22nd DIA Japan Annual Workshop for Clinical Data Management
Clinical Data Management in New Era
- Enhance Data Reliability and Utilization to Adapt to Renovation -
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Current status and practices of quality management for MID-NET®

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(PMDA)

DIA

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Establishment of PMDA Regulatory Science Center

The "Safety Triangle"

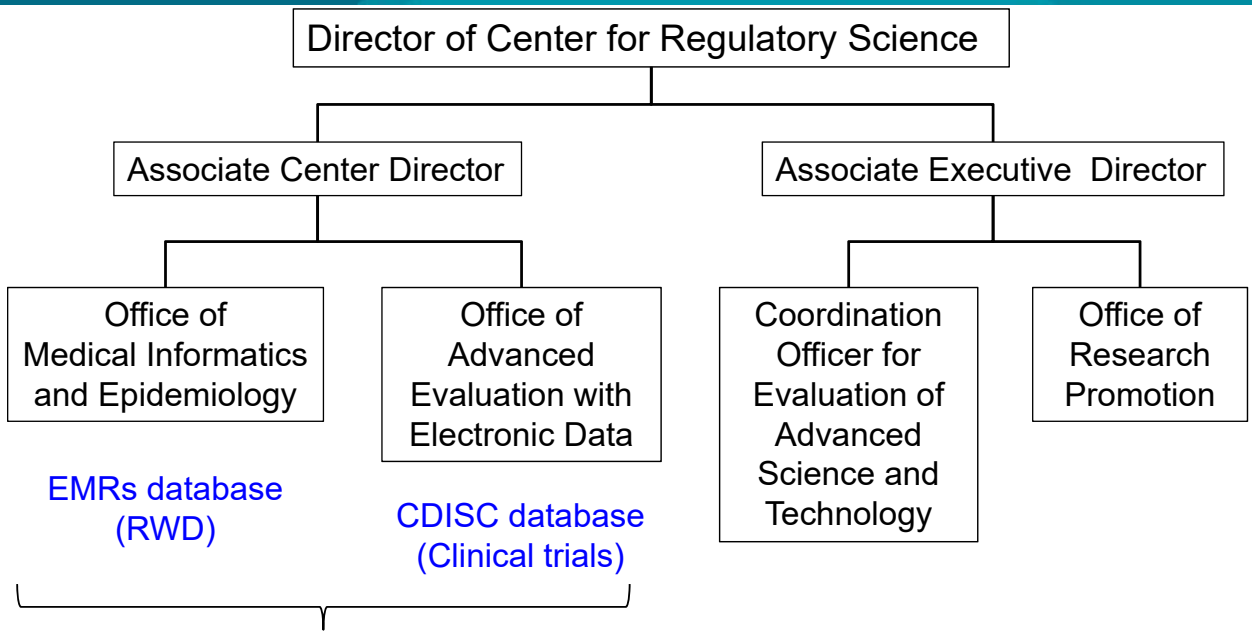
- Comprehensive risk management framework supported by three core operations -

- PMDA's Three Major Services:

PMDA is the only regulatory authority in the world to operate under this integrated 3-tier framework.

- Each of PMDA's services are guided by RS, and promote improvement of the standard of medical care by ensuring safe medical products of high quality

Regulatory Science Center (Organization Structure)



Active utilization of e-DATA/Big-Data in regulatory science

Closely working together with Offices of New Drugs, Offices of Safety etc.

Active utilization of e-DATA

Regulatory Science Center

Nurturing of talented experts, accumulating scientific knowledge

Office of Research Promotions

Coordination and project management in regulatory science research and publishing guidelines (Governance office of Science board etc.)

Office of Advanced Evaluation with Electronic Data

Utilization of clinical trial data on CDISC database (modeling & simulation, cross-product analysis for better benefit/risk assessment)
-CDISC data has been submitted by MAHs since October 2016

Office of Medical Informatics and Epidemiology

Utilization of EMR database for pharmaco-epidemiological analysis (PEpi-study, cross-product analysis for better benefit/risk assessment)
-Implemented in 2016

MIHARI
MID-NET

Pre-approval

Analysis for identifying an important factor on efficacy and/or safety of drug(s)

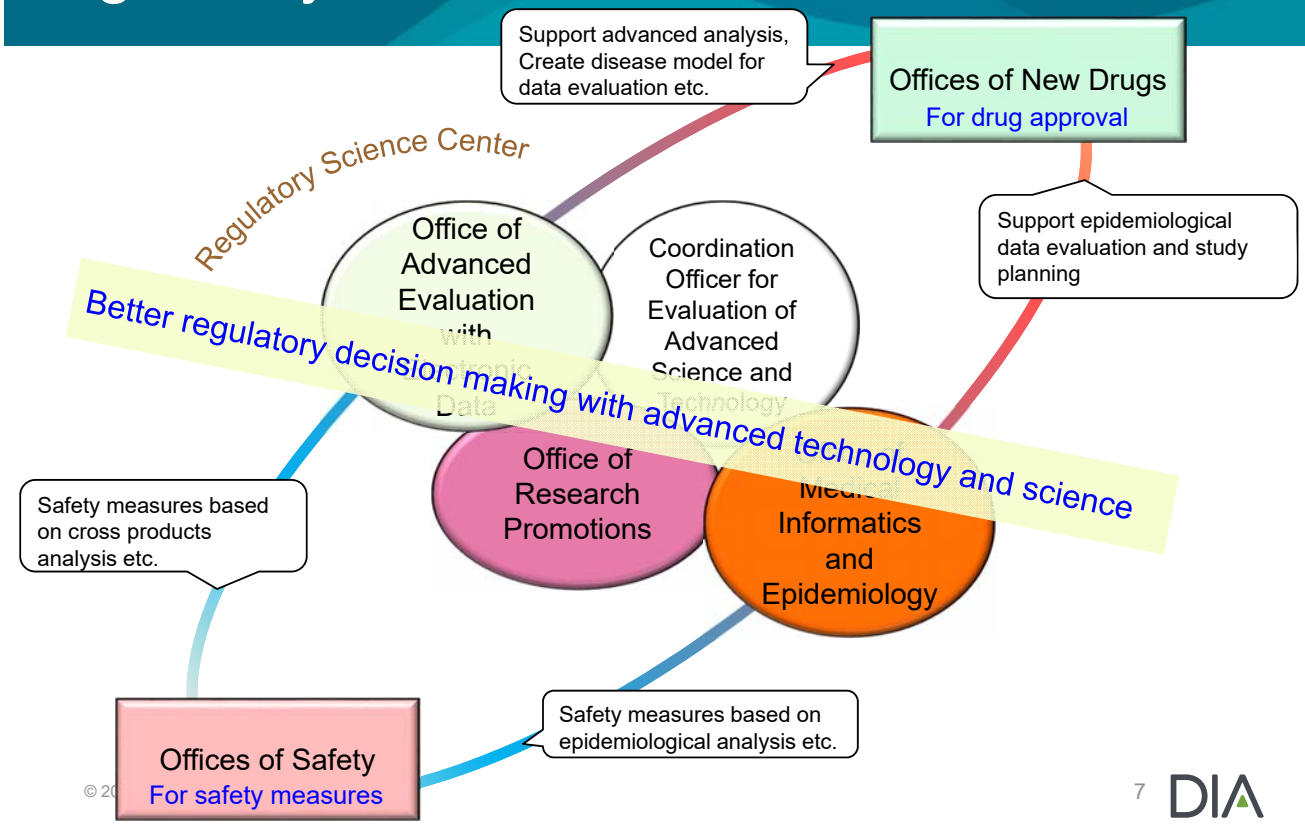
Post-Approval

Analysis for examining a causality between safety/effectiveness and candidate factors

Continuous assessment on Benefit/Risk of a drug (e.g.: proper target population, doses, warning)

Maximal and effective utilization of valuable data

Collaborative Functions of Regulatory Science Center with other offices



DIA

4th Mid-term Plan(FY2019-2023) of PMDA

- PMDA was established in April 2004 (the 1st Mid-term plan was implemented).
- The 4th Mid-term Plan(FY2019-2023) is going to be implemented from April 2019.
- The plan(draft) shows the importance of regulatory science and the utilization of medical information databases including MID-NET® in risk-benefit assessment and pharmacovigilance.
- The plan(draft) mentions the future direction of utilization and management of MID-NET®.
- The draft of the plan was disclosed on 28th January, 2019. The details can be accessed on the website of PMDA.

https://www.pmda.go.jp/about-pmda/advisory-council-information/meetings/0070.html#order

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Reference: Draft of 4th Mid-term Plan

- Excerpt from the draft of 4th Mid-term Plan related to MID-NET®
  - ・Reference: https://www.pmda.go.jp/files/000227739.pdf

第４期中期計画（案）における取組の内容
＜MID-NET®等の医療情報データベースを活用した薬剤疫学調査に基づく安全性評価の推進＞ • MID-NET®やNDB等を活用して能動的な安全性情報の収集と薬剤疫学的解析結果を安全性評価に活用することで、安全対策の質を向上 • 重要な安全対策措置を講じた場合には、その効果について検証
＜MID-NET®の利活用推進に向けた体制の構築＞ • 品質管理やデータ標準化、システム等の管理を適切に実施し、運営を安定化 • 運用の合理化等を進め、中長期の見通しを踏まえた運営基盤の見直し • 協力医療機関の拡充、クリニカル・イノベーション・ネットワーク（CIN）をはじめとした他のデータベース、協力医療機関以外の医療機関とのデータ連携等について検討を進め、利活用可能なデータの規模を拡充 • 連携の拡充にあわせて、MID-NET®の利活用の範囲について見直しを行うとともに、個人情報の適切な取扱いが確保されるよう必要な措置を実施 • 我が国における医療情報の活用が促進されるよう、MID-NET®の経験を関係機関と共有し、医療情報データベースのデータ品質の標準化に協力

Abstract

- MID-NET® was launched in April, 2018, holding the medical information, claims data and DPC (Diagnosis Procedure Combination) data from 10 healthcare organizations in including 23 hospitals.
- It has the strength of providing high quality data and the uniqueness of including laboratory test results.
- PMDA takes responsibility for operation and management of MID-NET® in compliance with MID-NET rules and GPSP.
- Here I would like to introduce the current status and practices of quality management for MID-NET®.

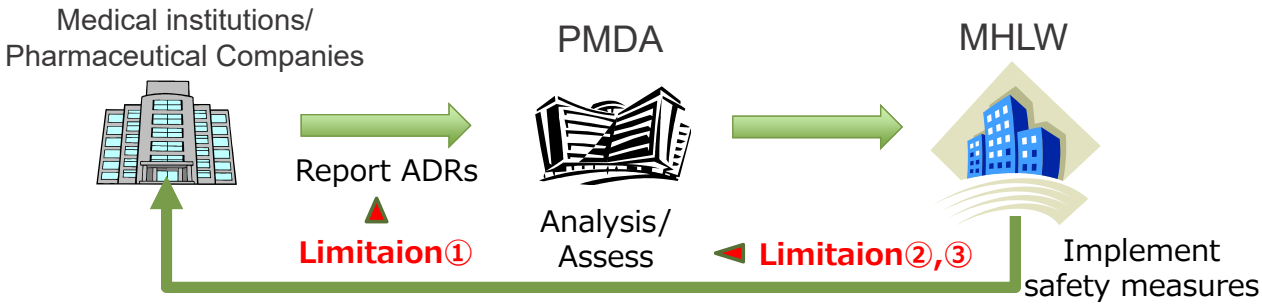
Today's Agenda

1. Utilization of RWD for drug safety

2. About MID-NET®
   - Overview
   - Utilization
   - Data quality management
   - Legislation and application to GPSP
   - Pilot studies

3. Challenges for accelerating utilization of RWD

Post-marketing drug safety assessment



Limitations:

① Adverse drug reactions(ADRs) will not be reported unless the healthcare professionals recognized them.

② Incidence rates of ADRs are unclear as the number of patients who are taking the drug is not monitored.

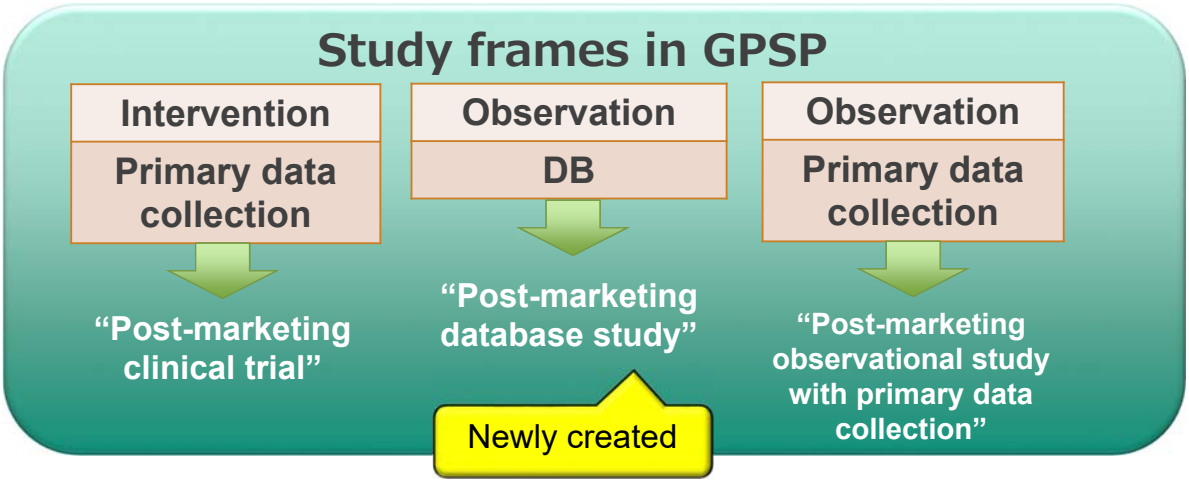
③ It is difficult to distinguish between ADRs and symptoms of the primary disease due to the lack of data of patients who are not taking the drug.

PMDA established new approaches for drug safety assessment by utilizing RWD.

- MIHARI Project was launched in 2009
- MID-NET® was fully implemented in April, 2018

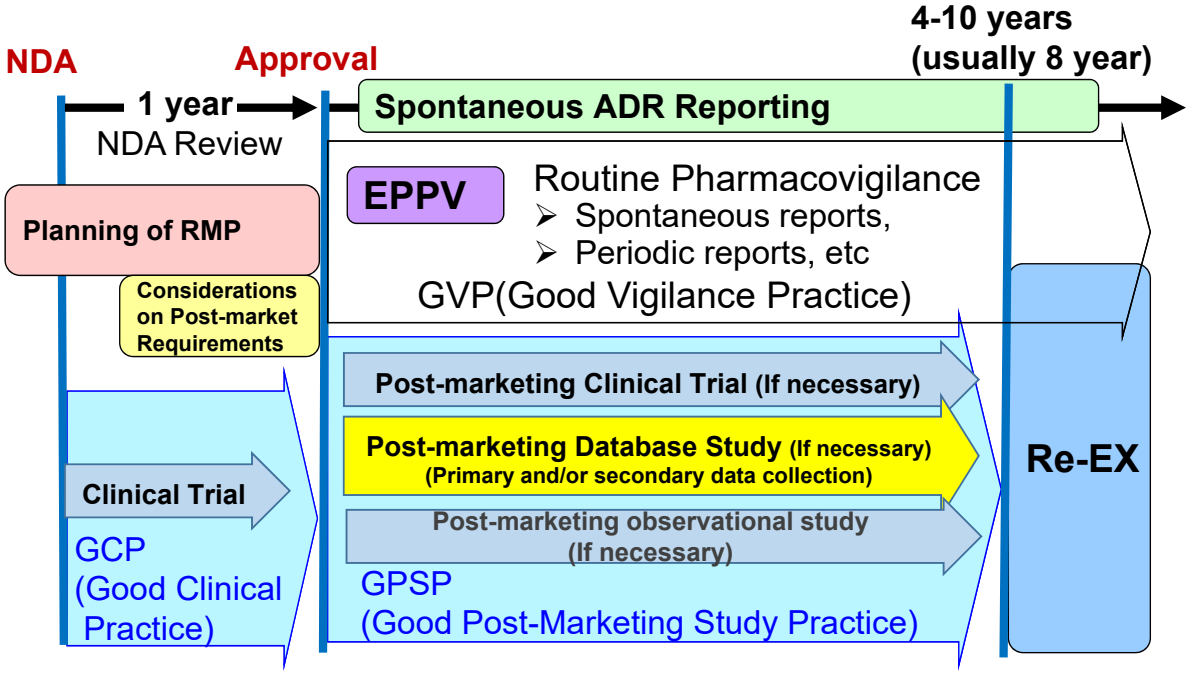
The revision of GPSP(Good Post-marketing Study Practice)

(The Ministerial Ordinance, Implemented on April 1st 2018)



Revised GPSP clearly mentions that Post-marketing database study is acceptable for re-examination under the Japanese Pharmaceuticals and Medical Devices Act.

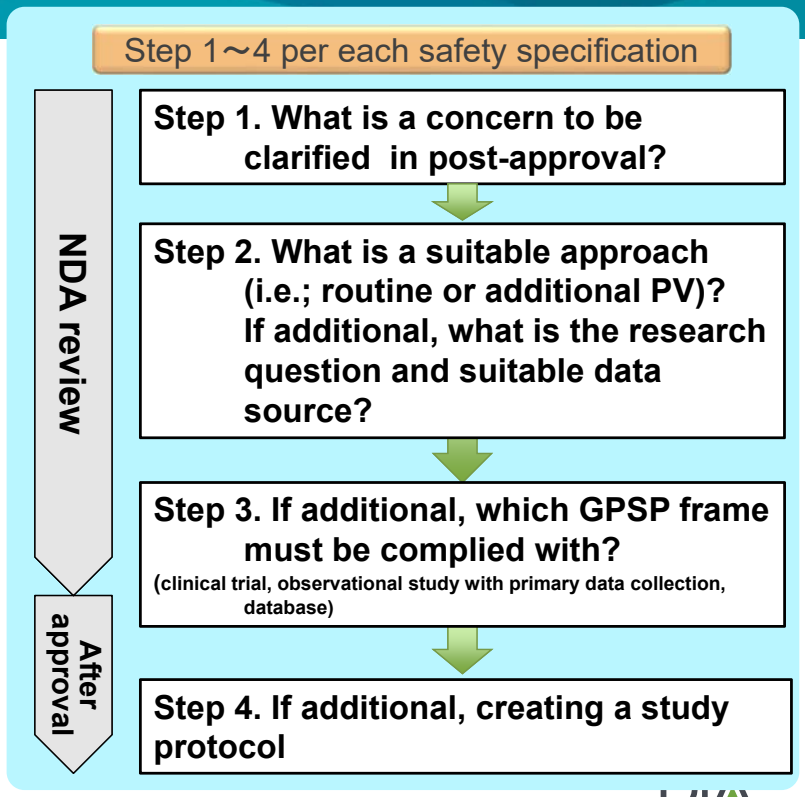
Overview of the Regulatory Schemes of Pharmacovigilance in Japan



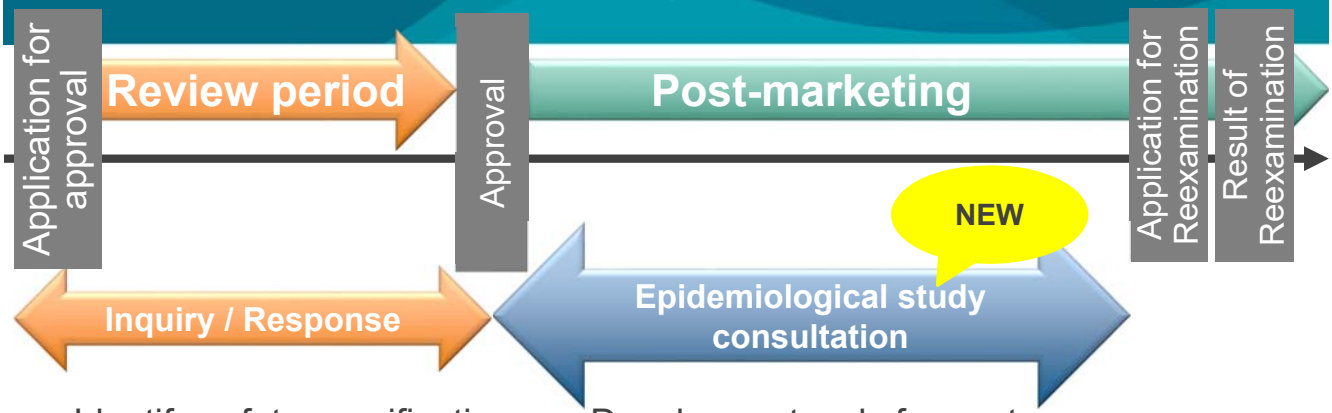
EPPV : Early Post-marketing Phase Vigilance (6 months intensive monitoring)
RMP : Risk Management Plan
Re-EX : Re-examination

Procedures for Developing Post-Marketing Study Plan (January 23, 2018)

- ✓ Describes basic principle on how to plan a post-marketing study under Japanese pharmaceutical regulations
  - Four steps approach to plan an appropriate post-marketing study



Review/Consult Timeline for Post-marketing Database Study



- Identify safety specifications.
- Select the best pharmacovigilance（PV）activities to address safety concerns.
- Prepare and submit a draft RMP for agreement with PMDA.
- Develop protocols for post-marketing database studies.
  - ✓ Feasibility analyses and validation studies may be conducted, if necessary.
- PMDA provides scientific advice on a study protocol.

Epidemiologists

Related Guidelines (1)

- "Instructions for Post-marketing Database Study Protocols" (PMDA, Jan 2018)
- A revision of "Case Examples of Risk Management Plan" (PMDA, Dec 2017), including a case of database study
- "Basic Principles on the Use of Medical Information Databases in Post-marketing Pharmacovigilance" (Notification No. 609, MHLW, June 2017)
- "Guidelines for the Conduct of Pharmacoepidemiological Studies in Drug Safety Assessment with Medical Information Databases" (PMDA, March 2014)

A number of related guidelines focusing on RWD utilization were recently published along with the revision of GPSP.

https://www.pmda.go.jp/safety/surveillance-analysis/0011.html

Related Guidelines (2)

"Points to consider for ensuring the reliability in conducting post-marketing database study"
(Notification No. 221, MHLW, Feb 2018)

- The contents:
  1. Scope of application
  2. Definition of terms
  3. Points to consider for ensuring the reliability in application documents for reexamination
- Appendix:
  The examples of procedure manuals made by DB holders about medical information databases.
  (Aimed to show pharmaceutical companies the points to confirm.)

https://www.pmda.go.jp/files/000223003.pdf

Challenges and Actions for Accelerating Adequate Utilization of RWD

Challenges	Actions
Conducting scientifically appropriate PMS	☑ Publish regulatory guidelines to promote post-marketing studies utilizing RWD ☑ PMDA consultations for planning PEpi Study
Ensure the quality of study plan & results	☑ Amendment of GPSP and regulatory inspections ☑ Publish regulatory guideline on the reliability of post-marketing studies utilizing RWD
International cooperation	? More collaborations for sharing experiences and knowledge about utilization of RWD for regulatory purpose ? International harmonization on standards for data quality and analytical methods in utilizing RWD

Scientific approaches and careful considerations in utilizing and evaluating RWD are the key to promote RWD utilization for regulatory purpose

Active Utilization of RWD toward Advanced Medical Care

MHLW/PMDA

Regulatory decisions based on better scientific evidences

- Proper safety assessment utilizing RWD in addition to the traditional approaches

Pharmaceutical companies

RMP implementation utilizing RWD

- Efficient risk management
- Better quality of safety information

Medical Institutions

Provide leading-edge medical therapy with ensuring safety

- Scientific and speedy safety measure

Public

Better quality of medical care

- Maximize benefit/risk ratio

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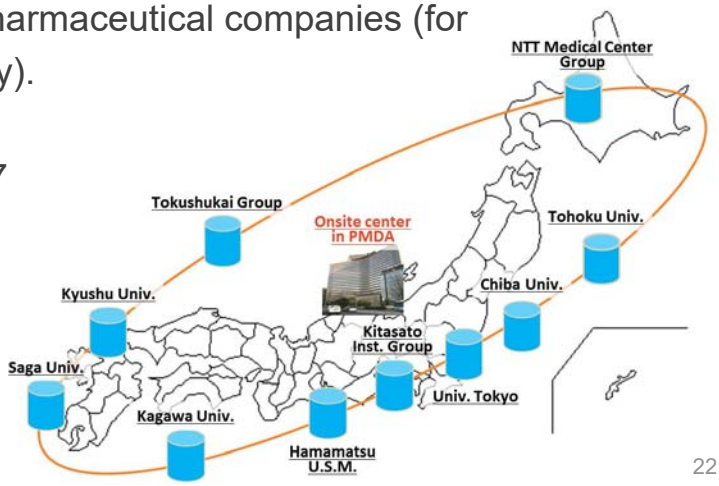
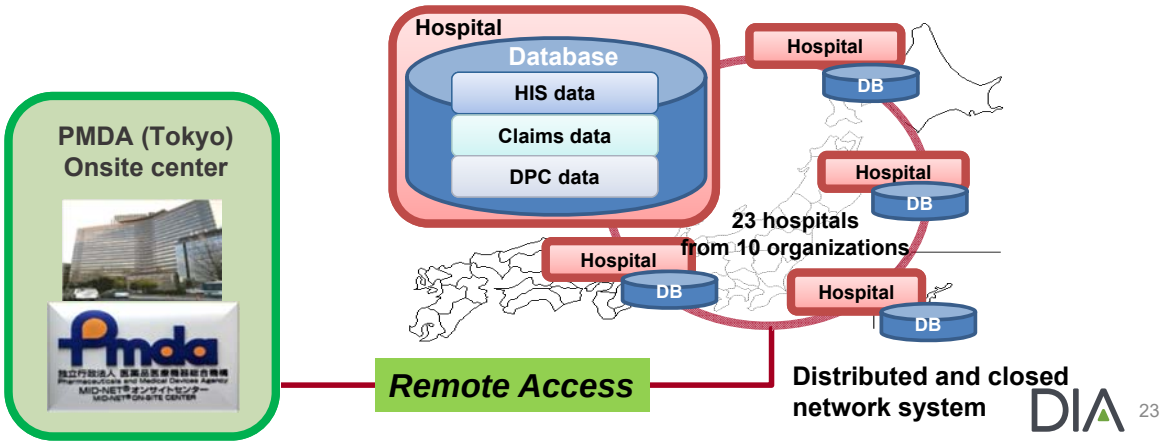
About MID-NET® (1)

- The Medical Information Database Network officially launched in April 2018 in Japan.
- PMDA takes responsibility for operation and management of MID-NET in compliance with MID-NET rules and the Ministerial Ordinance on GPSP.
- Aimed for the real-time assessment of drug safety by the government, academia and pharmaceutical companies (for post-marketing database study).
- 10 organizations(23 hospitals)
- 4 million patients in 2009-2017

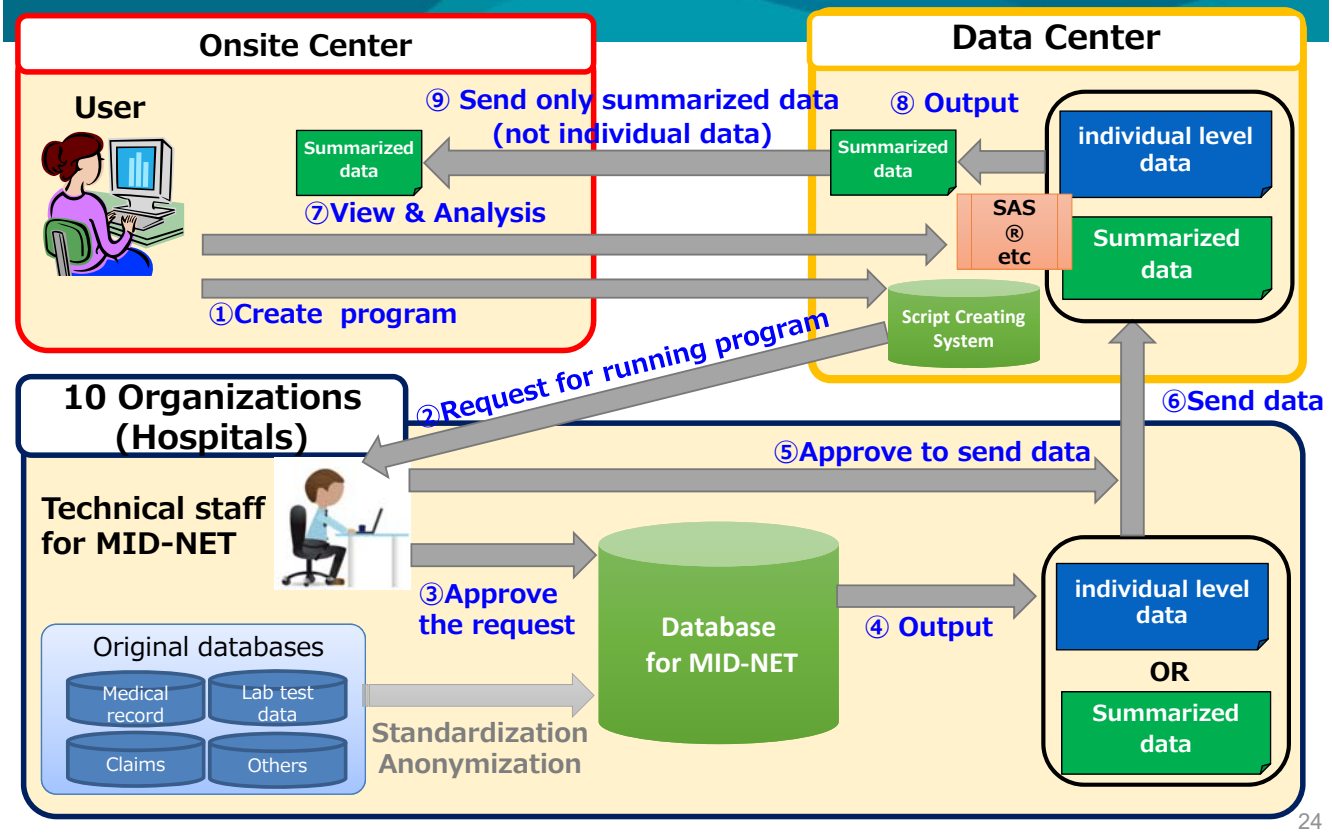


About MID-NET® (2)

- Updated in real-time（every 1 week or 1~3M）
- Including medical records, claims data and prospective payment data for acute inpatient
- Standardized codes are available (YJ, ICD-10, JLAC10 etc.)
- Laboratory test results are available
- The users can access the data only from the onsite center in PMDA.



Overview of the MID-NET® System

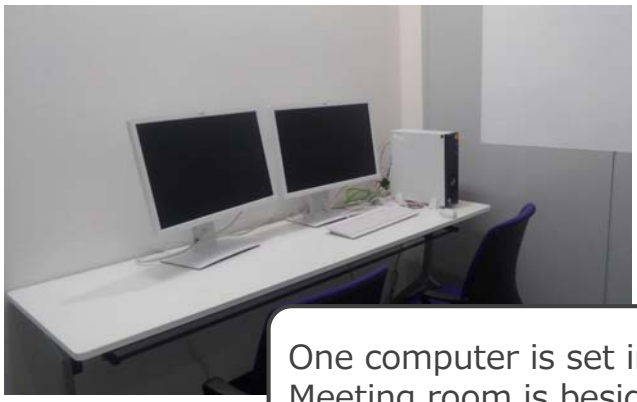


Onsite Center in PMDA

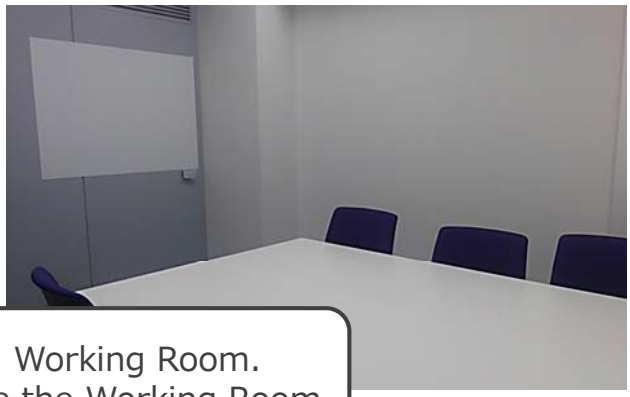
- Reception

IC cards for Working Room and Meeting Room will be rented to users who are properly identified in reception.

- Working Room (with security camera)

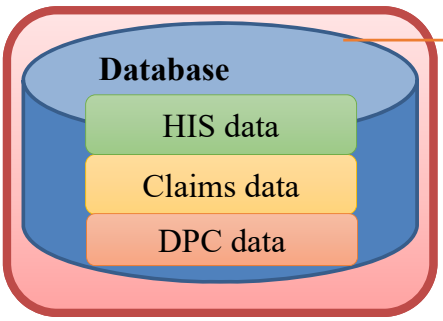


- Meeting Room



One computer is set in Working Room.
Meeting room is beside the Working Room.

MID-NET® Common Data Model



HIS data

- Patient identifying data
- Medical examination history data (including admission , discharge data)
- Disease order data
- Discharge summary data
- Prescription order/compiled data
- Injection order/compiled data
- Laboratory test data
- Radiographic inspection data
- Physiological laboratory data
- Therapeutic drug monitoring data
- Bacteriological test data

Example of standard code

Contents	Standard Code
Disease	ICD-10
Drug	YJcode, HOT9
Laboratory test	JLAC10
Bacteriological test	JANIS

- Local code of each content is mapped to standard code to analyze the data from different hospitals all together.

Standardized Data Coding Process -Example: Laboratory test-(1/3)

- MID-NET has defined about 200 laboratory tests which need code standardization. (In fact, the rate of application of standardized codes is not high in hospitals.)
- “Japan Laboratory Code Version 10 (JLAC10)” is applied as standardized code. The codes of JLAC10 are 17 digits which consist of analyte(5 digits), discrimination(4 digits), material(3 digits), assay(3 digits) and result of discrimination(2 digits).
- The hospitals manage the information of materials, laboratory tests and assays. On the other hand, the individual patients level data of MID-NET only includes the local names of laboratory tests. In order to identify the materials and assays from the local names, PMDA makes inquiries to the hospitals for further information.

Materials	The local names of laboratory tests
Urine	Sodium（Urine）
Urine	Sodium
Serum	Sodium（Serum）
Serum	Sodium
Urine	Albumin
Serum	Albumin

Assays	The local names of laboratory tests
Blood Count	White blood cell count
Mechanical measurement	White blood cell count
Potentiometric measurement	Glucose
UV spectrophotometry	Glucose

Standardized Data Coding Process -Example: Laboratory test-(2/3)

- PMDA applies the standardized codes of JLAC10 to local codes of laboratory tests through the processes as follows:

i. Obtain the data from each hospital.
   - ✓ The results of each laboratory test (Twice a year)
   - ✓ The master of laboratory tests (Monthly)

ii. Select the candidates of each local code which need standardizing by screening the data obtained from hospitals.

iii. Make a list of the local codes for a standardized code by inquiries to the hospitals.

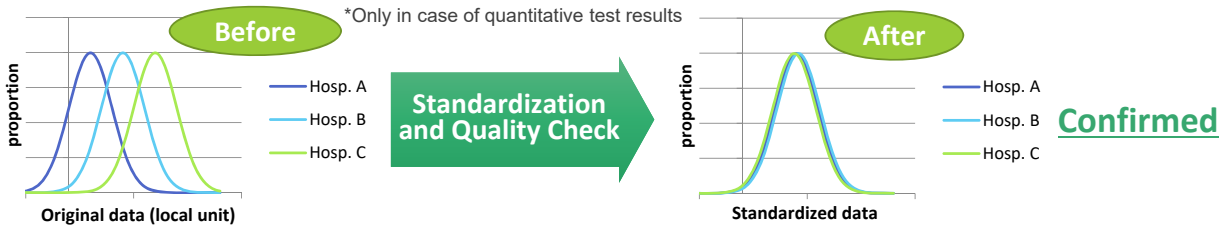
iv. Confirm the appropriateness of each standardized code by checking the distribution of laboratory test results among hospitals. When a outlier is detected, make inquiries again to the hospital.

v. Finalize the list of local codes for each standardized code of targeted laboratory tests.

Standardized Data Coding Process -Example: Laboratory test-(3/3)

- Confirm the appropriateness of a standardized code by checking a distribution of laboratory test results* among hospitals.

Distribution of laboratory test results* among hospitals

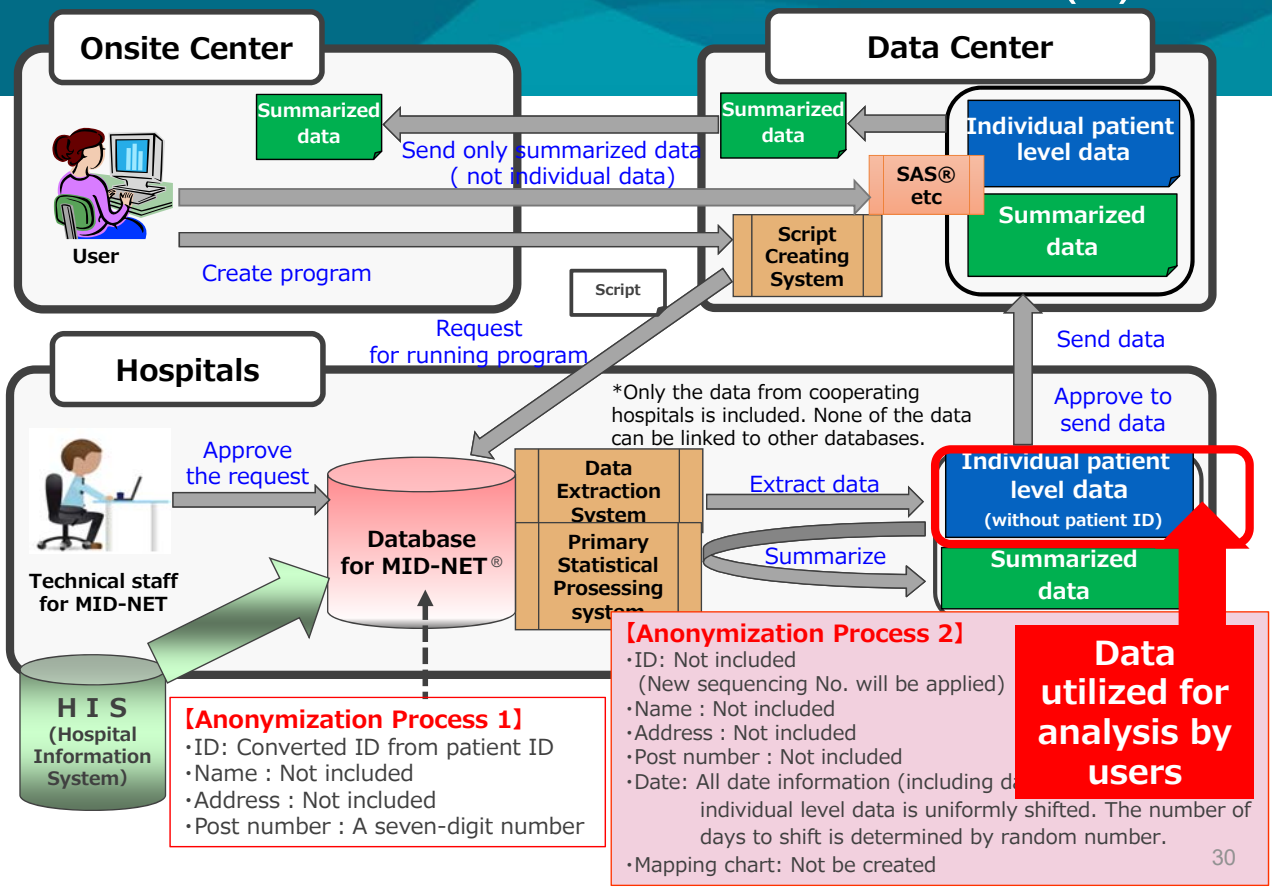


Further investigation will be conducted when there is a different distribution to clarify the reason and identify the appropriate code.

Examples of available laboratory tests

ALT, AST, BUN, K, Creatinine, LDH, Gamma-GT, Cl, ALP, MCHC, MCH, Uric Acid, GFR, TG, Cholesterol, Amylase, Blood Glucose, LDL-C, Inorganic Phosphate, HDL-C, PT-INR, PT, APTT, CEA, Fe, FT4, IgG, TSH, Sedimentation rate, RPR, IgM, HbA1c(NGSP), TPHA, AFP, Ferritin, Hb, Reticulocyte, Blood Gases(TCO_2), Blood Gases(pH), etc.

The Characteristics of the Data (1)



The Characteristics of the Data (2)

- **The data which is utilized by the users (the data extracted from the database for MID-NET) is all anonymized.** In principle, **the data does not fall within the coverage of "personal information"** that is defined in the Article 2-1 of Act on the Protection of Personal Information or the Article 2-2 of Act on the Protection of Personal Information Held by Independent Administrative Agencies.
- **Based on the characteristics of HIS data, the following consideration is taken in case that it cannot be totally denied that the data includes "the personal information need to be considered"** which is defined in the Article 2-1 and 2-3 of Act on the Protection of Personal Information and the Article 2-2 and 2-4 of Act on the Protection of Personal Information Held by Independent Administrative Agencies.

<u>The necessity of informed consent</u>
It is unnecessary to obtain informed consent from the patient in that MID-NET® is operated and managed under the PMDA Act.

<u>The consideration toward to patients</u>
The cooperating hospitals announce that the anonymized HIS data will be utilized in MID-NET. In addition, PMDA discloses the information related to the utilization of MID-NET and **secures the opportunities for patients to reject** to provide their HIS data to MID-NET.

Validation of Outcomes

- A new project was launched in 2017 to promote the conduct of reliable pharmacoepidemiological studies utilizing electronic medical records.
- PMDA and the partner medical institutions conduct validation studies on approximately 20 health outcomes.
  - To establish a clinically valid and reliable definition for a outcome based on the electronic codes in database.

anaphilaxis	interstitial pneumonia	heart failure
neutropenia	rhabdomyolysis/myopathy	cerebral infarction
cerebral hemorrhage	acute coronary syndrome	acute/late-onset hepatic failure
severe skin disease	pulmonary thromboembolism	deep vein thrombosis
ventricular arrhythmias	supraventricular arrhythmia	bradyarrhythmia
acute pancreatitis	gastrointestinal perforation	Intestinal obstruction

Sample Size of MID-NET®

- MID-NET® was launched in April, 2018. Data size was about 4 million patients in 2009-2017 (10 organizations(23 hospitals)).
- The data size expects to rise 400,000 every year.
- During the 4th mid-term, 10 more hospitals of Tokushukai group is going to join to MID-NET® as cooperating hospitals.
- PMDA is going to conduct the quality management for the data from the new 10 hospitals of Tokushukai group. All the data is available after the quality management and standardization of codes by PMDA and Tokushukai.

Advantages and Limitations of MID-NET®

Advantages

- Various kinds of data including laboratory test results
- High data quality (daily and periodical check)
- Real-time data update (every 1-4 weeks)

Limitations

- May be not enough sample size (currently 4M)
- No linkage of a patient among hospitals
- Need to consider data generalizability due to limited cooperative organizations (mainly mid-large size hospitals like University hospitals)

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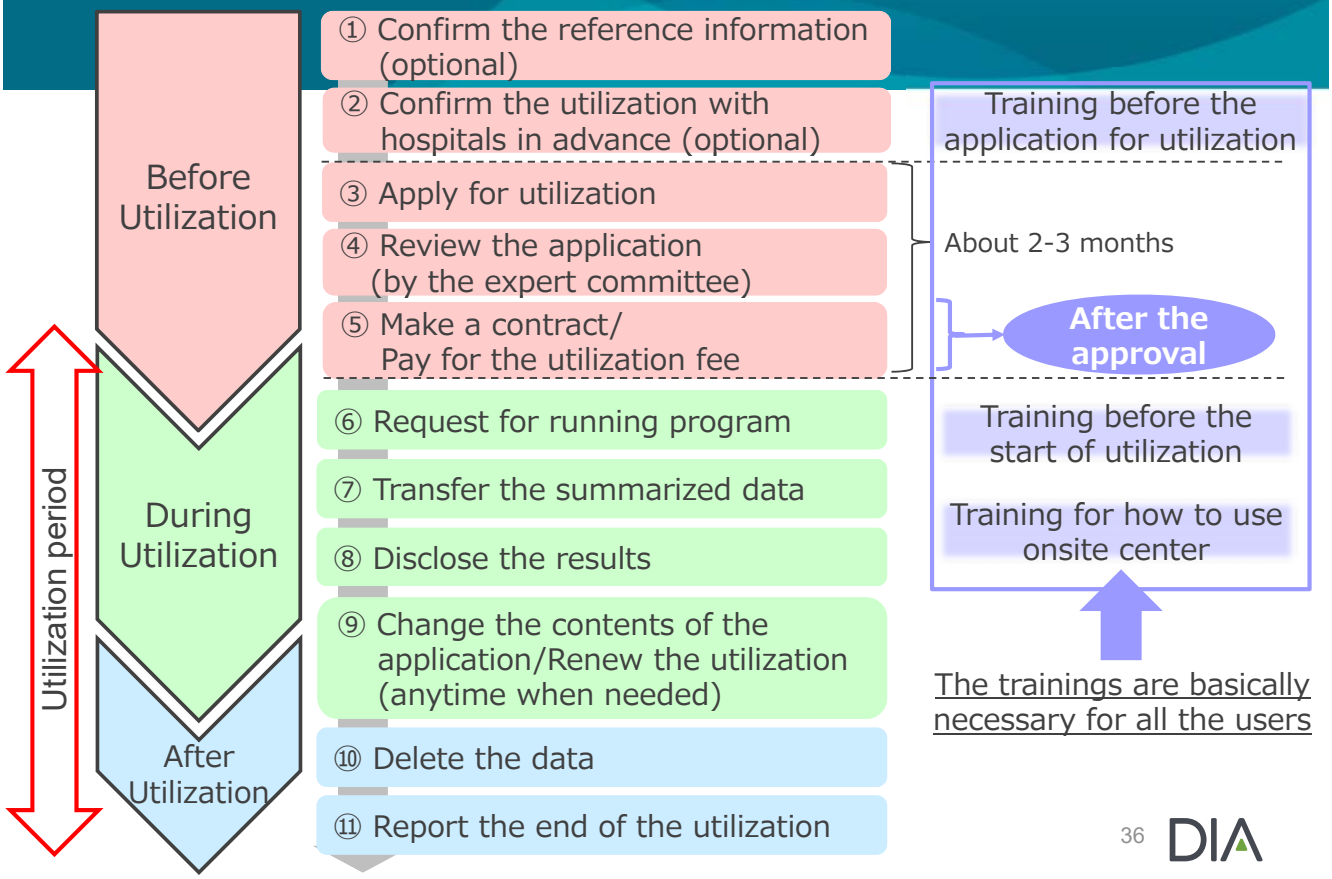
3. Challenges for accelerating utilization of RWD

The flow chart of utilization (1)



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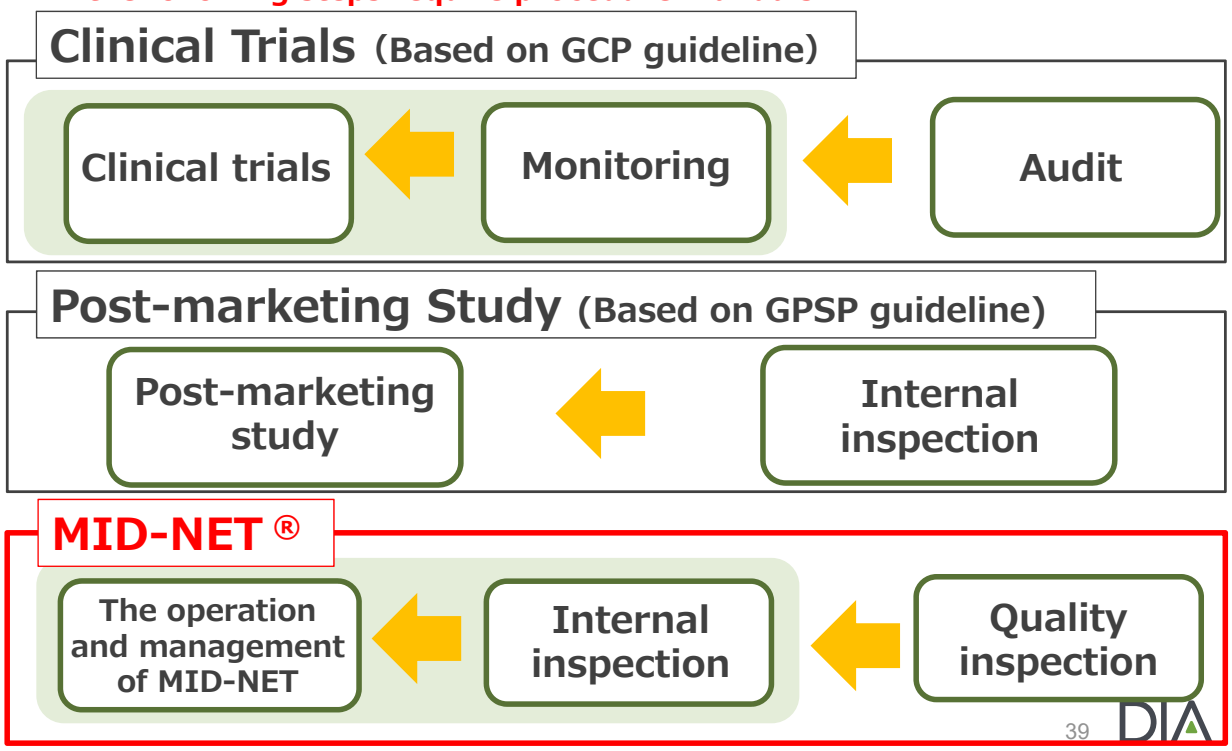
Importance of Data Quality Management

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

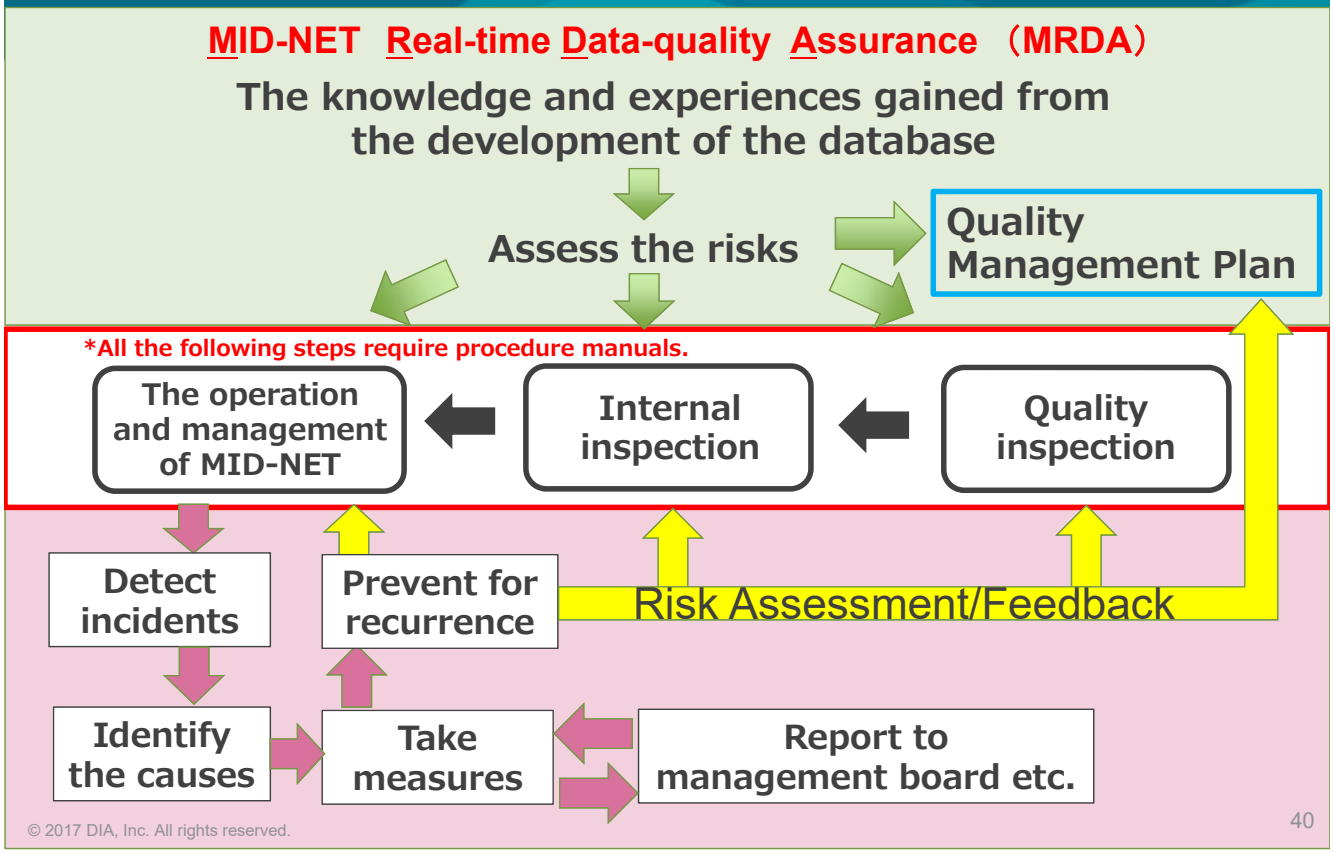
High quality data as well as appropriate analysis is pre-requisite in utilizing RWD for providing scientifically interpretable results.

Quality Management of MID-NET®

*All the following steps require procedure manuals.



The Design of the Process of Quality Management for MID-NET®



Quality Management Plan for MID-NET®

○ The quality of the data and the system of MID-NET® is guaranteed under the following processes:

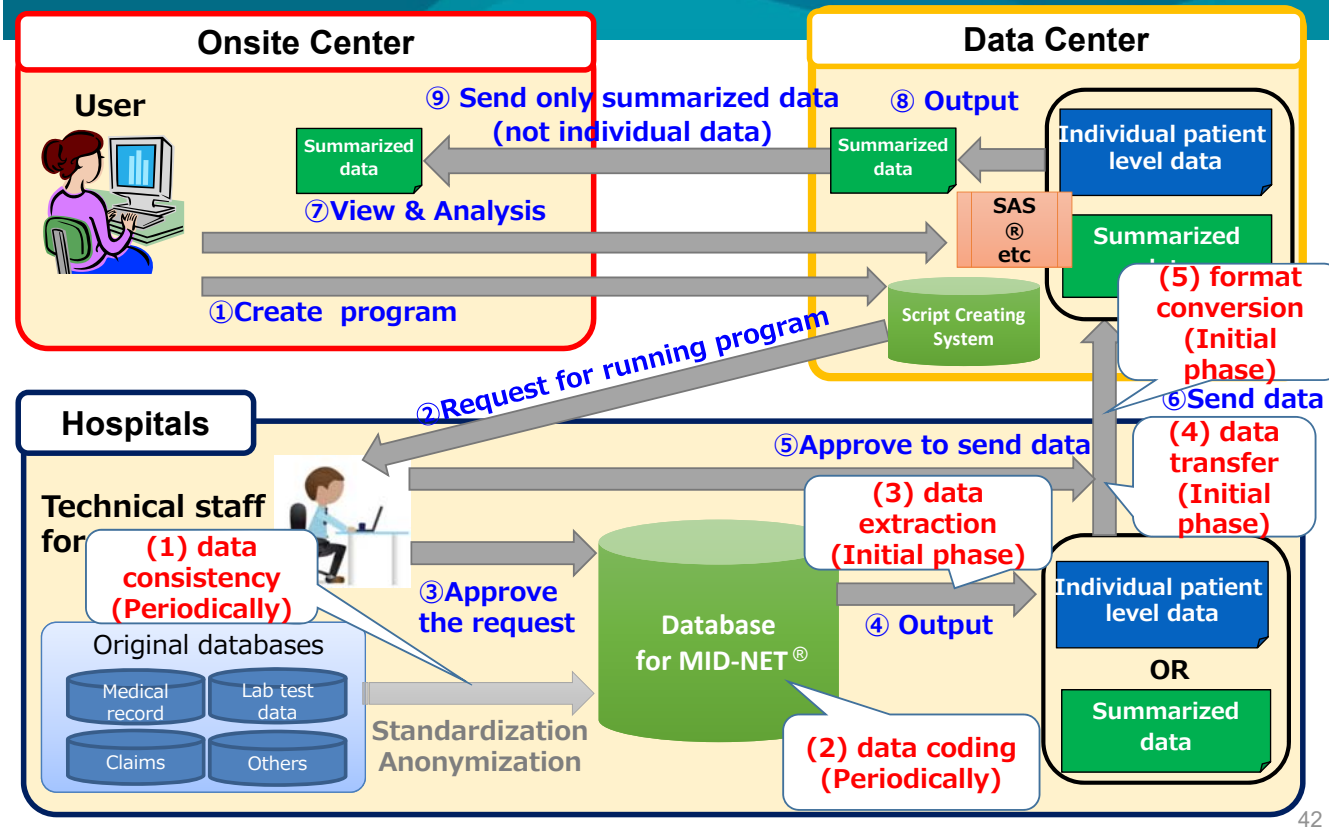
A. Quality Management for Data (Periodically, once per year)
Data consistency

B. Quality Management for System (Initial phase, renovation)
①Data coding ②Data extraction
③Data sending ④SAS format conversion

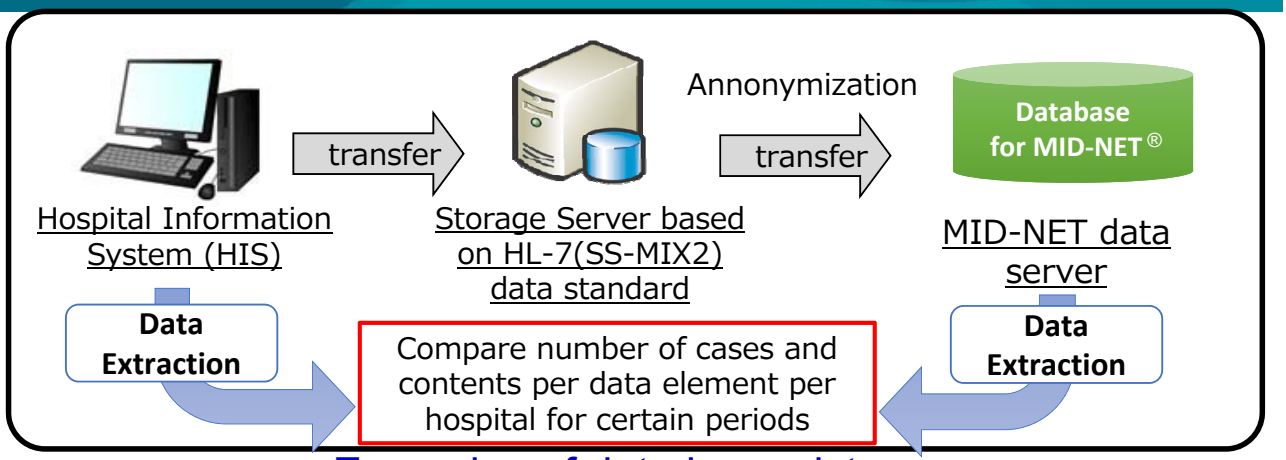
C. Routine monitoring for Data and System(daily/monthly)
①The number of received messages in transmission (daily)
②The number of messages sent and received in transmission (monthly)
③The storage status of files of claims data and DPC data (daily)
④The operation status of the database for MID-NET (daily)
⑤The processing status of the requests (daily)
⑥The operation and backup status of the devices (daily)

The situation of management and quality assurance of MID-NET® has been confirmed by several pharmaceutical companies and no problem has been pointed out until now.

Major Points of Quality Management for Data and System



Example: Data Consistency Check

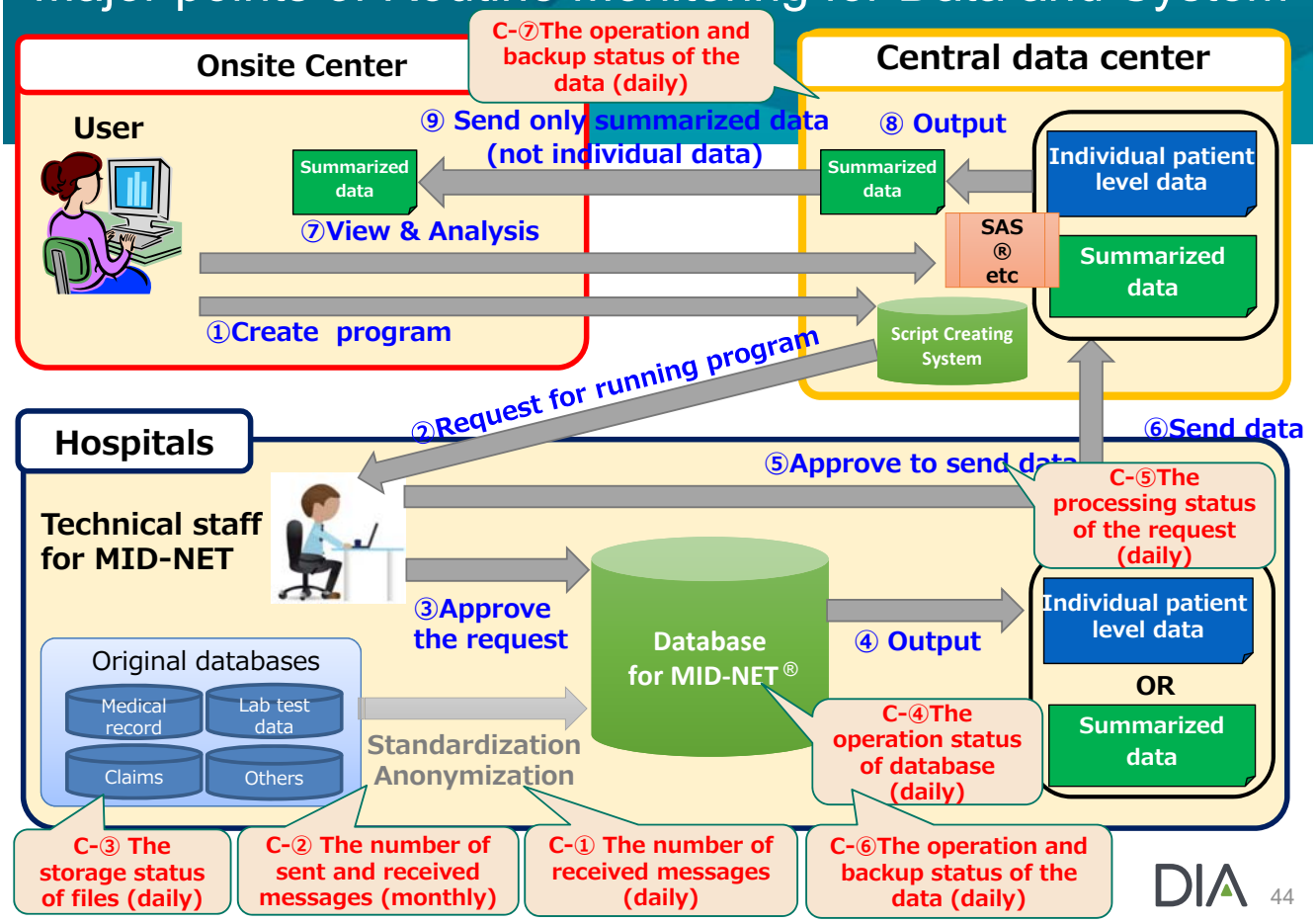


Examples of data inconsistency

- Lack of a unit
- Difference in a place of data storage among sites etc.
  e.g.; single dose, daily dose vs total dose

At the beginning, approximately hundreds of issues per site were identified for further investigation or consideration

Major points of Routine Monitoring for Data and System



The points to consider in utilization of MID-NET®

It is indispensable to assure the quality of the database and the analyses as below to gain the reliable results from the medical information database.

- **The quality of the data**
  - ・All the data is transferred precisely into the database.
  - ・The standardized codes are adapted properly.
  - ・The data is extracted and transferred precisely.

What PMDA should assure and users should confirm.

- **The understanding toward the characteristics and the limitations of the database**
- **The quality of analyses**
  - ・The codes for data extraction are selected precisely.
  - ・The program(script) is created precisely.
  - ・The data extracted based on the program is appropriate for analyses.

What users should assure.

Points of a Reliable and Valuable Database

◆Data quality management with routine monitoring

- In addition to the daily monitoring, consistency between data stored in the database and original data (EMRs) should be checked and confirmed periodically
- Data coding process should be standardized among all sites

◆Deep understanding regarding real situations in a site for sending data

- Appropriate measures can only be taken with the deep understanding

◆Strong collaborations among all relevant organizations (hospitals, IT companies, academia, operating center, regulatory agency etc.)

Today's Agenda

1. Utilization of RWD for drug safety

2. About MID-NET®
   - Overview
   - Utilization
   - Data quality management
   - Legislation and application to GPSP
   - Pilot studies

3. Challenges for accelerating utilization of RWD

The legislation related to Post-marketing Database Study (1)

The Ministerial Ordinance on GPSP（Article 6-2）

The pharmaceutical companies is required to...
①Select the proper business partner who is capable of handling medical information database to fulfill the purpose of post-marketing survey.
②Make a contract in the form of a document for post-marketing survey.

The Pharmaceutical and Medical Device(PMD) Act (Article 14-4)

All the documents for application of the re-examination is required to be created according to the Article 61 of the Ordinance for Enforcement of the PMD Act (Data Reliability Standards for Applications).

The Ministerial Ordinance on the standard of conducting post-marketing surveillance and examination for drugs
(*related to the Article 61 of the Ordinance for Enforcement of the PMD Act)

1. The document is made precisely based on the survey or examination which is aimed to create the document itself. → **Accuracy**
2. If there is any suspicious outcome in quality, effectiveness or safety of the drug, the results of the survey and examination is required to be assessed and the results have to be documented. → **Comprehensive**
3. The sources of the evidence are required to be preserved by the last day of re-examination based on the PMD Act Article 14-4(1). → **Convervative**

Introduction of a Notification (1/2)

"Points to consider for ensuring the reliability in conducting post-marketing database study"
(Notification No. 221, MHLW, Feb 2018)

- The contents:
  1. Scope of application
  2. Definition of terms
  3. Points to consider for ensuring the reliability in application documents for reexamination
- Appendix:
  The examples of procedure manuals made by DB holders about medical information databases.
  (Aimed to show pharmaceutical companies the points to confirm.)

https://www.pmda.go.jp/files/000223003.pdf

Introduction of a Notification (2/2)

●Before concluding a contract with DB holders, the applicant should confirm whether the medical information database sufficiently fulfill the purpose of the study and check the points as follows.

①Organizational structure and business plan of the DB holder
②Details of the business outsourced by the DB holder
③Design and outline of the database
④Operating procedures related to the medical information database

Types of Documents	The Contents
Criteria and Procedures	Quality management of medical data collected from information source, data cleaning, encoding
Rules and Procedures	Security, data backup and recovery, education and training for person(s) involved in construction and maintenance
Rules	Verifying the appropriate construction and preparation of analysis dataset, quality management, quality assurance, retention of the records related to preparing application dossier for re-examination, etc.
Plan	Quality management

● The applicant should specify the range of duties and functions entrusted or requested to the DB holder.

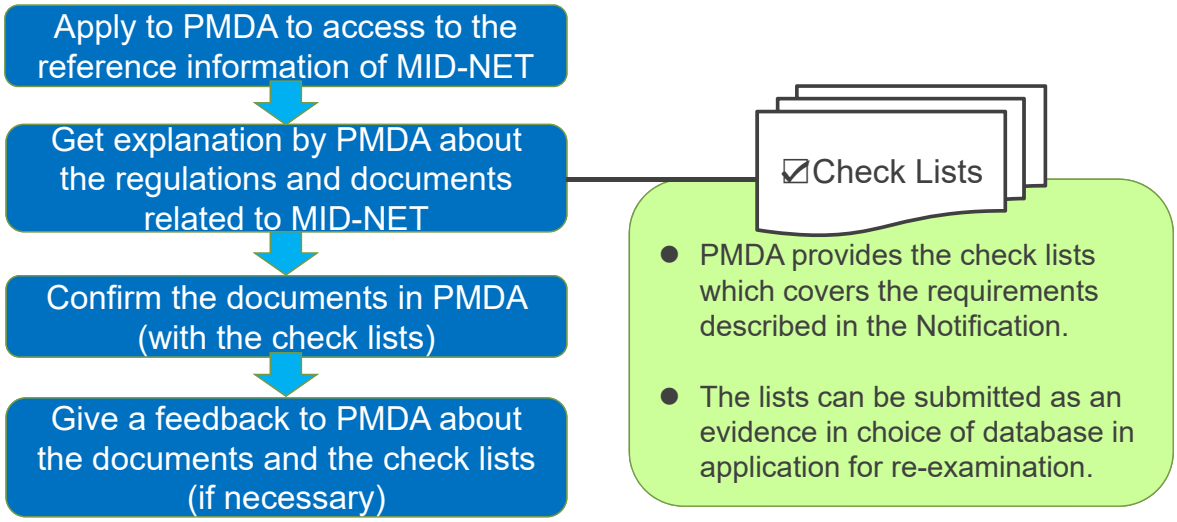
The Utilization of MID-NET® (Post-Marketing Database Study)

- The operation and management of MID-NET® comply with the requirements described in the “Points to consider for ensuring the reliability in conducting post-marketing database study”(Notification No. 221, MHLW, Feb 2018)
- Applicants who are planning to utilize the MID-NET can access and confirm the reference information of MID-NET.
- After the confirmation, applicants conclude a contract with PMDA for utilizing the MID-NET.

MID-NET® is operated and managed in compliance with GPSP guideline and related regulations, therefore it can be utilized for post-marketing database studies.

The Utilization of MID-NET® (Post-Marketing Database Study)

- A flowchart to show how pharmaceutical companies access the reference information of MID-NET before application for utilization.



The status of operation and management of MID-NET has been confirmed by several applicants (pharmaceutical companies) and no issues have been identified until now.

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Challenges and Future Plan

World trend in utilization of RWD

ICH-GCP, an international standard, is expected to be revised by the early of 2020s.

The direction of revision

To provide proper and flexible indicators for various designs of clinical trials and sources of data (such as patient registry, electronic medical records etc).

The point of revision

- **Implementation of "Quality by Design"**
  To place more emphasis on the design and the process rather than the outcome in terms of management of the quality of clinical trials and researches.

- **The clinical researches also fall within the scope of ICH-GCP.**
  To apply ICH-GCP to general clinical researches which would provide the evidence and information for regulatory decision making
  - Clinical research utilizing RWD
  - Pharmacoepidemiological study
  - Comparative effectiveness research
  - Large Simple Safety Study etc.

  ⇒ Implementation of Quality Management System is expected in the future.

The high quality of operation and management of the electronic medical records database in MID-NET would be a future model as an international standard.

MIHARI
Medical Information for Risk Assessment Initiative

MID-NET®
Medical Information Database Network

- **PMDA web site**

http://www.pmda.go.jp/english/index.html

wakaru-midnet@pmda.go.jp

Thank you very much for your kind attention!

Ask

DIA