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Catching the Wave of Disruptive Innovations in Real World Evidence

Yousuke Nishida
Real World Data Science Dept.
Chugai Pharmaceutical Co., Ltd.

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Today’s goals

- In the healthcare industry, advances in real-world data and digital solutions are being accompanied by the onset of disruptive innovation.
- The days of drug companies vying for higher market value are coming to an end, and an era of competition with heavy hitters such as GAFA and Rakuten is beginning.
- Data scientists who are able to adapt to the changing environment without shying away will survive. →Catching the wave of innovation.
- This presentation will be structured around a discussion of database research, an innovation in Japan’s Good Post-marketing Study Practice (GPSP). And we will end with a vision for a future that utilizes Medical Data Vision (MDV) and Amazon Web Services (AWS), which will form the core of innovation.

What is the difference between Real World Data and Real World Evidence?

The way I see Real World Evidence

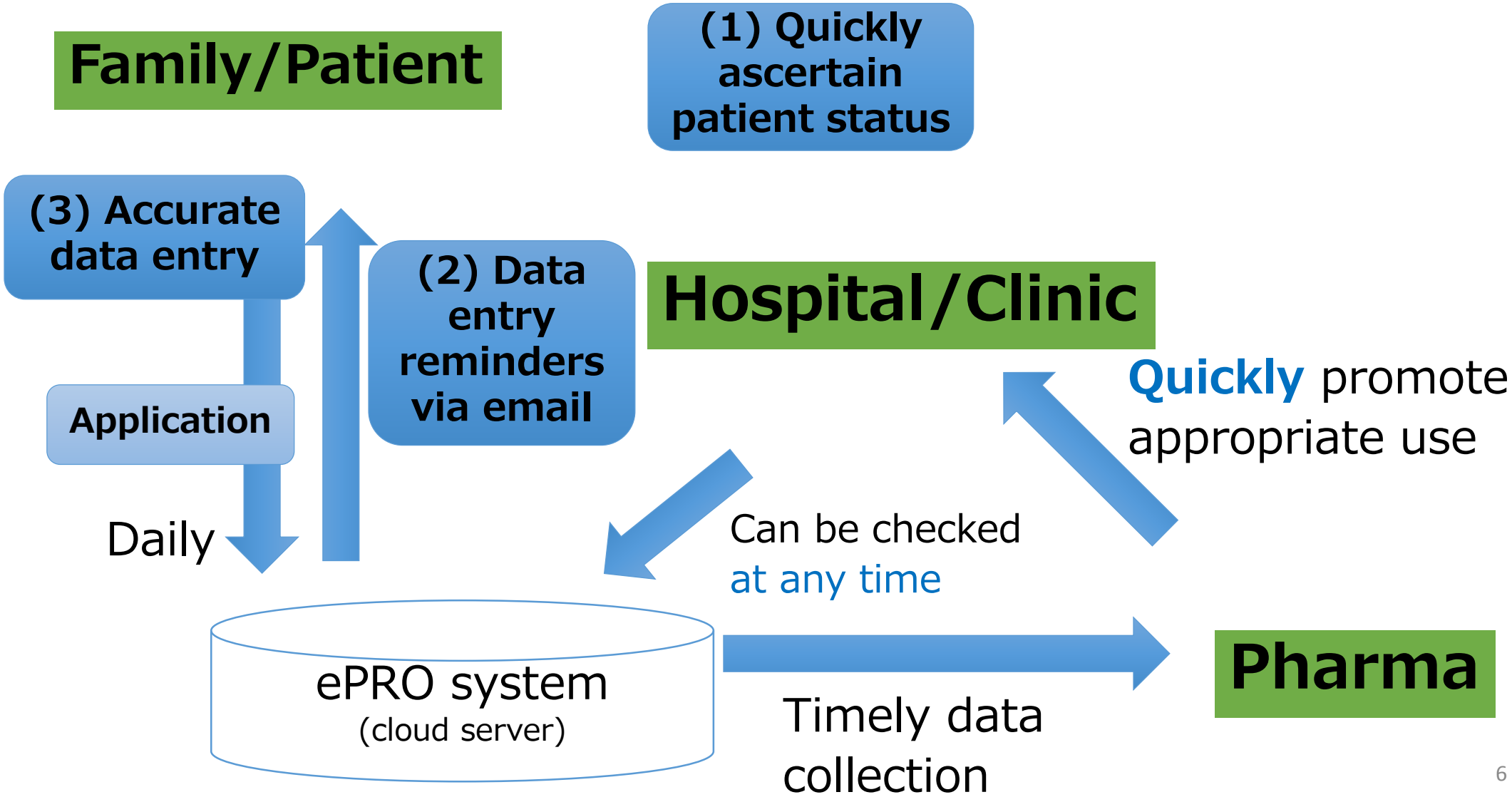
Real World Evidence is the truth obtained by utilizing real world data such as “subjective patient data” and “objective patient data.”

Subjective patient data
SNS, PRO, QOL, PGHD, PX,
Journey map, Communication Log

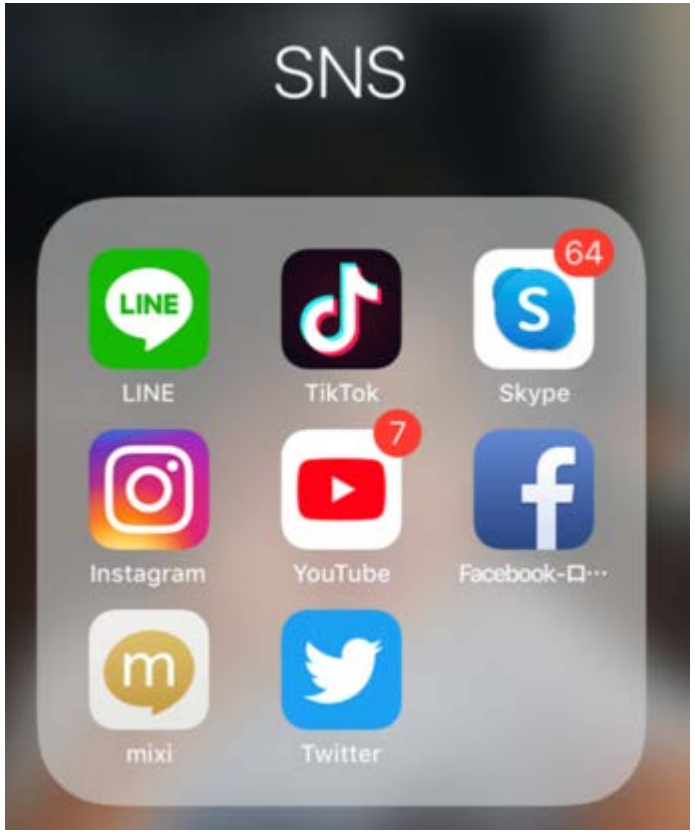
Objective patient data
DPC, prescription and electronic medical record data, registries, etc.

Real World Evidence

Subjective patient data
Example: ePRO



Subjective patient data
Example: Natural language on social media



Natural language processing

Events that are difficult to communicate to a doctor. Abnormal occurrence of an event.

Discussion of a database study utilizing healthcare data

・Participants in today’s session include many of the leaders and managers who are promoting database research.

・I will provide an overview of the WT3 Pilot Study, which used the two commercially available diagnosis procedure combination (DPC) databases (commercial databases), including my experience—as well as some of my trials and tribulations—as team leader. In particular I will discuss some of the pitfalls for data analysts.

What is the WT3 pilot?

- In 2016, before use of MID-NET started following amendment of GPSP, arrangements were made with Japanese regulators to enable initiation of database studies using commercial databases.

- The Japanese regulatory agency wanted to “perform a pilot study to confirm that there are no problems” before issuing official notifications or ordinances on database studies.

- A pilot study was performed by Working Team 3* (WT3) of the Federation of Pharmaceutical Manufacturers’ Associations of Japan (4 of the companies participating in WT3).

* A team comprising members from MHLW, PMDA, and the industry, tasked with exploring topics related to pharmacoepidemiology and database utilization.

Key achievements

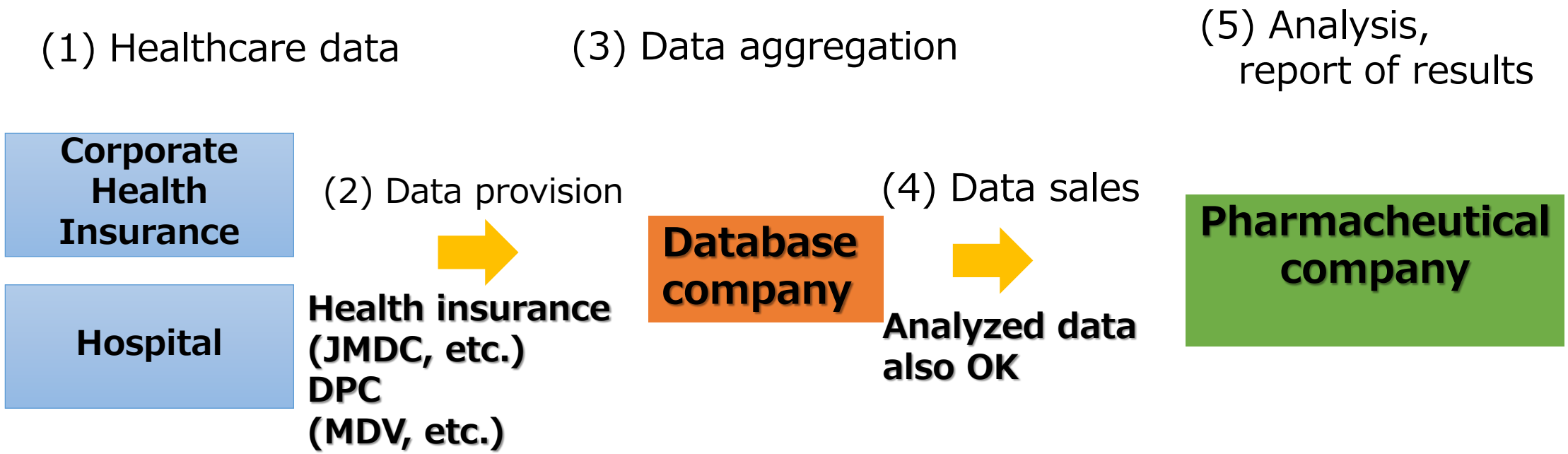
●Clarifying issues with ensuring reliability when implementing database studies

→ “Considerations for ensuring reliability of postmarketing database studies of pharmaceuticals

●Creation of template wording for protocols. Industry-wide standardization of terminology and definitions

→ “Template wording for postmarketing database study protocols”

Studies using commercial databases



●Database studies are easy to plan if the design specifies a comparator.
But it is necessary to understand the characteristics of each type of database.
(an understanding of pros and cons)
→Databases are not universal.
Select the study method that best fits the research question. There are many cases in which general drug use surveillance is appropriate.

Clinical question used in pilot

- **During treatment with Y-type agents, acute pancreatitis occurs in rare cases.**
- **There are different descriptions in the package inserts of various companies' Y-type agents.**
- **There are a small number of reports of acute pancreatitis in past cumulative data on Drug A.**
  - No adverse reaction reports of acute pancreatitis in Japanese clinical studies of Drug A or postmarketing all-patient surveillance of Drug A.
    Very small number of cumulative acute pancreatitis adverse reactions to Drug A.

→ Compared to treatment with similar drugs (Y-type agents), is the incidence of acute pancreatitis comparable? Different?

PECOT framework of pilot

PECOT	Details
Participants	**In patients with Cancer X who are eligible for treatment with Y-type agents,**
Exposure	**If Drug A is administered,**
Comparison	**Compared to treatment with similar drugs (Y-type agents),**
Outcome	**Is the incidence of acute pancreatitis comparable?**
Time	**From marketing start of Y-type agents to study implementation**

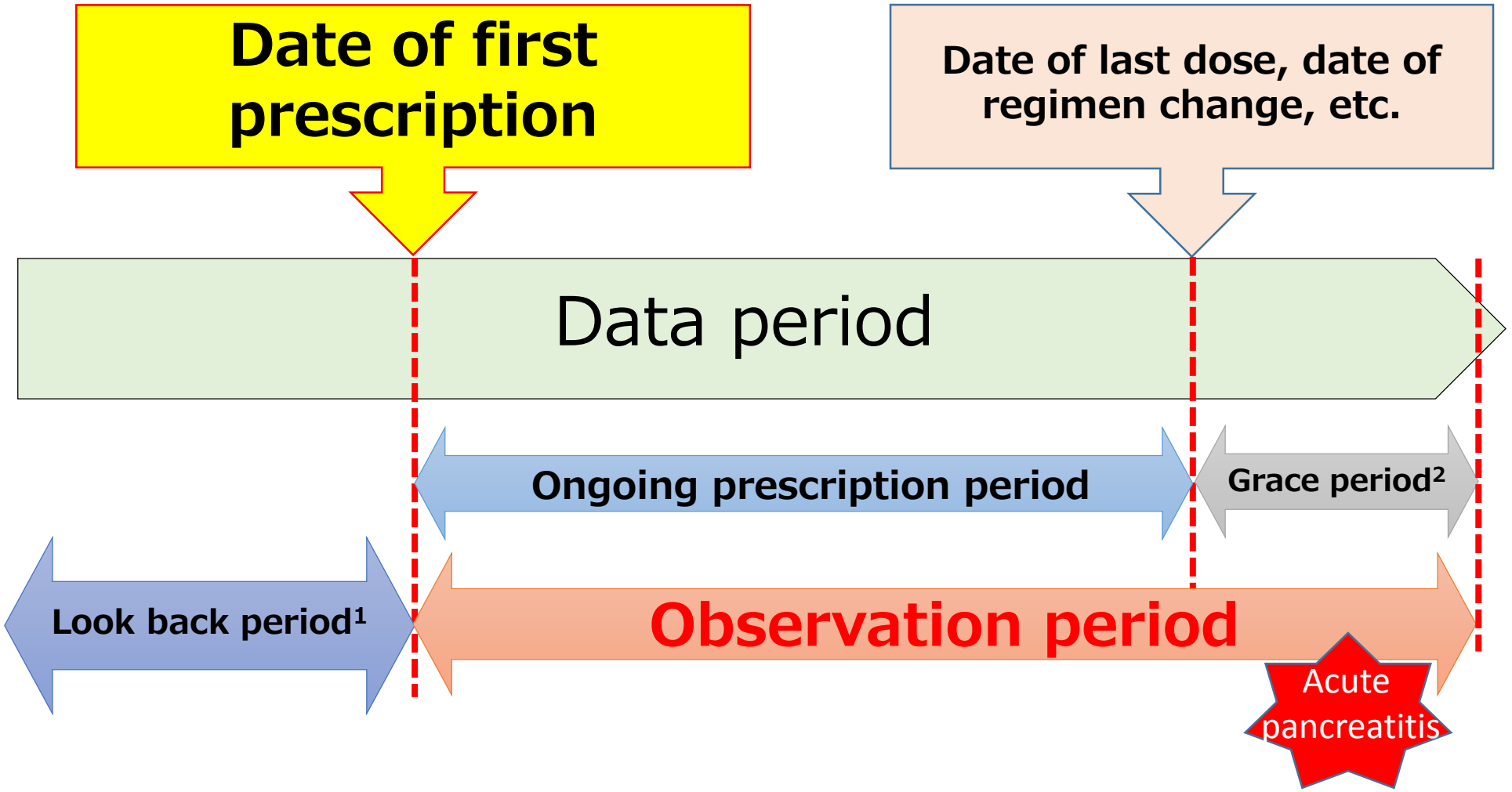
Calculate the incidence of acute pancreatitis when using either Drug A or Y-type agents to treat patients who have Cancer X, and consider the adjusted odds ratio corrected for patient baseline characteristics.

Study overview

Design	Cohort design
Sample size	Not set (because event incidence <0.1%; signal detection objective)
Outcome definition	(1) (primary) Acute pancreatitis, ICD-10: K85 (excluding pancreatic abscess) (2) (secondary) In line with (1), intervention for acute pancreatitis, drug
Items for assessment	Incidence of cases with acute pancreatitis in Drug A group and comparator group
	Perform logistic regression using whether acute pancreatitis occurred as the response variable and treatment group, sex, age, gallstones, and alcoholism as explanatory variables. Assess risk by calculating the adjusted odds ratio and 95% confidence interval of the Drug A group relative to the comparator group.

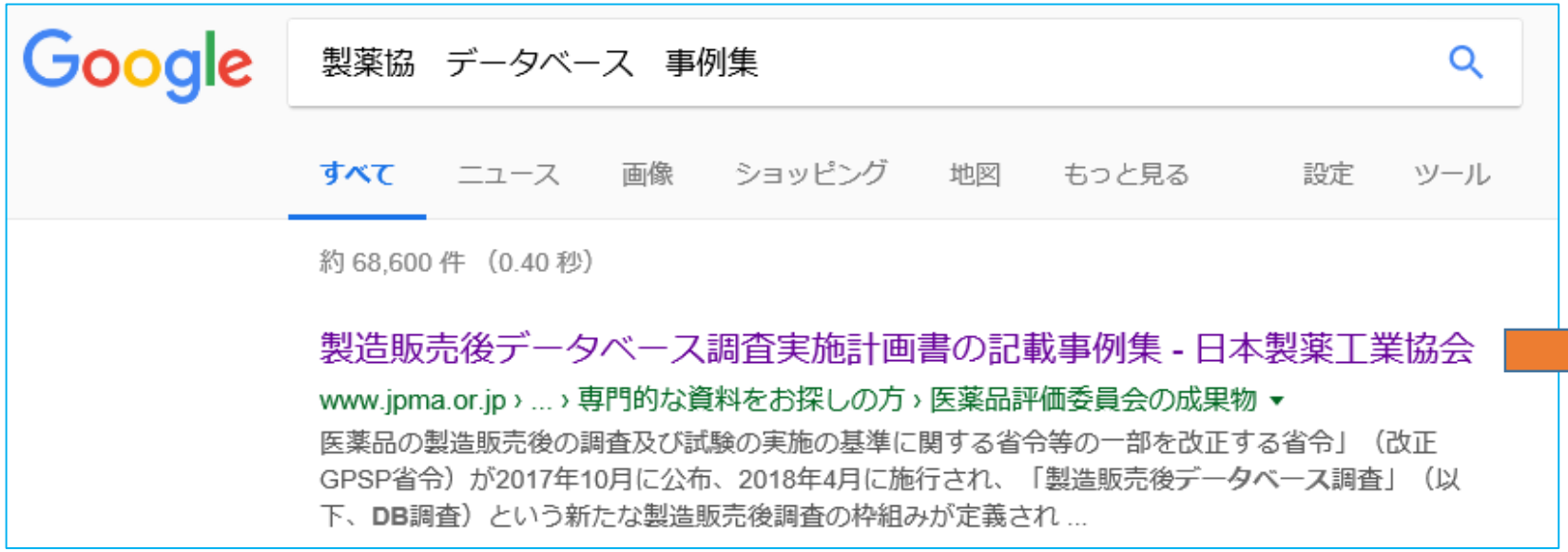
ICD: International Classification of Diseases

Observation period



1: Period for confirming pre-exposure confounding factors. Set separately according to characteristics of each database.
2: Set at +30 days. Sensitivity analysis of 0 days and +60 days conducted separately.

Details of pilot protocol are available below (in Japanese)



URL:http://www.jpma.or.jp/medicine/shinyaku/tiken/allotment/db_inspect.html

Lessons from the pilot

- **Different characteristics of health insurance and DPC databases**

  Definition of sample size, age groups, look back period, new user design

  →Each database has its strengths and weaknesses

  It is necessary to select the appropriate database after considering the characteristics of the particular field in light of the research question.

- **Some confounding factors are not present in databases.**

  →History of alcohol consumption is not available, so presence of alcoholism is used instead.

Lessons from the pilot

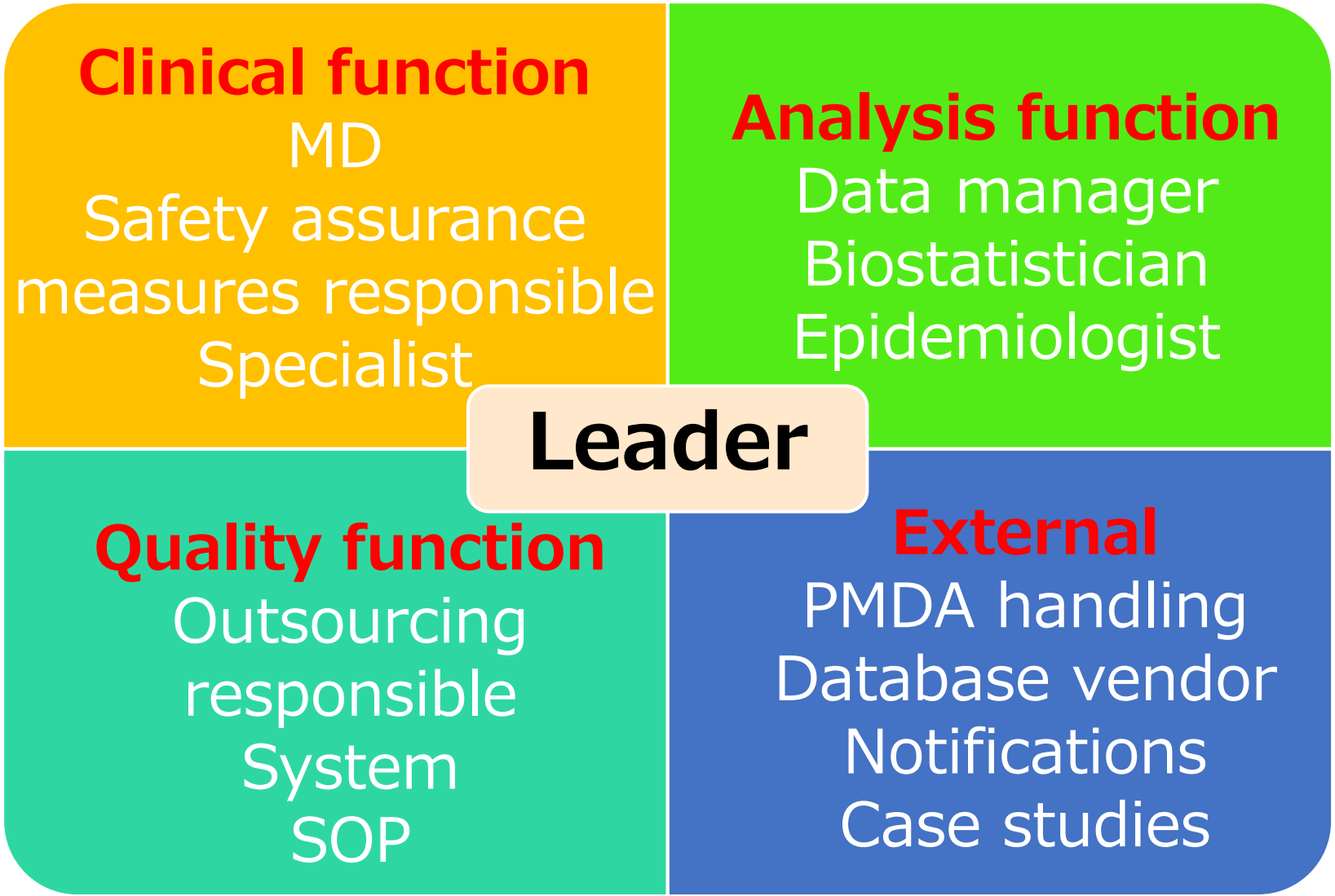
- **Consideration of study design**
  - Dealing with competing risks → whether tracking time is needed?
  - Propensity score method (matching, inverse probability weighting) → effects of small sample size, confounding factor alternatives?
  - Approach to unexpected confounding (instrumental variables method) → issue with adherence to preconditions?

- **It is better for pharmaceutical data scientists to also be knowledgeable about diseases and GxP.**

In particular, study leaders need to have a wide-ranging, comprehensive skill set and not stop at specializing in one field.

Leader's wide-ranging area of expertise

- **It is essential for database study leaders to have a sense of balance!!**



Key points about using medical data

- **Awareness of selecting the optimal database for a research question according to a clear understanding of the characteristics of health insurance and DPC data.**

Type	Strengths	Weaknesses
Health insurance database	Highly traceable and consistent. →Can set a long look back period. →High degree of reliability regarding confounding factors and new user design.	Data on those ≥65 years old unavailable. Lab test results unavailable. (medical check data available)
DPC database	Not age-dependent. Lab test results available (10% of total). High coverage of conditions mainly treated at acute care facilities. Database of >25 million people available.	Restricted to acute care hospitals. Issues with traceability.

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