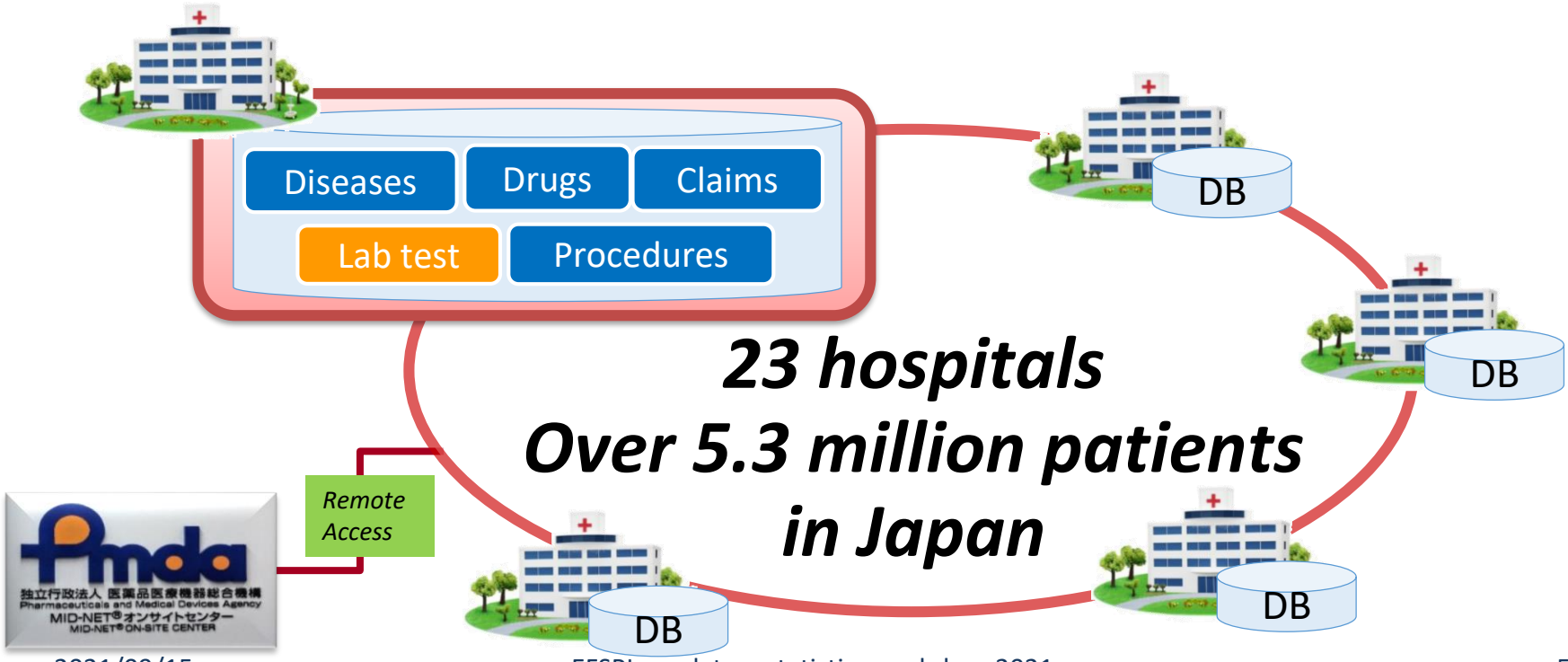
Various types of study design and analytical methods

A long journey to obtain reliable and useful real world evidence

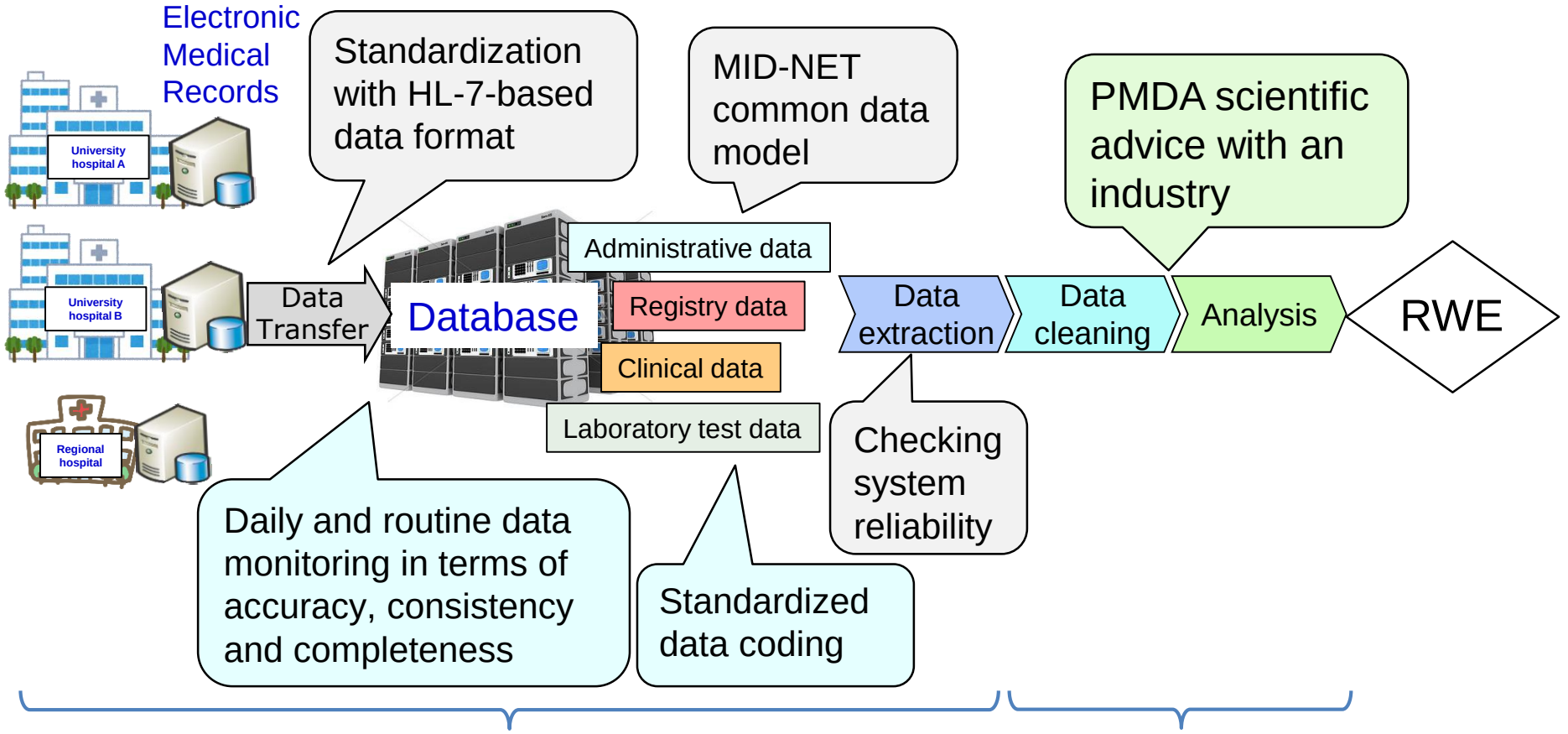
PMDA-Qualified Real World Data
Medical Information Database Network (MID-NET®)

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

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Proactive efforts to promote RWD/RWE-based drug assessment

Examples of RWE in new drug applications

Product	Approval	Indication	Usage of disease registry
Alglucosidase alfa	2007.4	Pompe disease (type II glycogen storage disease)	Use of the survival rate from retrospective cohort study in US as comparator
Argartroban hydrate	2011.5	Heparin induced thrombocytopenia type II	Selected historical controls in the same trial site by the same selection criteria with subjects
Tacrolimus hydrate	2013.6	Interstitial pneumonia in patients with PM/DM	Use of the survival rate from retrospective cohort study as comparator
Asfotase alfa	2015.8	Hypophosphatasia	Use of the survival rate from retrospective cohort study in US as comparator

Previous framework of activities for registry data utilization – CIN Working Group

Expected future of utilization of registry data

- Utilization of registry data as external control when conducting a traditional RCT is not feasible → Application for approval
- Utilization of registry data for post-marketing surveillance → Application for re-examination

PMDA (CIN Working Group) ⟷ **MHLW** ⟷ **AMED**

- Clinical trials/epidemiological study designs
- Data integrity standards, etc.
- Data set that need to be collected in each registry

→

- Cross-sectional research project
  - Data reliability, study designs (-2018)
  - Ethical issues (-2018)
  - Registry survey and integrated gateway
  - Regulatory use of new data sources and international harmonization
  - Analysis of registry data
- Registry development
  - Muscular dystrophy
  - Amyotrophic lateral sclerosis
  - Orphan-fractionated cancer
  - Neurosurgical and neuroendovascular devices

CIN: Clinical Innovation Network

Activities for utilization of Registry

- Consultations for registry utilization (from May 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

- 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.

Basic Principles on Utilization of Registry for Applications

(PSEHB/PED Notification No. 0323-1, Mar 23, 2021)

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

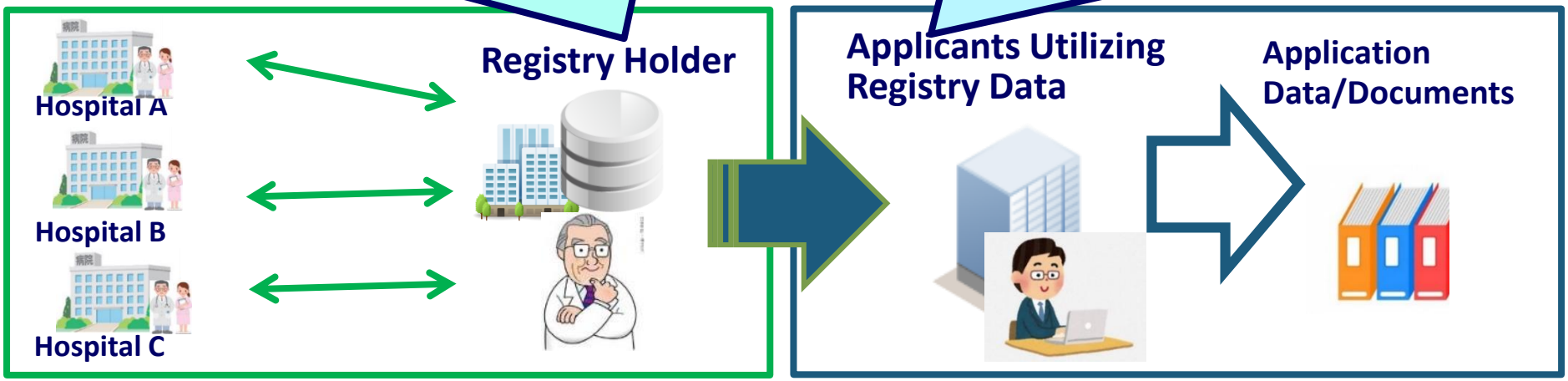
- Registry patient population
  - Population covered by the registry, and similarity of population characteristics between registry and clinical study
  - Pre-specification of statistical analysis plan including extraction conditions of patients from the registry to justify the comparison
  - Potential 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

(PSEHB/PED Notification No. 0323-2, Mar 23, 2021)

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

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

CIN WG

"Evolutive" 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

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

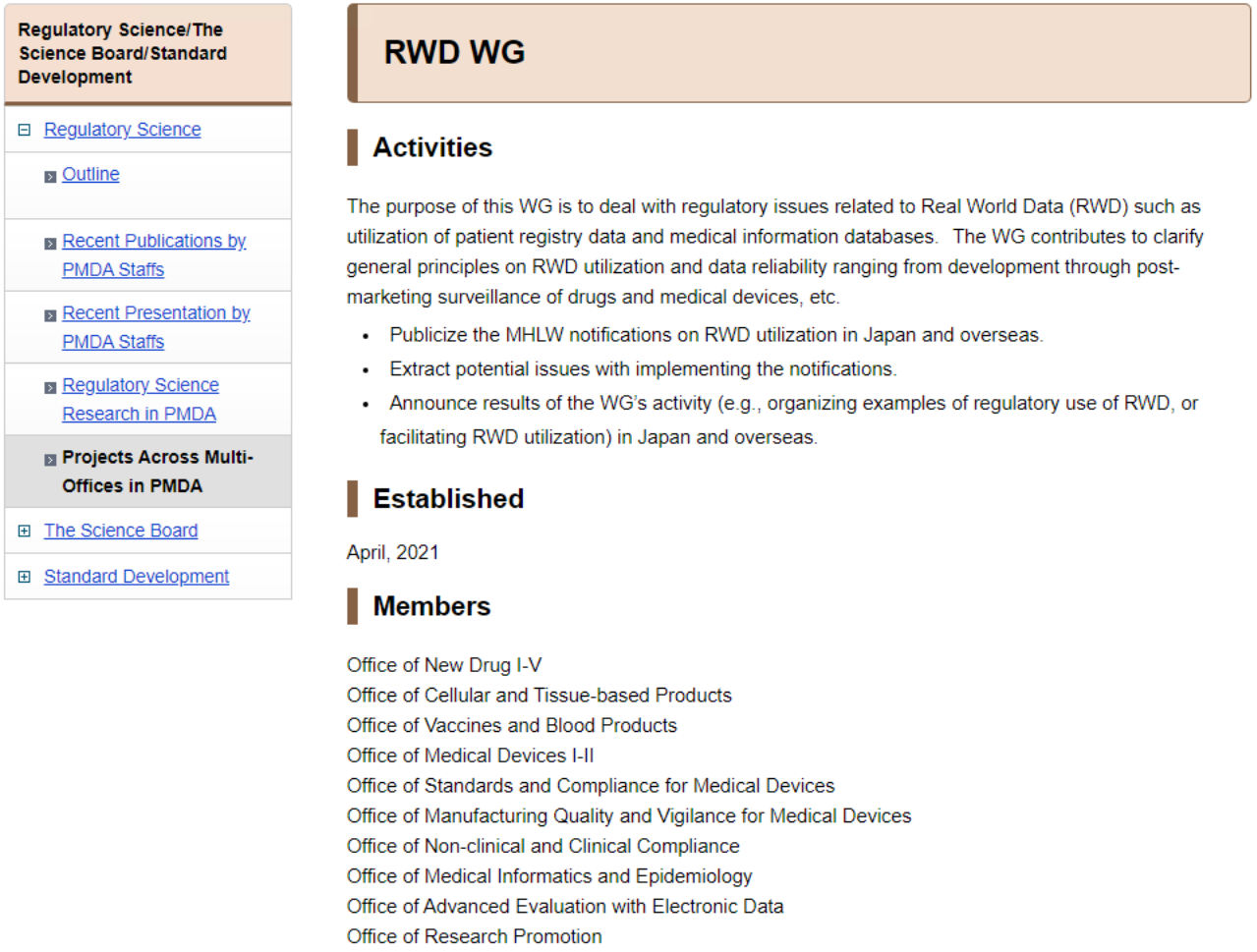
Utilization SWG
Discuss general principles on RWD utilization for efficacy and safety assessment

CIN: Clinical Innovation Network

Conclusion

- PMDA has been actively working on the utilization of RWD for post-marketing surveillance and new drug 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 will consider general principles on RWD utilization and data reliability in regulatory setting.
- The experiences of the consultation meetings and of reviewing new drug applications with RWD are still limited.
- We would like to continue to actively participate in discussions for the utilization of RWD.

Related information will be provided on PMDA RWD WG website



Regulatory Science/The Science Board/Standard Development

- ⊟ Regulatory Science
  - Outline
  - Recent Publications by PMDA Staffs
  - Recent Presentation by PMDA Staffs
  - Regulatory Science Research in PMDA
  - **Projects Across Multi-Offices in PMDA**
- ⊞ The Science Board
- ⊞ Standard Development

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
Office of Manufacturing Quality and Vigilance for Medical Devices
Office of Non-clinical and Clinical Compliance
Office of Medical Informatics and Epidemiology
Office of Advanced Evaluation with Electronic Data
Office of Research Promotion

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