Using Real-World Data/Evidence in Regulatory Decision Making

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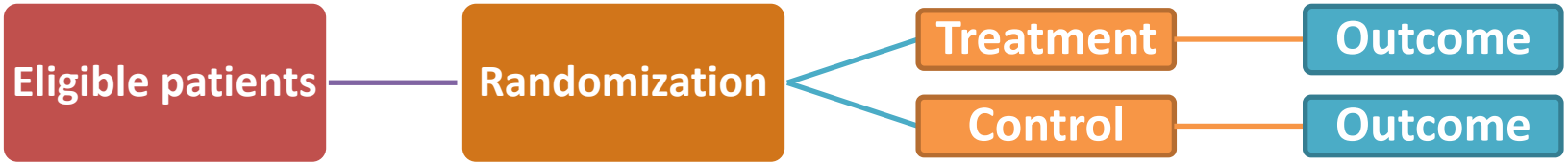
Outlines

1. What are RWD & RWE?
   From RWD to RWE
2. Applications of RWD/RWE
   In Regulatory Decision Making
   Taiwan Experiences
3. RWD Sources in Taiwan
   Individual database and
   HWDC in Taiwan

Evidentiary Standards for Drug Approval

Is there substantial evidence of drug safety and efficacy for the claimed indication?

Confirmatory randomized controlled trials (RCTs) ***– An ideal Setting***



✓ Strict inclusion and exclusion

✓ Proper randomization
✓ Concealed allocation
✓ Appropriate blinding

↑ Internal validity
↓ External validity

Artificially homogeneous

Minimize the chance of bias from patient selection, treatment assignment, patient evaluation and data analysis

Increasing use of real-world evidence to support decision making

Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

Clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD

US FDA guidance, 2017

Ability of RWD to generate RWE

Sufficient?
enough drug exposure, meaningful endpoint, population…..

Sufficient & Assured?
data accrual (protocol), source verification, minimizing missing data/outliers, sites monitoring/audit

Adequate?
appropriate methodology

Minimize source of bias?

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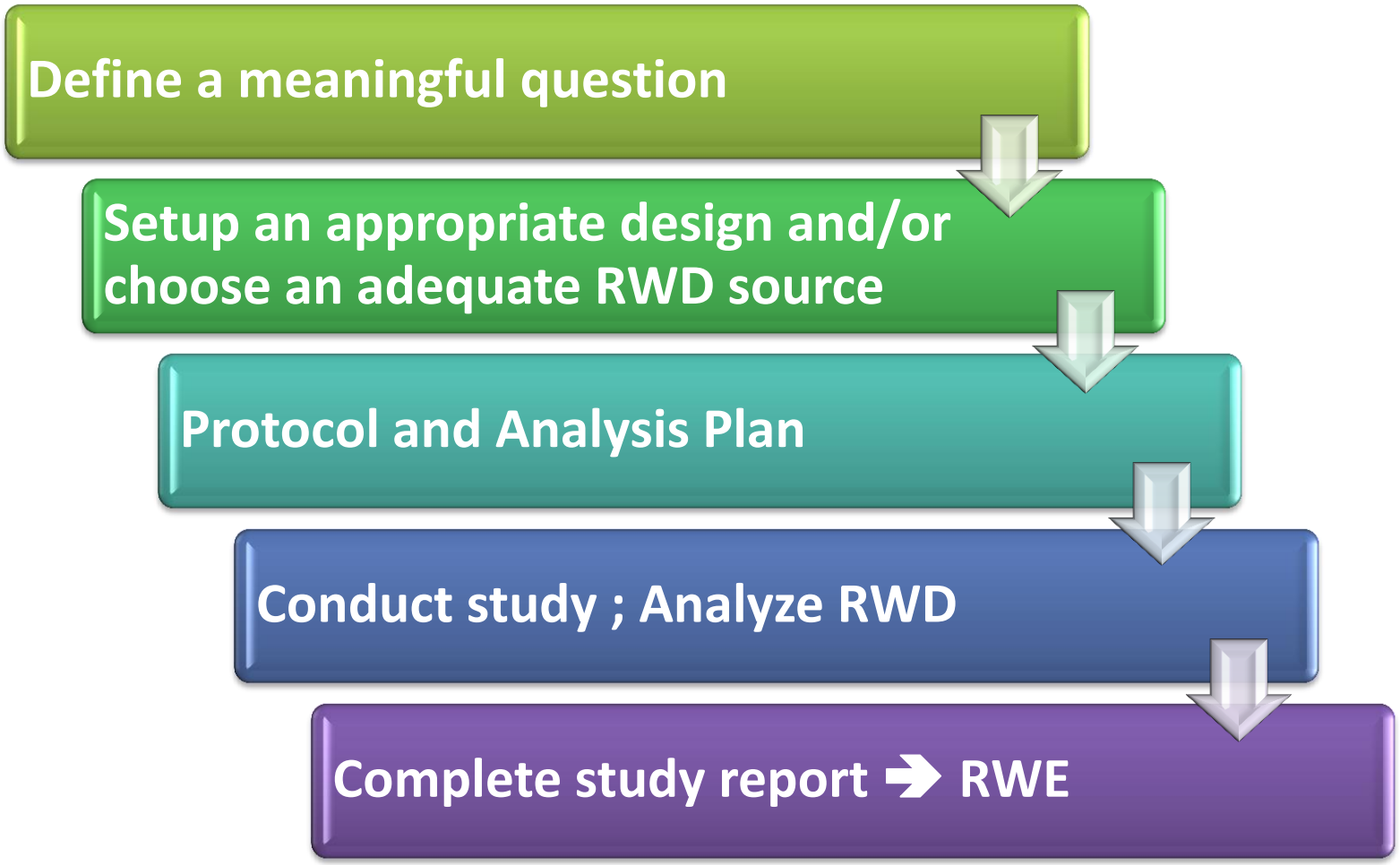
How to Translate RWD into RWE



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Taiwan regulatory experience with RWD/RWE

Change of approved product label

- Update label information of drug-drug interaction and safety

Post-market safety surveillance

- Phase IV safety study requested by regulatory
- Post-marketing pharmacovigilance

Pre-market safety assessment

- PSURs/PBRERs from other countries can be used as the sources of pre-marketing safety evaluation

Pre-market efficacy assessment

- Provide critical efficacy evidence (e.g. rare disease)
- As a historical control for single arm control

01 Case 1

The approval of Sapropterin Tablet for Hyperphenylalaninemia (HPA)

02 Case 2

Oral Ketoconazole, Hepatotoxicity

Case Study 1 – The approval of Sapropterin Tablet for Hyperphenylalaninemia (HPA)

- ✓ **HPA is diagnosed as an abnormal elevation in blood phenylalanine level (>120 µmol/L)**
- ✓ **Caused by**
  - **Phenylalanine hydroxylase (PAH) deficiency: phenylketouria (PKU), or**
  - **Tetrahydrobiopterin (BH4) deficiency**
- ✓ **Incidence**

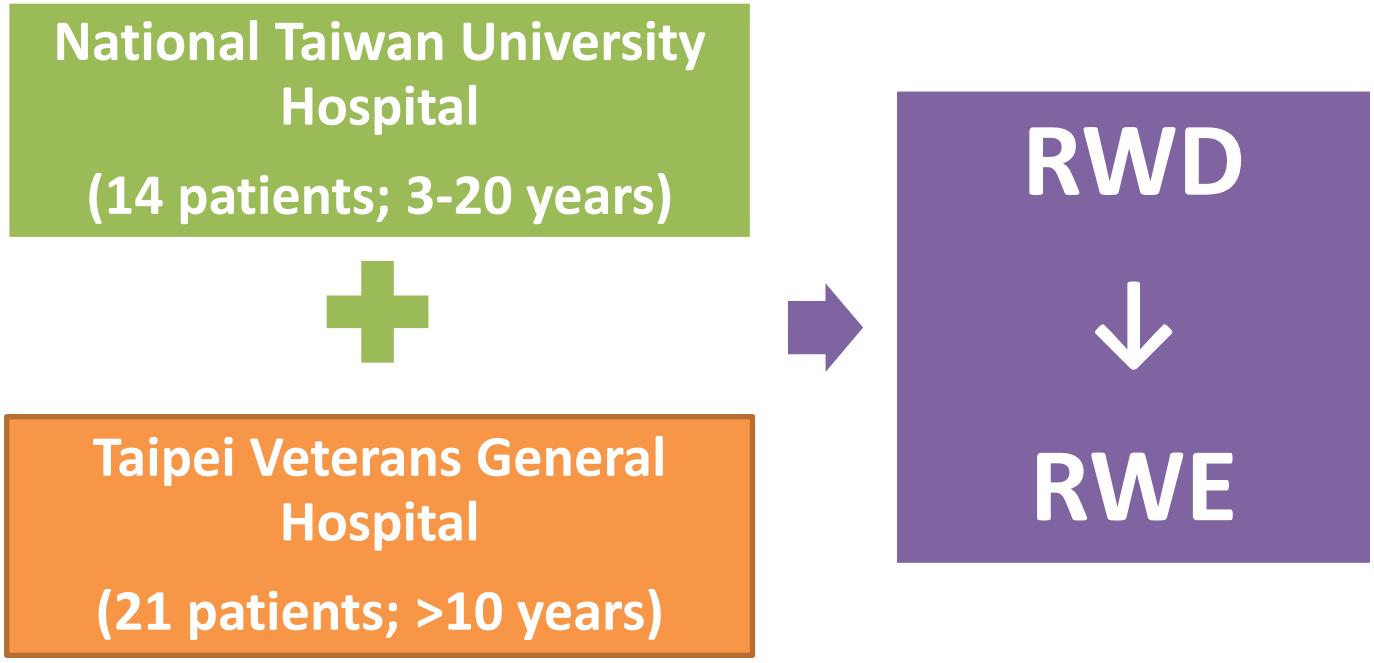
  Caucasian: ~ 1 in 10,000 & 1.5-2% of HPA are BH4 deficiency type

  Taiwanese: ~ 1 in 34,000 & 30% of HPA are BH4 deficiency type
- ✓ **In Taiwan, Sapropterin tablets (BH4) have been imported and used for the treatment of BH4 deficiency for many years without registration.**

Clinica Chimica Acta 313 Ž2001. 157–169

Case Study 1 – Sapropterin Tablets ("Excelsior" BH4)

- ✓ **Well collected patient clinical data derived from two retrospective observational studies in patients with BH4 deficiency.**



Case Study 1 – Sapropterin Tablets ("Excelsior" BH4)

- ✓ **The "Excelsior" BH4 Tablet (sapropterin) was approved for the treatment of hyperphenylalaninemia due to tetrahydrobiopterin (BH4) deficiency, based on following consideration:**
  - **Claimed indication is a rare disease**
  - **Clear mechanism of action**
  - **Surrogate endpoint (blood Phenylalanine level)**
  - **Well-collected patient clinical data (real world data)**

Case Study 2 – Oral Ketoconazole / Hepatotoxicity

- ✓ In Taiwan, oral ketoconazole was indicated for the treatment of fungal infections.
- ✓ Concerns raised internationally on liver toxicity associated with oral ketoconazole

EMA: Suspended

FDA: Restriction of use & lots of warnings

Oral Ketoconazole / Hepatotoxicity

✓Taiwan National ADR Reporting Database

Item	Hepatobiliary disorders	All
No. of cases	31	58
Age（year）		
Mean ±SD	45±15	51±20
Range	16-86	16-94
Gender（N）		
Male	8	18
Female	23	40
Outcome of adverse reaction（N）		
Death	1	2
Life threatening	4	5
Hospitalization	20	25
Non-serious	6	26

- ✓ Some uses without prescription
- ✓ Use due to mild skin conditions

ADR=Adverse drug reaction

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Oral Ketoconazole / Hepatotoxicity

✓ Taiwan National Health Insurance (NHI) Claim Database

Medical care institute	No. of prescription（%）
Medical centers	280（1.1%）
Regional hospitals	354（1.4%）
District hospitals	1,103（4.5%）
Primary care clinics	19,103（77.3%）
Pharmacy	3,864（15.6%）
Total	24,704（100.0%）

- ✓ Difficulty in providing intense liver function monitoring
- ✓ Liver function test within 30 days before treatment: 2.7%

Case Study 2 – Oral Ketoconazole / Hepatotoxicity

✓ Literatures

- Within the recommended dosage, the incidence and severity of liver injury caused by oral ketoconazole are higher than those of other azoles
- Liver injury occurs mostly between 1 and 6 months, but there are still many case reports occurring within 1 month (including few days).

Cannot reduce the risk by limiting the dosage/duration

✓ There are other available medicines in the market.

Taiwan: withdrawal

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RWD Sources in Taiwan

Patient-level data of nation-wide population

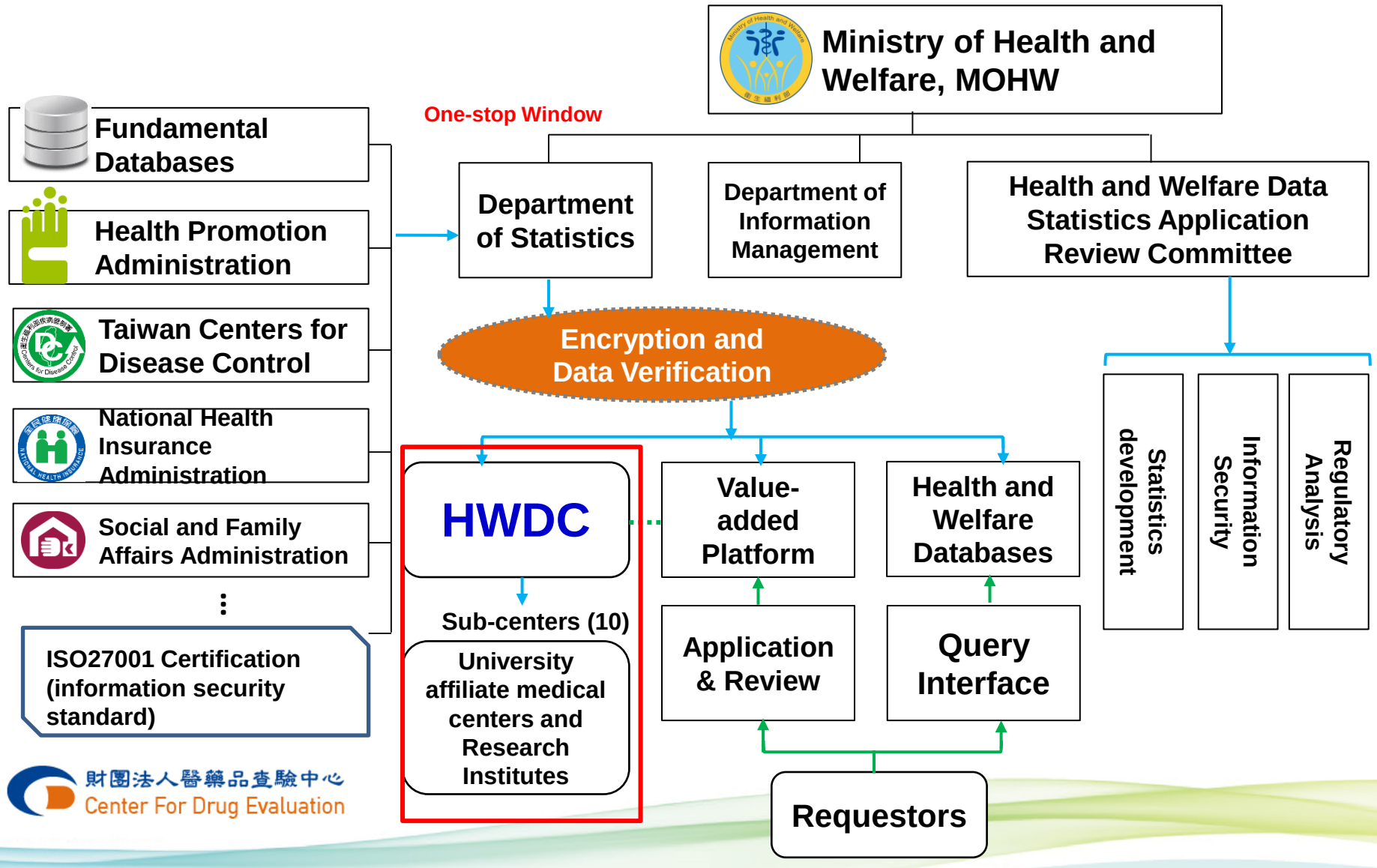
- National Health Insurance (NHI) Claim Database
- Disease Registry: Cancer Registry Database
- Cause of Death Mortality Database[1]
  - ✓ De-identification and encryption
  - ✓ Limited access with IRB approval

Summary data of national health statistics

- Population Projections (Taiwan)[2]
- Healthcare statistics annual reports[3]
- Cancer registry annual reports[4]
- NHI healthcare quality public disclosure
  - ✓ Aggregate data by age and gender
  - ✓ Open access on official website

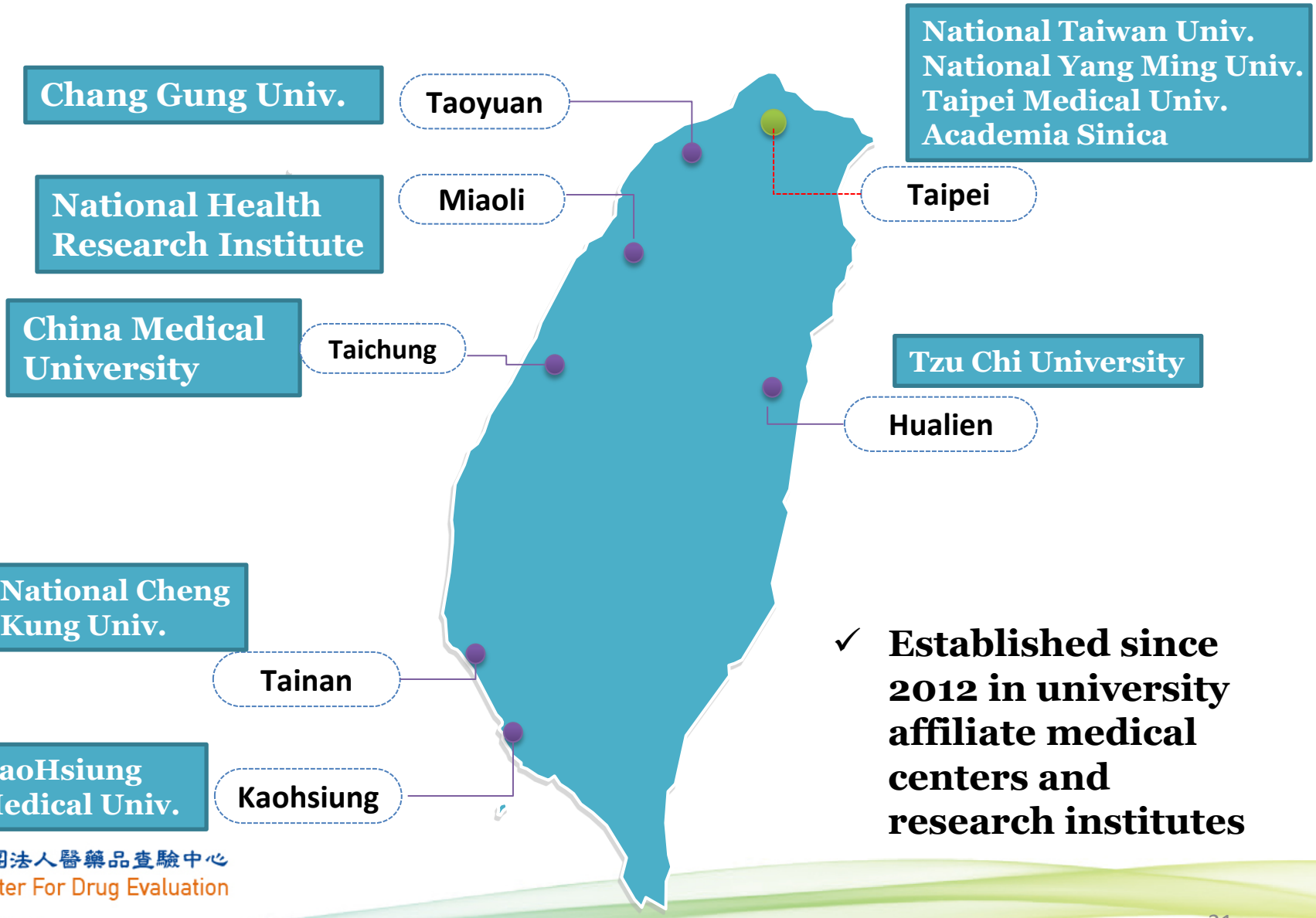
[1]https://dep.mohw.gov.tw/DOS/np-1776-113.html
[2]https://www.ndc.gov.tw/Content_List.aspx?n=84223C65B6F94D72
[3]https://dep.mohw.gov.tw/DOS/np-1918-113.html
[4]https://www.hpa.gov.tw/Pages/List.aspx?nodeid=119

Data Linkage among Various Databases



- ✓ **Health and Welfare Data Science Center (HWDC)**
  - Manage all databases relevant to health and social welfare from birth to death
  - NHI claim database (2-millions sampling database)
  - Cancer registry, rare disease, catastrophic illness, disability
  - Health Survey: birth cohort, women, elderly, adolescent
  - Disease-specific database: diabetes, hypertension, chronic kidney disease
- ✓ **Research proposal and IRB approval is required before submission**
  - Preparation process from application to data access: 6 months
- ✓ **Encrypted personal ID for de-identification**
  - Researchers have to analyze data on-site (main- and sub-centers)
  - Statistical output will be carefully reviewed by HWDC to ascertain data security

10 HWDC Sub-centers for Research in Taiwan



- ✓ **Established since 2012 in university affiliate medical centers and research institutes**

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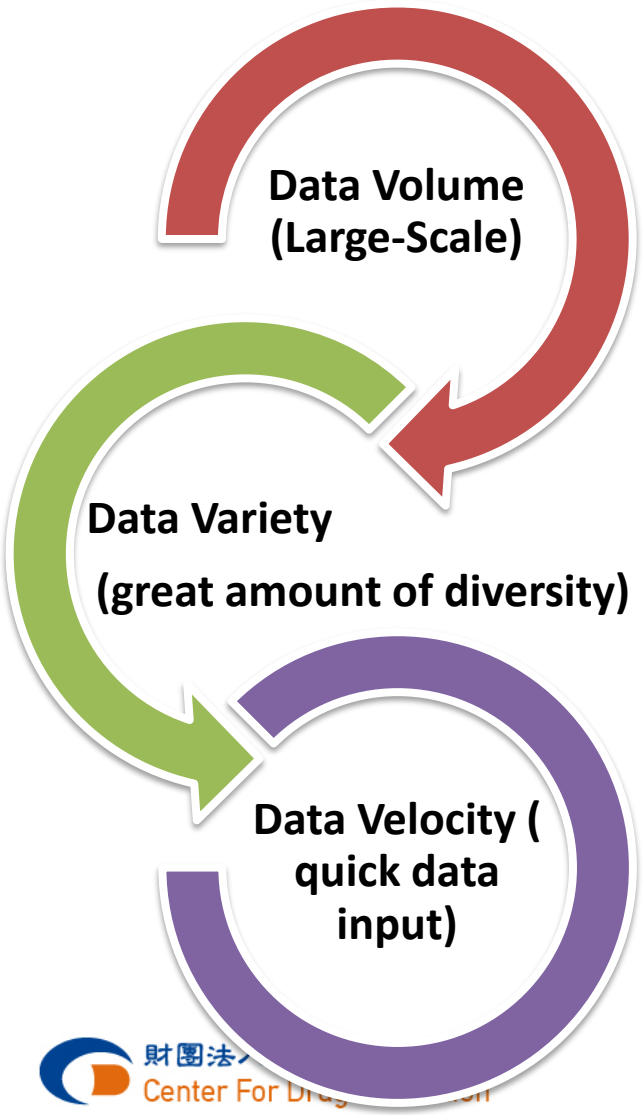
Facts and Opportunities



Data value

Ask right questions
↓
Collect high-quality data
↓
Conduct proper analyses
↓
Generate reliable and robustness evidence

Regulatory

- Pharmacovigilance
- Safety label changes
- Drug-drug interactions
- Conditional approval requiring collection of on-market data
- Extension of indication

Industry

- Discover drug pathways
- Identify unmet clinical need, profile target populations
- Uncover new indication
- Profile patient compliance/adherence

Challenges of Using RWD in Taiwan

- ✓ **Comprehensive RWD access is limited to some stakeholders**
  - Databases in HWDC are not available for non-academic use, ex. pharmaceutical company
  - Collaboration between stakeholders is a possible solution

- ✓ **RWD is not collected for research purposes**
  - Inherent bias: selection bias, information bias, confounding bias
  - Development of statistical methods and pharmacoepidemiology design

- ✓ **Data linkage between electronic health records (EHRs) and other RWD is still difficult**
  - Ethical issue and informed consents of patients
  - Some medical centers establish data warehouse of EHRs for further application

Acknowledgements

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Question!!