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5月22日 ICH Day
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May 22 | ICH Day
May 23-25 | Conference & Exhibits
Beijing International Convention Center
Japanese guidance and PMDA’s experiences in utilizing real world data for drug safety assessment

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Data sources for post-market safety assessment of a drug

PMDA

Conventional Information Sources

- Spontaneous ADR report DB
- Literatures
- Overseas regulatory actions
- Presentation in Academic Conference
- etc

Electronic Healthcare Data

- Claims DB
- DPC DB

Launched in 2009

MHLW
Medical institutions

- Safety measure
- Risk communication

Overseas regulatory actions

MHLW

- Medical institutions

Conventional Information Sources

- Spontaneous ADR report DB
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- etc

Electronic Healthcare Data

- Claims DB
- DPC DB

Launched in 2009
PEpi Assessment in PMDA

Office of Medical Informatics and Epidemiology

Role of Pharmacoepidemiologist

- In pre-approval
  - Review Risk Management Plan
  - Propose appropriate post-marketing studies etc.

- In post-approval
  - Conduct PEpi studies utilizing EMRs database for drug safety assessment
  - Review PEpi data/reports submitted by industries etc.

Office of Safety (I and II)
Office of New Drug (I - V)

Linkage
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
Revised GPSP clearly mentions that safety study based on database is acceptable for re-examination under the Japanese Pharmaceuticals and Medical Devices Law.
Many related guidelines focusing on Real World Data utilization were recently published in synchronization to the GPSP revision. Related Guideline

- Guideline on **pharmacoepidemiological study** for drug safety assessment based on medical information database (March 2014)
- Basic Principles on the utilization of health information databases for Post-Marketing Surveillance of Medical Products (June 2017)
- General steps for considering a plan of post-market studies of a drug (January 2018)
- Points to consider for ensuring data reliability on post-marketing database study for drugs (February 2018)

Describes basic principle on how to plan a post-market study under Japanese pharmaceutical regulation

- Four steps approach to plan an appropriate post-market study

General steps for considering a plan of post-market studies (January 23, 2018)

Step 1. What is a concern to be clarified in post-approval?

Step 2. What is a suitable approach (i.e.; routine or additional PV)? If additional, what is the research question and suitable data source?

Step 3. If additional, which GPSP frame must be complied with? (clinical trial, observational study with primary data collection, database)

Step 4. If additional, creating a study protocol

Step 1 ~ 4 per each safety specification
More details, More timely
The Medical Information Database Network in Japan for a real-time assessment of drug safety (currently >4M patients).

An integrated real time EMRs database with high quality
Data categories in the MID-NET® system

- Database
  - HIS data
  - Claims data
  - DPC data

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

<table>
<thead>
<tr>
<th>Contents</th>
<th>Standard</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>ICD-10</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>YJcode,</td>
<td>HOT9</td>
</tr>
<tr>
<td>Laboratory test</td>
<td>JLAC10</td>
<td></td>
</tr>
<tr>
<td>Bacteriological test</td>
<td>JANIS</td>
<td></td>
</tr>
</tbody>
</table>
Data integration method of MID-NET

Onsite Center

User

1. Create program
2. Request for running program

Technical staff for MID-NET

3. Approve the request
4. Output
5. Approve to send data
6. Send data
7. View & Analysis

Central data center

SAS® etc

8. Output

Individual level data
Summarized data

Individual level data
Summarized data

Original databases
Medical record
Labo test data
Claims
Others

Standardization Anonymization

Common data model database for MID-NET
PMDA has worked with cooperative hospitals for assuring data quality of MID-NET®.

Before quality management

<table>
<thead>
<tr>
<th>Data Type</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease order data</td>
<td>99.1%</td>
<td>99.9%</td>
</tr>
<tr>
<td>Prescription order data</td>
<td>67.0%</td>
<td>100%</td>
</tr>
<tr>
<td>Laboratory test data</td>
<td>55.8%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
A pilot study of MID-NET®
At the post-market, the label change and warning letter were issued for awaking the risk of hypocalcemia associated with denosumab.

A) More laboratory test on serum calcium etc.
B) Co-administration of calcium/vitamin D
C) Special caution to patients with severe impairment of renal function
D) Prepare for emergency situation
Objective

✓ To examine impacts of label change and warning letter in clinical practice for the risk of hypocalcemia associated with denosumab

Monthly transition of the incidence of hypocalcemia

- Calculate the incidence of hypocalcemia during 28 days from a prescription date.
- Perform segment regression analysis based on the incidence of hypocalcemia / month.
Advantages and Limitation of MID-NET®

**Advantages**
- Various kinds of data including laboratory test results
- High data quality (confirmed consistency with the original data source)
- 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)
Lessons Learned in utilizing RWD

- High data quality is pre-requisite in utilizing real world data such as claims and electronic medical records database.

- To obtain clinically meaningful results, it is important to
  - understand characteristics of the database in details
  - validate outcome definitions
  - utilize appropriate methods for controlling confounding (e.g., propensity score matching)
  - conduct sensitivity analysis
Other recent activities
Utilization of National Claims Database (NDB)

- **Medical care** from a **Medical Institution** leads to a **Claim**.
- **Patient** pays a **Copayment**.
- **Insurance Card & ID** is used for **Insurance Fee**.
- **Payment (as agent)** to **Insurer**.
- **Claim** is submitted to **National Institution for claims review & paying agent**.
- **Claim data** is sent to the **National Claim Database (NDB)**.

MID-NET

Health Insurance Association's Claim Database
## Characteristics of MID-NET® and NDB

<table>
<thead>
<tr>
<th>Data Type</th>
<th>Electronic Medical Records</th>
<th>Health Insurance Claims</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Provider</td>
<td>23 hospitals of 10 Medical institutions</td>
<td>All health insurers in Japan</td>
</tr>
<tr>
<td>Covered patients</td>
<td>People provided medical service by each institution (~4 Million)</td>
<td>Entire Japanese population (120 Million)</td>
</tr>
<tr>
<td>Obtainable Health Information</td>
<td><strong>Detailed information in medical practices</strong> by each institution</td>
<td>Standardized information relevant to reimbursement</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Medical procedure</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Pharmacy Dispensing</td>
<td>YES (on-site pharmacy)</td>
<td>YES</td>
</tr>
<tr>
<td>Laboratory test result</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>OTC Drug</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>
Establishment of patients registries for regulatory purpose

Current patient registries mainly focuses on academic research for grasping patient backgrounds in clinical practice

- A lack of items for regulatory review
- Less interventional data (e.g.: prescription date, drug name, dose, prescription period etc.)
- Less standardized data
- Non-coded data
- A lack of quality management
- Small sample size

It is highly needed to establish a patient registry which can be utilized for regulatory purpose

Clinical Innovation Network (CIN)
Clinical Innovation Network (CIN)

- Study group for epidemiological methods and data quality standards
- Study group for ethical issues for registries and relationships with industries

Utilizing registry data for promoting cost effective clinical studies, accelerating drug development, and B/R assessment
PMDA Regulatory Science Center
Regulatory Science Center
(Organization Structure)

Director of Center for Regulatory Science

Associate Center Director
- Office of Medical Informatics and Epidemiology
  - EMRs database (RWD)

Associate Executive Director
- Office of Advanced Evaluation with Electronic Data
  - CDISC database (Clinical trials)
- Coordination Officer for Evaluation of Advanced Science and Technology
- Office of Research Promotion

Big-Data analysis in regulatory science

Closely working together with Office of New Drugs, Office 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

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

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

- Offices of New Drugs
  - For drug approval
  - Support epidemiological data evaluation and study planning

- Coordination Officer for Evaluation of Advanced Science and Technology
  - Support advanced analysis, Create disease model for data evaluation etc.

- Office of Advanced Evaluation with Electronic Data
  - Support advanced analysis, Create disease model for data evaluation etc.

- Medical Informatics and Epidemiology
  - Safety measures based on epidemiological analysis etc.

- Office of Research Promotions
  - Support advanced analysis, Create disease model for data evaluation etc.

- Office of Advanced Evaluation with Electronic Data
  - Support advanced analysis, Create disease model for data evaluation etc.

- Offices of Safety
  - For safety measures
  - Safety measures based on cross products analysis etc.

Better regulatory decision making with advanced technology and science
Active utilization of EHR databases toward advanced medical care

- **Regulatory decisions based on better scientific evidences**
  - Proper safety assessment utilizing HER databases in addition to the traditional approaches

- **RMP implementation utilizing EHR databases**
  - Efficient risk management
  - Better quality of safety information

- **Provide leading-edge Medical Therapy with ensuring Safety**
  - Scientific and speedy safety measure

- **Better quality of Medical Care**
  - Maximize benefit/risk ratio
Thank you very much for your kind attention !!