Drug Loss in Japan and the Potential of Real World Data (RWD) to Accelerate Clinical Development

第38回抗悪性腫瘍薬開発フォーラム
2025年6月28日

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Learning objectives

1. An overview of current measures and regulations to address access of Japanese patients to innovative medicine
2. Insights into recently approved drugs in FDA, EMA and MHLW
3. How external comparators could be used when data from local studies is missing and use of pseudonymized data

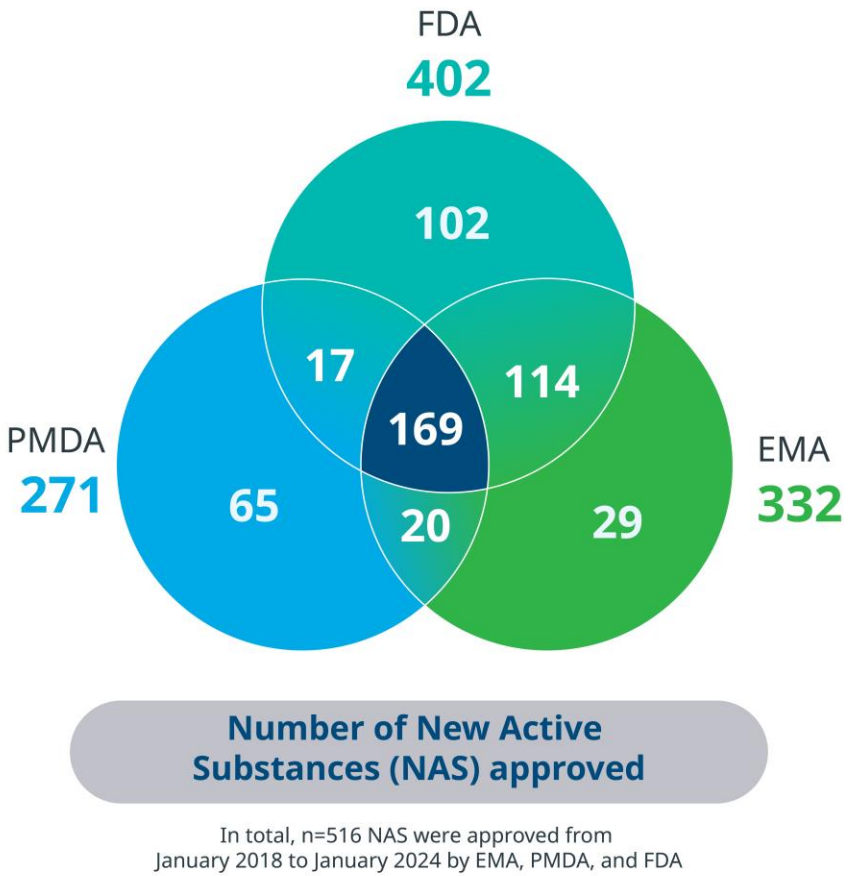
Drug loss in Japan

Overview

Comparison of approval dates of new medications

EMA, PMDA and FDA

EMA, PMDA and FDA NAS approvals
(time range: 01.01.2018–31.01.2024)

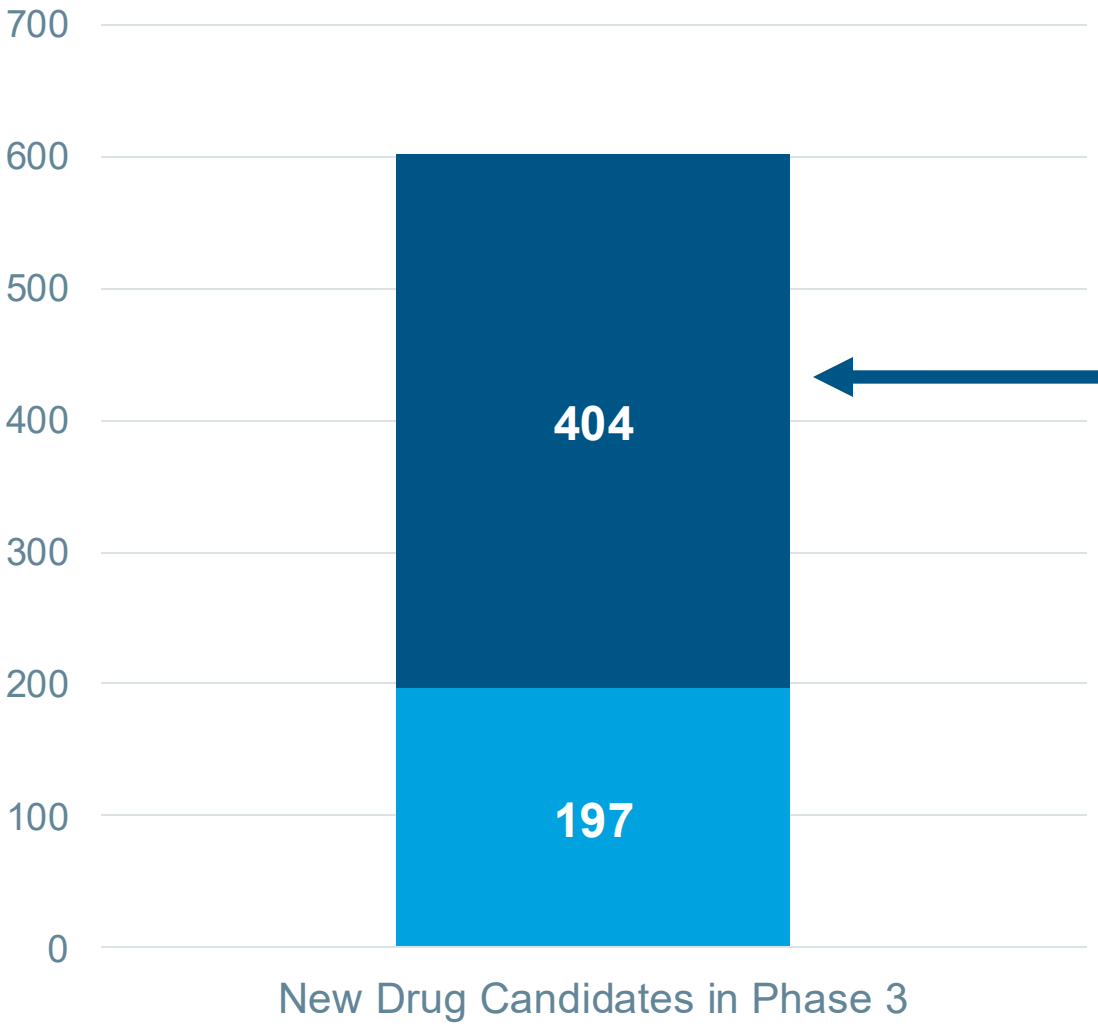


Time differences in approval dates for new active substances between EMA, PMDA and FDA

	Number	Percent
Approval by EMA and FDA	283	
Approval within 0.5 years	96	33.9
Approval by FDA >0.5–1.5 years earlier	104	36.7
Approval by FDA >1.5 years earlier	50	17.7
Approval by EMA >0.5–1.5 years earlier	12	4.2
Approval by EMA >1.5 years earlier	21	7.4
Approval by FDA and PMDA	186	
Approval within 0.5 years	51	27.4
Approval by FDA >0.5–1.5 years earlier	37	19.9
Approval by FDA >1.5 years earlier	79	42.5
Approval by PMDA >0.5–1.5 years earlier	8	4.3
Approval by PMDA >1.5 years earlier	11	5.9
Approval by EMA and PMDA	189	
Approval within 0.5 years	69	36.5
Approval by EMA >0.5–1.5 years earlier	19	10.1
Approval by EMA >1.5 years earlier	71	37.6
Approval by PMDA >0.5–1.5 years earlier	14	7.4
Approval by PMDA >1.5 years earlier	16	8.5

Batscheider, A, E Shlaen, S Demiya, Y Akachi, Y Li, D Schnauffer, M Rauch, RA Greiner, D Bonduelle と M Becker.「EPH246 Comparison of Approval Dates of New Medications Between Europe (European Medicines Agency, EMA), Japan (Pharmaceutical and Medical Devices Agency, PMDA), and the United States (US) of America (Food and Drug Administration, FDA)」. *Value in Health* 27, no. 12 (2024年12月1日): S266. https://doi.org/10.1016/j.jval.2024.10.1370.

Further drug losses are anticipated



Out of **601** new drug candidates in Phase 3 clinical trials in the U.S. and Europe, approximately **70% (404 drugs) have not started development in Japan**.

These 404 drugs are focused on **infectious diseases**, **oncology**, and the **central nervous system**.

Source: Nikkan Yakugyo dated 9-Apr-2025 (https://nk.jiho.jp/article/198119?searched_keyword[]=%E3%83%89%E3%83%A9%E3%83%83%E3%82%B0%E3%83%AD%E3%82%B9)

Current government actions

The Japanese government is taking following actions to address the gap

- MHLW is looking to seek funds for **boosting domestic capabilities** in pharmaceutical innovation
- Measures in the areas of **pediatric** and **rare diseases** and budget requests are being considered for
    - Enhancing measures against **drug losses** in the pediatric and rare diseases
    - Establishing a scheme for carrying out first-in-human (FIH) studies and a one-stop contact point to support overseas startups' clinical trials,
    - Nurturing talents in manufacturing and developing next-generation biologics
    - Building an ecosystem for drug innovation
    - Bolstering regulatory consultations and support in early stages
    - **Promoting the use of real-world data (RWD) in regulatory submissions**

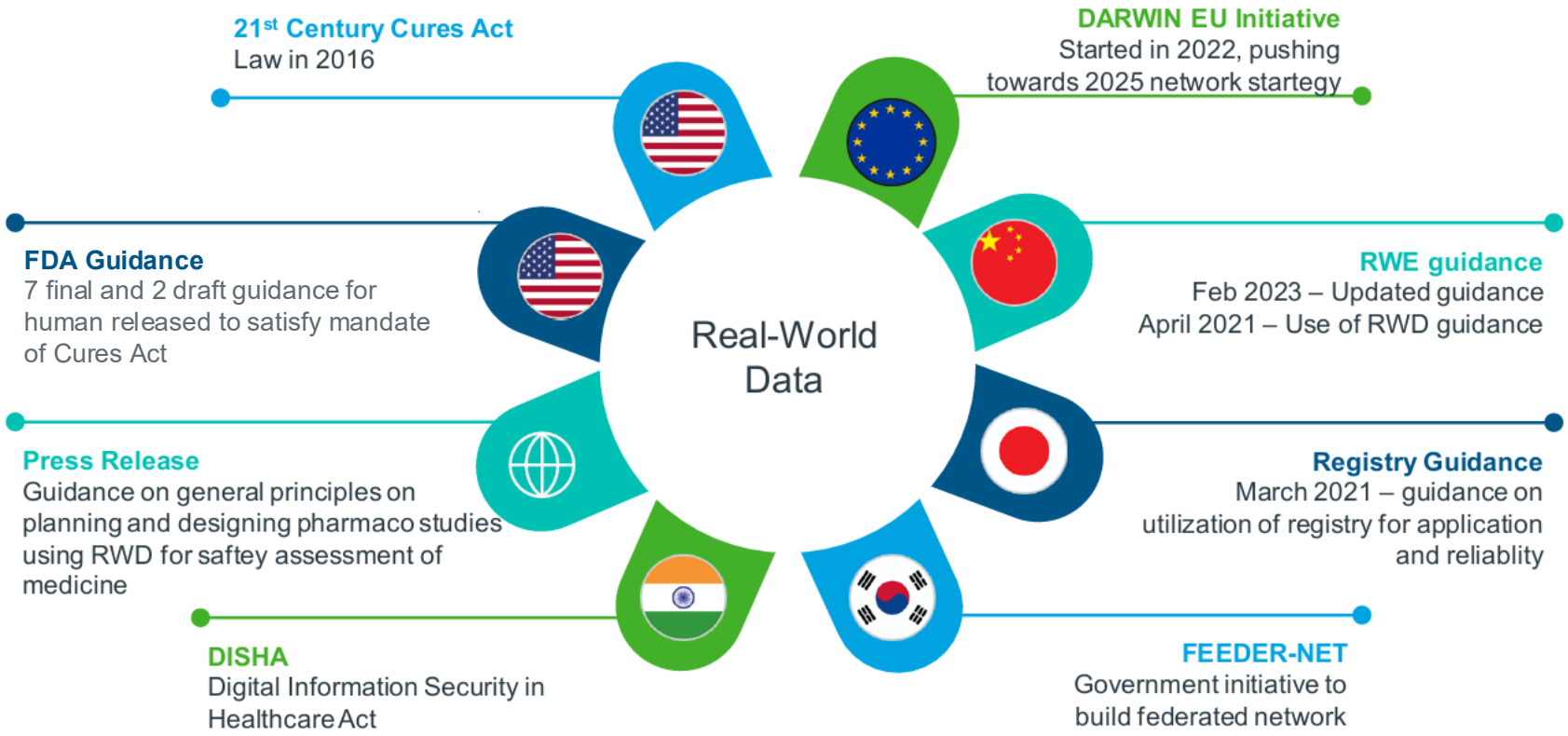
Source: PHARMA JAPAN dated 26-Aug-2024 (https://pj.jiho.jp/article/251551?searched_keyword[]=REAL&searched_keyword[]=World&searched_keyword[]=data)

Regulations for regulatory decision-making and challenges utilizing RWD

IQVIA

Trends in Real-world Data (RWD) Utilization

Regulators are increasingly interested in the utilization of RWD for decision-making.



Drug regulators across the globe increasingly consider RWE in decision making (As of June 2025)

FDA Selected Guidance

Sep 24 Integrating randomized controlled trials for drug and biological products into routine clinical practice (Draft guidance)

Jul 24 RWD: Assessing EHR and medical claims data to support regulatory decision-making for drug and biological products

Dec 23 Data standards for drug and biological production submissions containing RWD

Dec 23 RWD: assessing registries to support regulatory decision-making for drug and biological products

Aug 23 Considerations for the use of RWD and RWE to support regulatory decision-making for drug and biological products

Feb 23 Considerations for the design and conduct of externally controlled trials for drug and biological products (Draft guidance)

Sep 22 Submitting documents using RWD and RWE to FDA for drug and biological products

Dec 18 Framework for FDA's RWE program

Jul 18 Use of EHR in clinical investigations

Aug 17 Use of RWE to support regulatory decision-making for medical devices

Apr 24 CADTH summary report from Industry Task Force on RWE

Aug 23 CADTH RWD new industry task force to advance RWD

May 23 CADTH, HC and INESS joint guidance for reporting RWE

Jun 25 Updated Reflection paper on use of RWD in non-interventional studies to generate RWE for regulatory purposes

Apr 25 Updated Good practice guide for the use of the HMA-EMA Catalogues of RWD sources and studies

Apr 25 Updated Journey towards a roadmap for regulatory guidance on RWE

Aug 24 RWE framework to support EU regulatory decision-making: 2nd report

Apr 24 Guide on RWE provided by EMA: support for regulatory decision-making

Mar 25 Published Considerations for Externally Controlled Trials

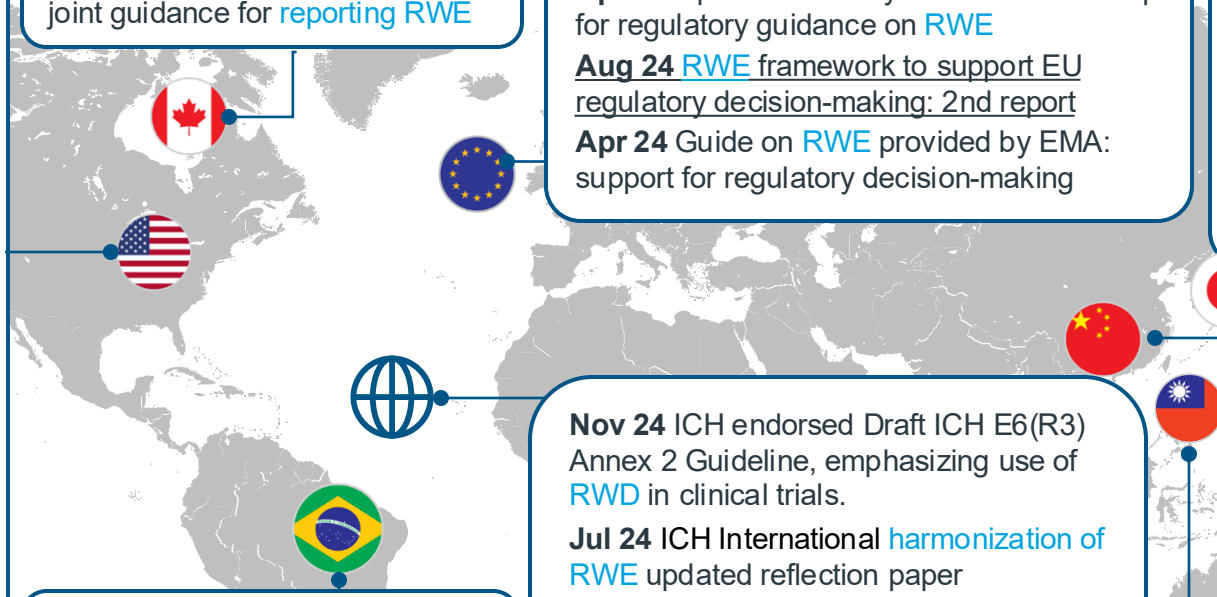
Oct 24 Guidance on using registry data for indication expansion and electronic package inserts

Jun 24 External Comparator (ICH E9(R1))

Nov 23 The Revised Next Generation Medical Infrastructure Act permits the use of pseudonymized data for regulatory purposes.

Mar 23 Guidance on registry and medical information database reliability Q&A

Mar 21 Guidance on registry utilization for application and reliability



Nov 24 Drafted Guidelines for the Application of RWD Based on Disease Registries

Feb 23 CDE guidelines on communication of drug applications supported by RWE

Jul 23 Triple release on technical guidelines regarding patient-centered clinical trials

Nov 24 ICH endorsed Draft ICH E6(R3) Annex 2 Guideline, emphasizing use of RWD in clinical trials.

Jul 24 ICH International harmonization of RWE updated reflection paper

Jun 24 CIOMS final RWD and RWE in reg decision-making

May 24 ICH M14 draft guideline on RWD for safety assessment

Dec 23 ANVISA updates regulatory agenda, emphasizing RWE initiatives

Sep 23 ANVISA RWE guidelines to support development of new drugs or new indications

Sep 23 ANVISA RWE reg expert group established

Dec 24 Key Considerations for RWD Research Design - Registry-Based Study

Oct 23 Evaluating HER and medical claims data supporting drug regulatory decision-making

*Note: Selected citations, not exhaustive, as of May 2025

= International application

PMDA: Considerations for Externally Controlled Trials

Issued by: Pharmaceuticals and Medical Devices Agency (PMDA) *Date: March 24, 2027*

Key Points:

- **Purpose**: ECTs are ecommended when RCTs are difficult. Consider when disease progression is predictable and sufficient information is available.
- **Comparison Groups**: Compare treatment group with external control group (historical controls or RWD).
  - **Limitations:** biases due to lack of randomization, baseline differences.
- **Planning and Implementation**: Careful planning to minimize biases. Discuss with regulatory authorities during planning.
- **Data Sources**: Use clinical trials, registries, RWD. Ensure reliability and appropriateness.
- **Statistical Considerations**: Establish detailed analysis plans before trial. Define methods to adjust for confounding factors and biases.
- **Intermediate Events**: Address events affecting endpoint interpretation (e.g., treatment discontinuation). Anticipate and manage during planning.

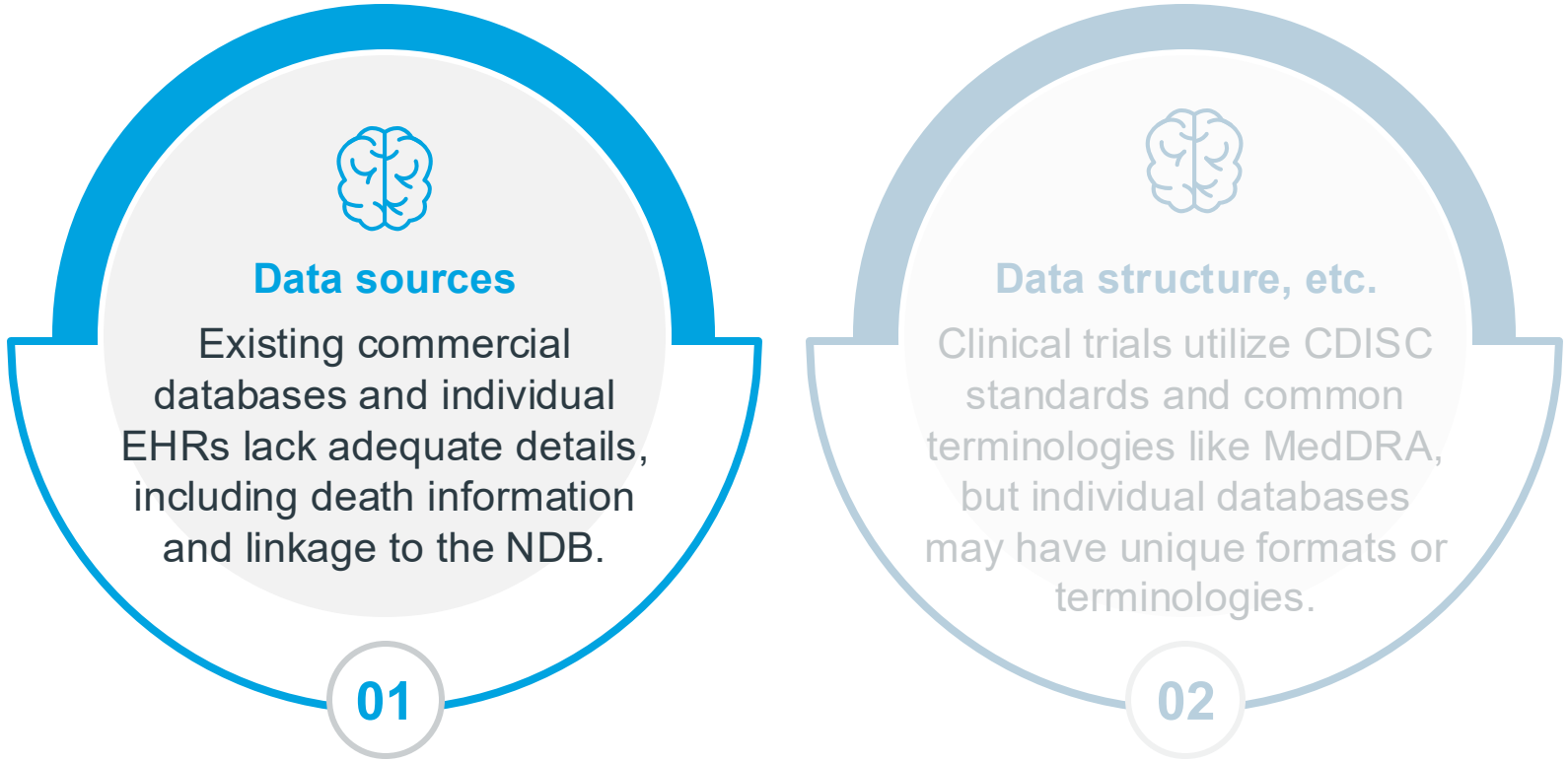
Emphasis on RWD

Detailed Planning Requirements

Regulatory Consultation

Challenges utilizing RDW for regulatory decisions in Japan

Are submission-ready databases available? How will the data structure be standardized?



Promoting the use of RWD in regulatory submissions

Outline of the Next-Generation Medical Care Infrastructure Act

Providing research results

- **Development of new drugs**
- Discovery of unknown side effects
- Formulation of effective policies

Use of pseudonymized personal information

1. Governmental certification
2. Prohibition of re-identification
3. Penalties for violation

Providing medical information

- Information is collected from patients and citizens through medical care and health check-ups
- Patients and citizens are notified about the use of their data, and it is possible to request stopping the provision of data

Flow of information

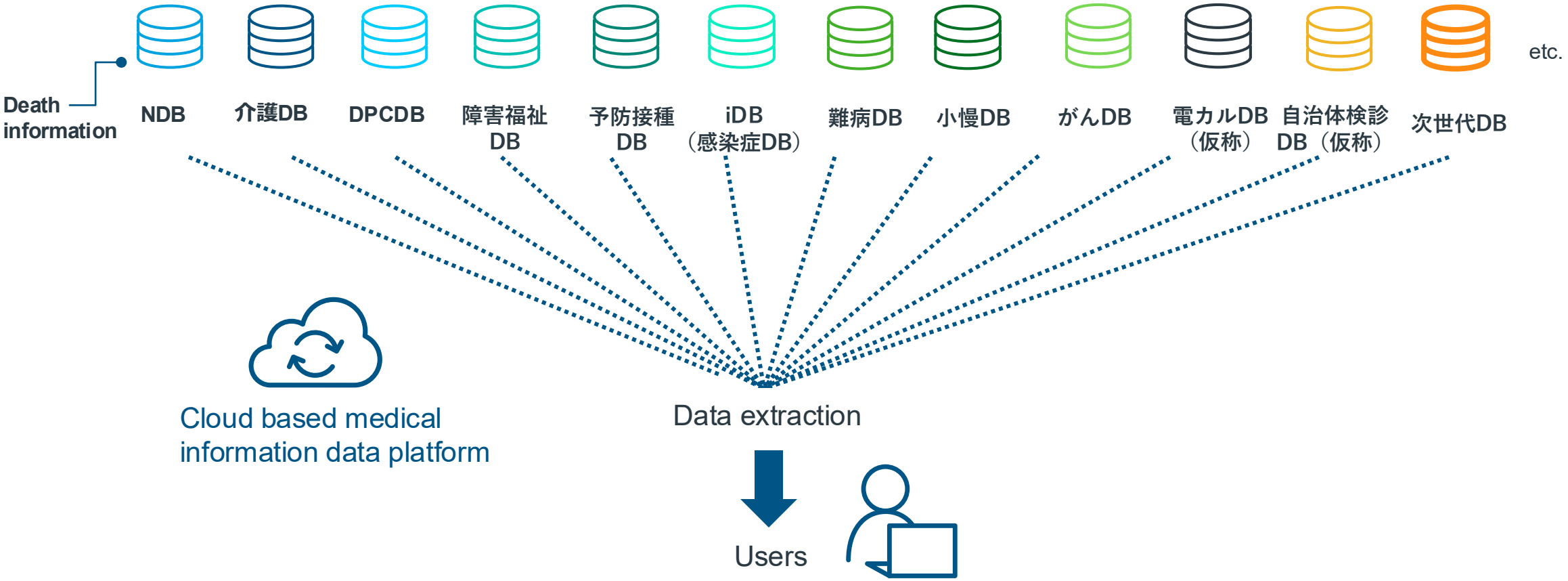
Process of pseudonymized data

- Authorized processors are certified by the government based on strict criteria
- Anonymized data can be provided in a form that can be linked to the national public database

Source: Cabinet Office (Japan). Training materials for business operators using pseudonymized medical information under the Next Generation Medical Infrastructure Act. January 2025 (https://www8.cao.go.jp/iryou/researchers/pdf/kenshu-pdf.pdf)

Secondary use of medical information databases

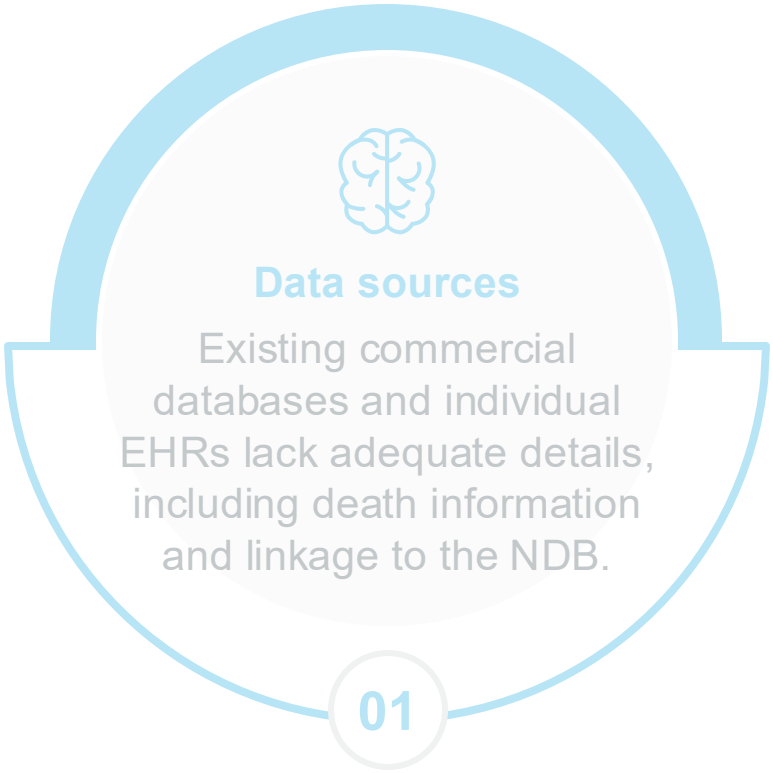
The next-generation medical care database, including pseudonymized data linked with other medical information databases, will be available soon

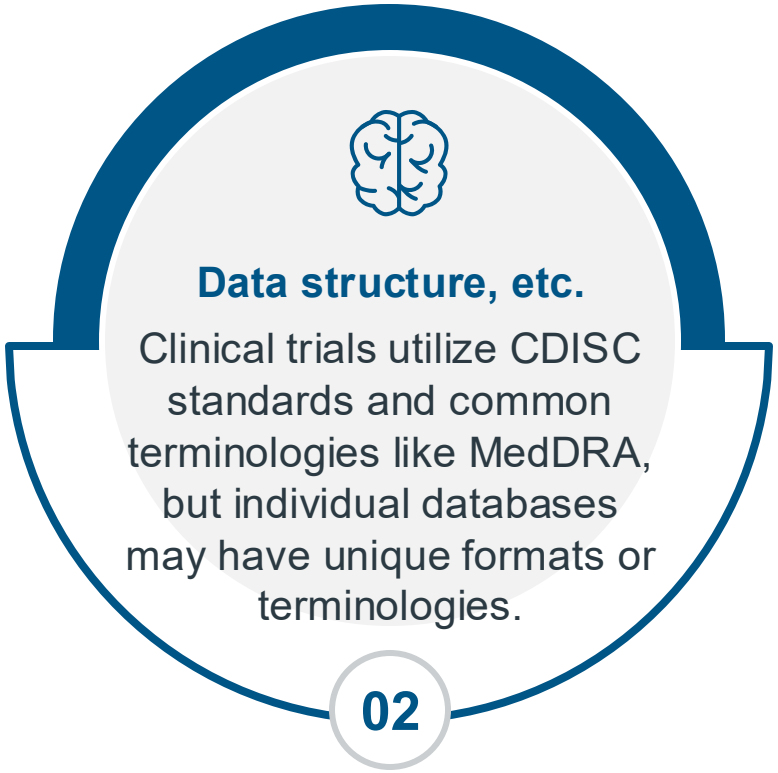


Source: Modified based on MHLW. Institutional response to the medical DX in the comprehensive reform of the health care delivery system towards 2040. November 2024 (https://www.mhlw.go.jp/content/10808000/001380624.pdf)

Challenges utilizing RDW for regulatory decisions in Japan

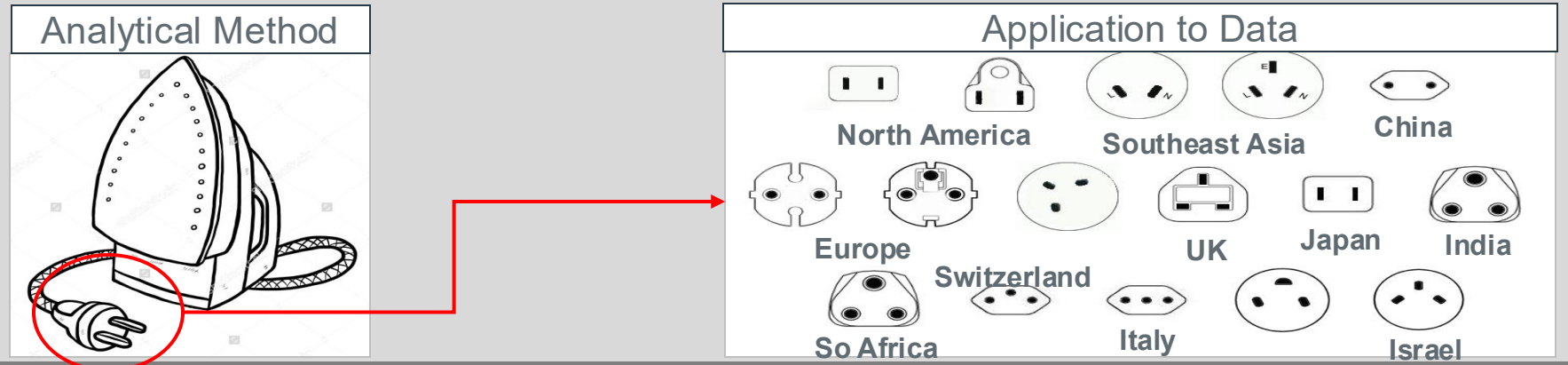
Are submission-ready databases available? How will the data structure be standardized?



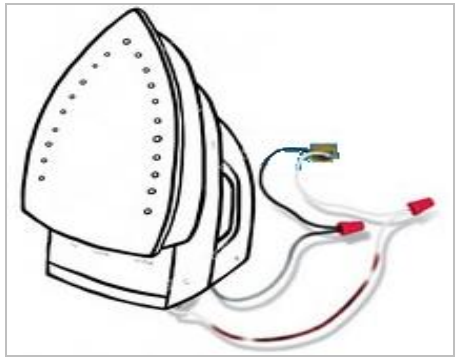


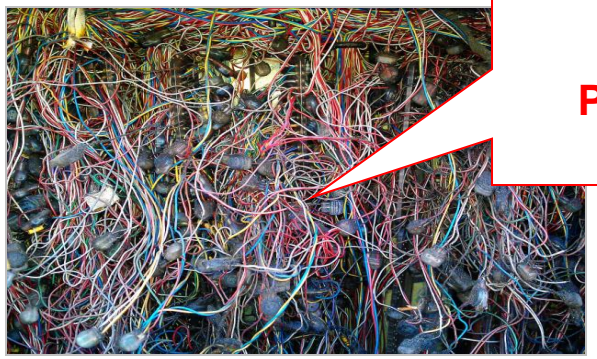
Current Approach: multiple study coding for the same question

Can I measure adherence to my drug across a series of databases?



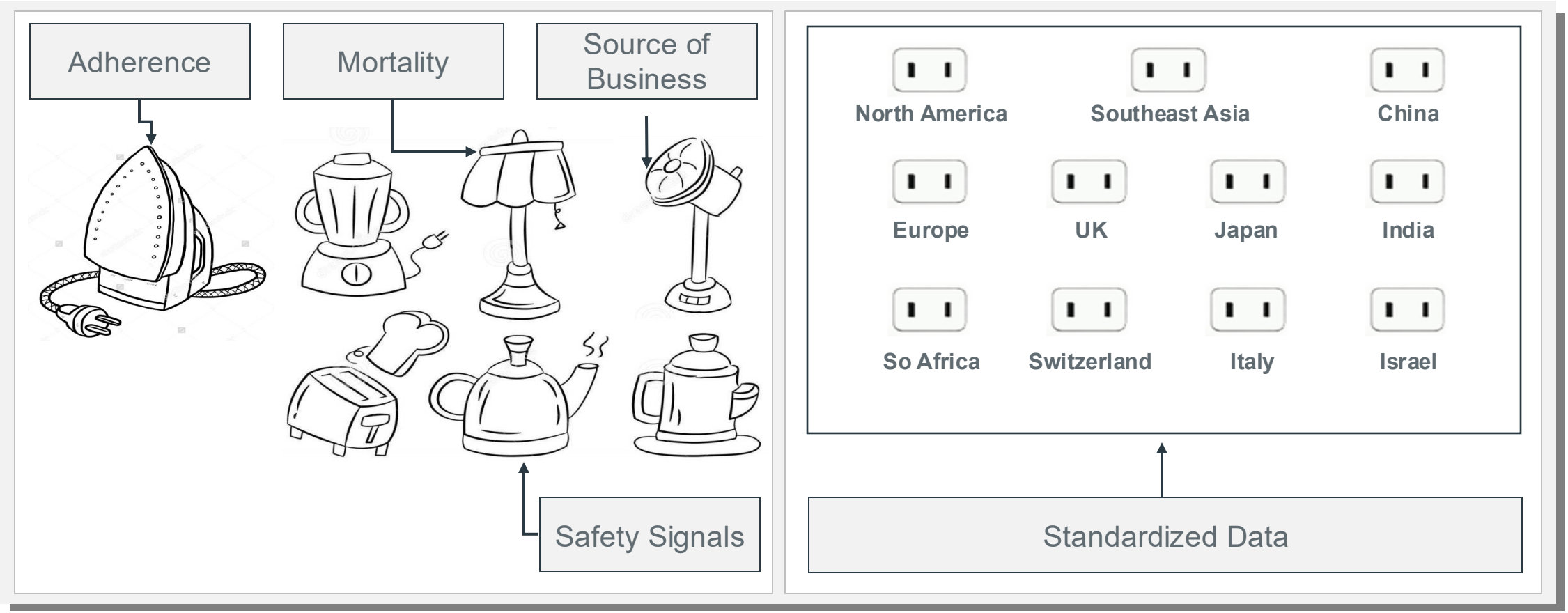
Current solution: multiple SAS/R coding for the same question





Unscalable
Expensive
Slow
Prohibitive for Routine Use

OMOP Solution: standard coding by type of question

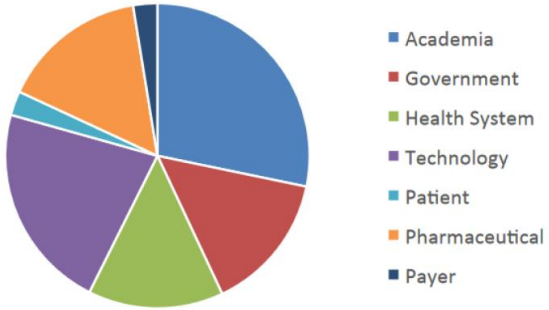


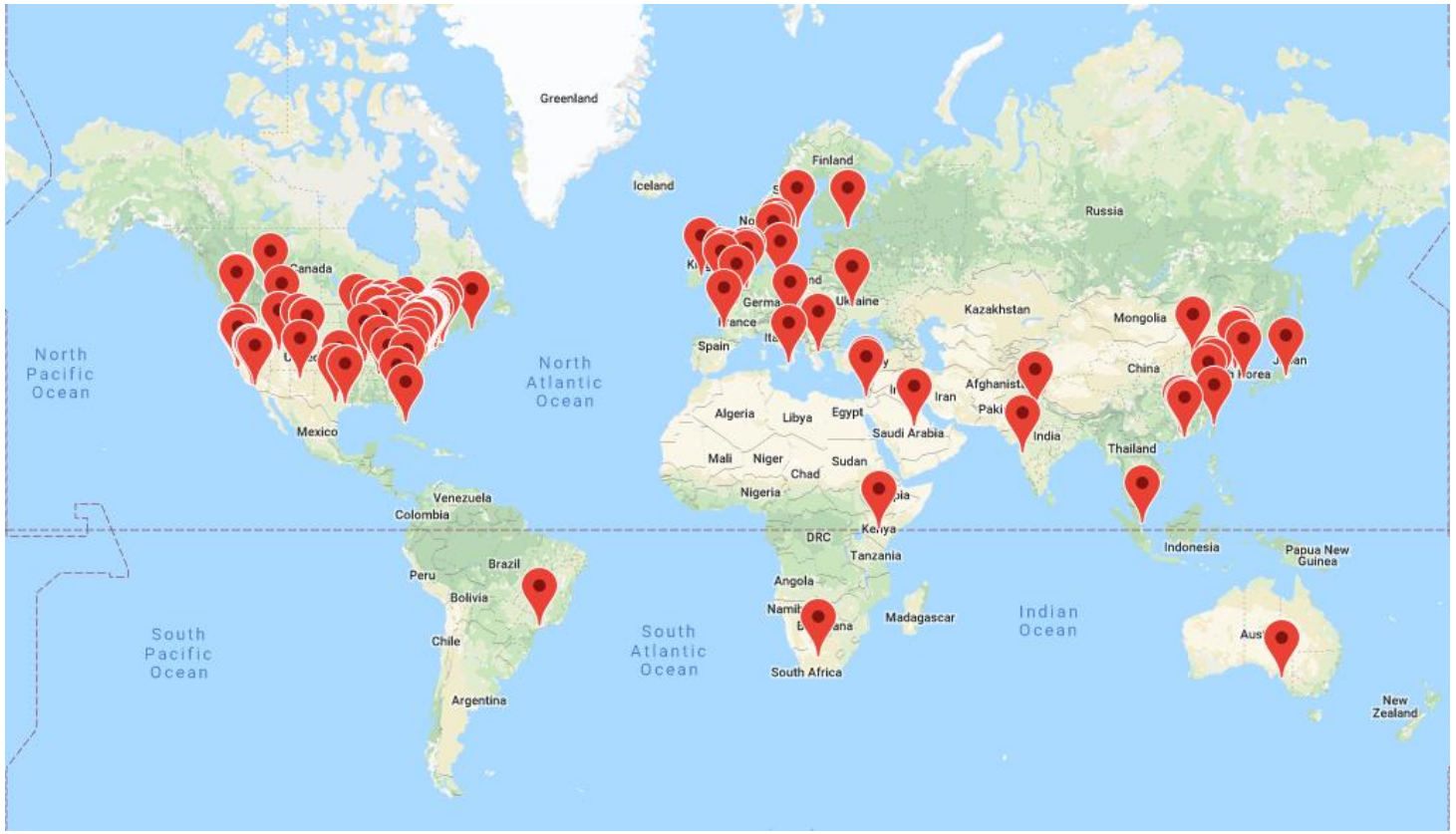
Introduction of OHDSI

OHDSI aims to improve the quality of healthcare by providing guidelines for a more harmonized approach to data science.

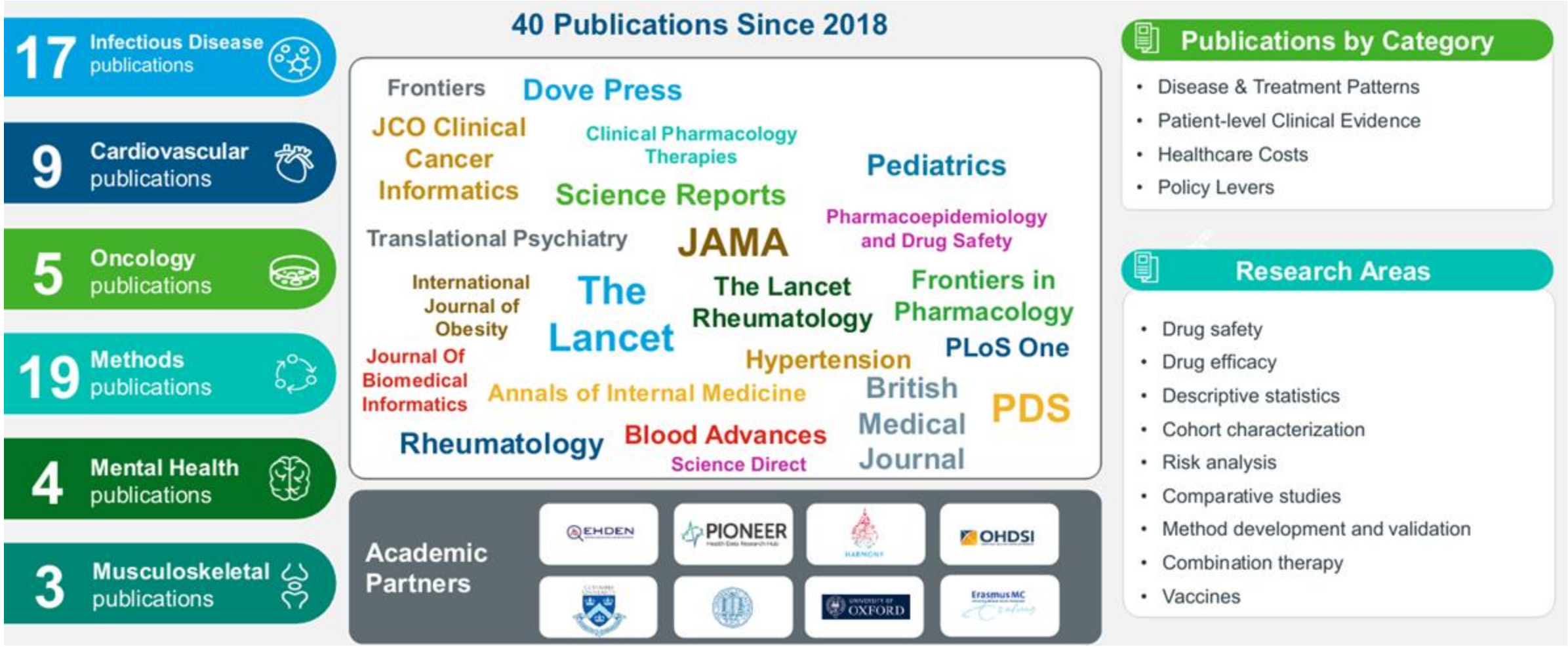
OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

- Open source
- Global
- > 320+ databases
- 2.7B patient records
- 34 countries





IQVIA OMOP Achievement



Case studies on the use of external comparators for regulatory decision-making.

IQVIA

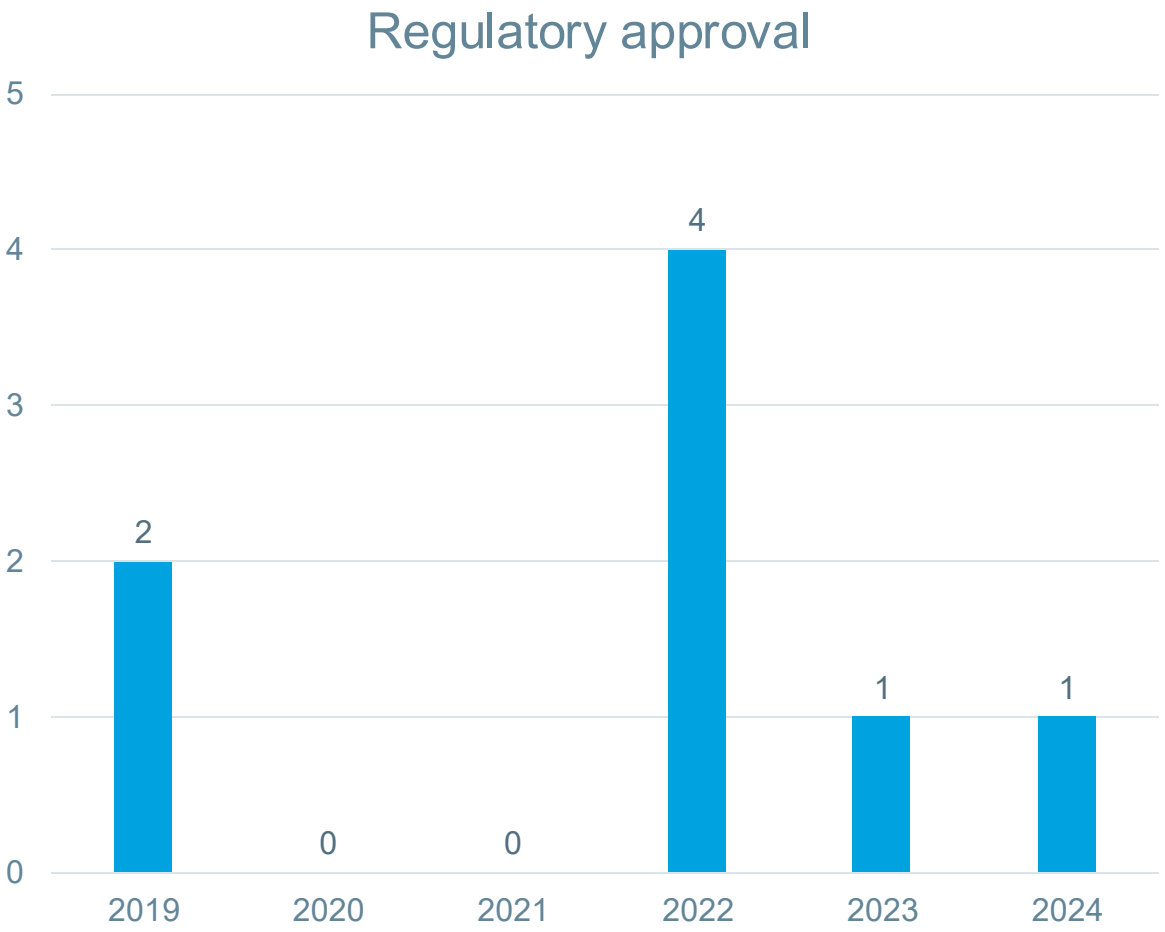
External comparator examples in FDA and EMA Submissions

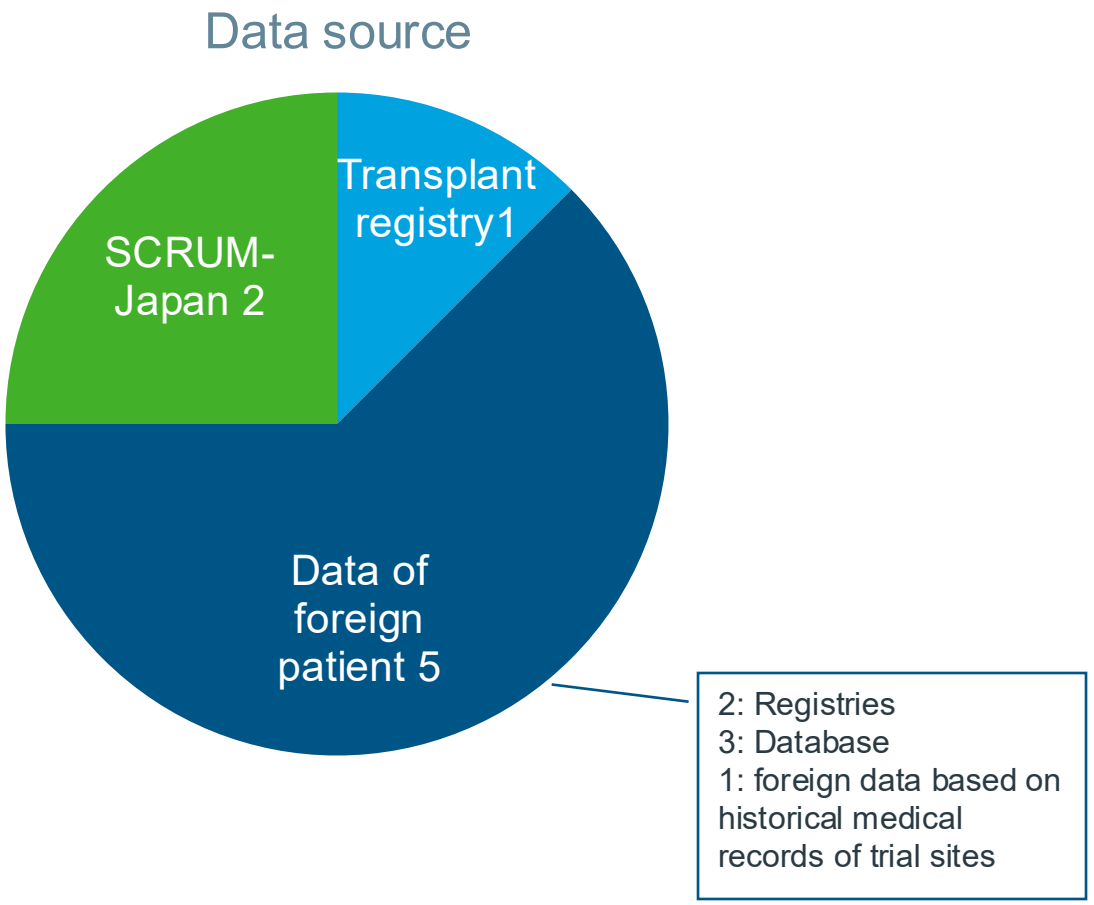
External comparator examples in FDA and EMA submissions in the last 5 years (not exhaustive)

Treatment	Company	Indication	Type of RWE	FDA Approved	EMA Approved
Avapritinib	Blueprint Medicines	Gastrointestinal stromal tumours	Chart review for contextualization	1/9/20	9/24/20
Koselugo	AstraZeneca	Neurofibromatosis-1	Retrospective natural history study	4/10/20	6/17/21
Libmeldy	Orchard Therapeutics	MLD	Retrospective natural history study	3/18/24	12/17/20
Monjuvi	Incyte	DLBCL	Observational, retrospective study	7/31/20	8/26/21
Nulibry	Origin Biosciences	Molybdenum cofactor deficiency type A	Retrospective natural history study	2/26/21	7/21/22
Prograf	Astellas	Organ rejection	U.S. Scientific Registry of Transplant Recipients	7/20/21	7/20/21
Orencia	Bristol-Myers Squibb	Acute graft versus host disease (aGVHD)	Blood and Marrow Transplant registry-based clinical study	12/15/21	5/21/07; reapproval withdrawn
Tabrecta	Novartis	NSCLC	Chart review for contextualization	5/6/20	6/22/22
Voxzogo	BioMarin Pharmaceutical Inc.	Achondroplasia	Observational, retrospective registry	11/19/21	8/6/21
Vijoice	Novartis	PIK3CA-Related Overgrowth Spectrum (PROS)	EPIK-P1: retrospective chart review study	4/6/22	Withdrawn

Regulatory approval using External Comparator in Japan

Following the guidance from 2022, there is an increasing trend. Out of 8, 7 are for orphan drugs





Source: Asano J, Sugano H, Murakami H, Noguchi A, Ando Y, Uyama Y. PMDA Perspective on Use of Real-World Data and Real-World Evidence as an External Control: Recent Examples and Considerations. Clin Pharmacol Ther. Apr 2025;117(4):910-919. doi:10.1002/cpt.3540

An External Comparator can add context when an internal control is not feasible, or sufficient to help demonstrate treatment benefit

Treatment Group

Internal Control

Not feasible because:

- Unethical to randomize
- Rare outcomes so impractical to randomize
- Patients unwilling to participate due to risk of not receiving drug

External Comparator

- Patient cohort derived from real-world data (RWD)
- Patients match the inclusion / exclusion criteria for the trial
- Benchmark the efficacy data from the treatment group in a cohort of similar patients

There are several threats of bias during a RWD external comparator study

Bias arising at time zero

Confounding by indication
Where RW and trial patients are treated with different intent (palliative vs curative)

Optimism bias
Physician interpretation may be overly optimistic, pushing patients to meet the eligibility criteria

Index date bias (selection bias)
RWD patients can have >1 potential index date, issues with systematically choosing one

Bias arising at data capture

Passive vs active reporting bias
Underrepresentation of AEs in RWD & differential reporting of SAEs and AEs

Unmeasured confounding
Missing RWD on baseline characteristics

Differential censoring of outcome
Differential censoring from competing event

Survival outcome misclassification
Recording lags and varying completeness of death

Bias arising at analysis

Mis-estimation of index date/line of therapy
Line of therapy is hard to accurately determine in RWD

Selection bias
Propensity score methods to trim patients with extreme values

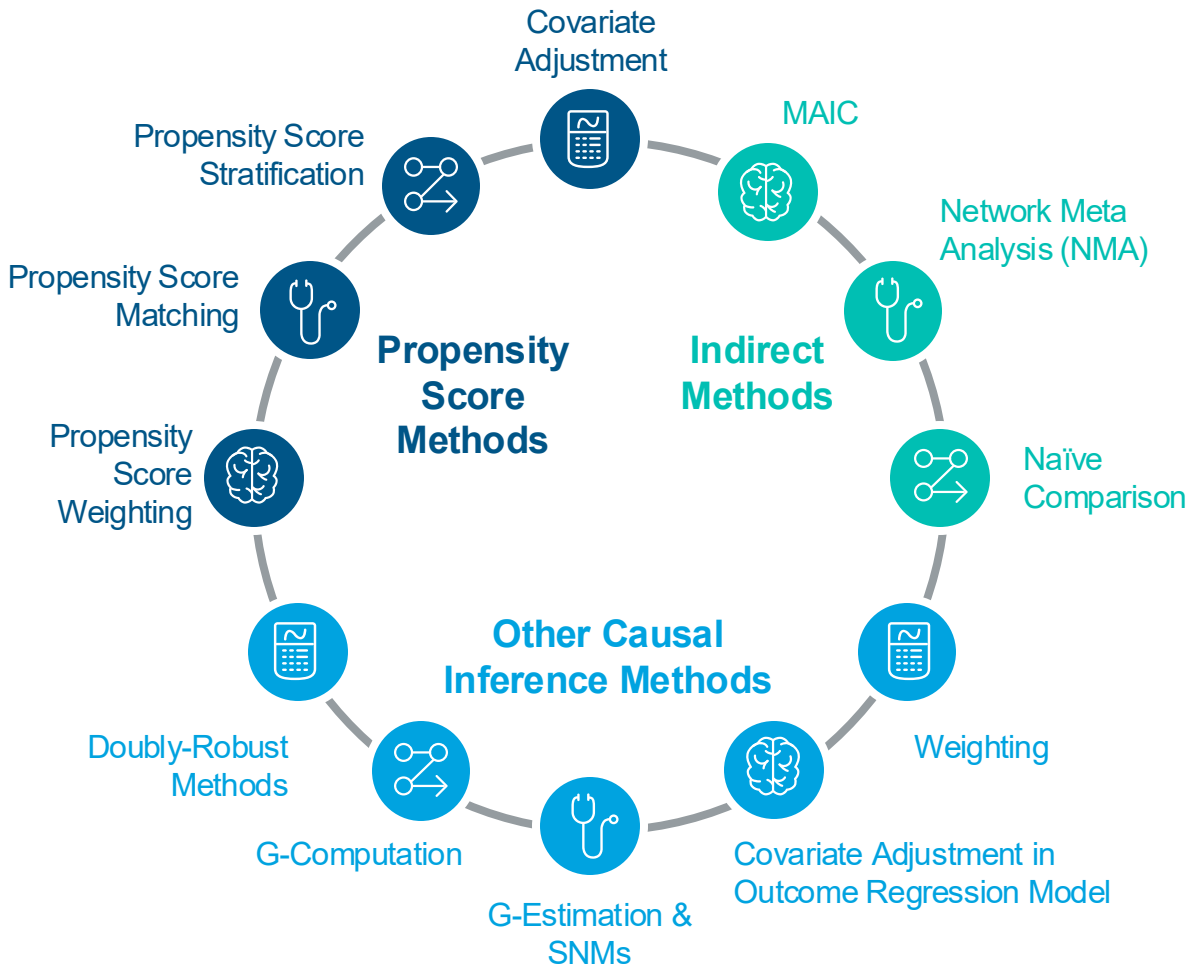
Misspecification of estimand
Matching RWD patients to the trial ITT patients or 'as-treated' patients

Immortal time bias
When the event cannot occur in all time between the index date and the outcome

Defining the right analysis for an External Comparator is critical

The most appropriate analytical method is dependent on the specifications of each study

Different Methodological Approaches:
(Not Exhaustive)



Pursuing EMA label expansion through a single-arm trial with an external comparator

CASE STUDY
Global Chart Review EC

Situation

- Client was pursuing the addition of a new indication to an oncology product in Europe
- Submitting pivotal single-arm trial data to the EMA
- Approached IQVIA to design and conduct a global external comparator study to benchmark single-arm trial data
- Client was looking for patients that would meet highly selective inclusion criteria
- Required strong scientific and regulatory strategy support

Solution

- Global real-world benchmark study using chart review data collection across 7 countries and >150 patients used to deliver the external comparator

Key Takeaways

- Innovative design included a historical RWD benchmark and a contemporaneous RWD benchmark
- Comprehensive regulatory strategy to facilitate timely data collection

Overview of using RWE as Basis for Label Extension

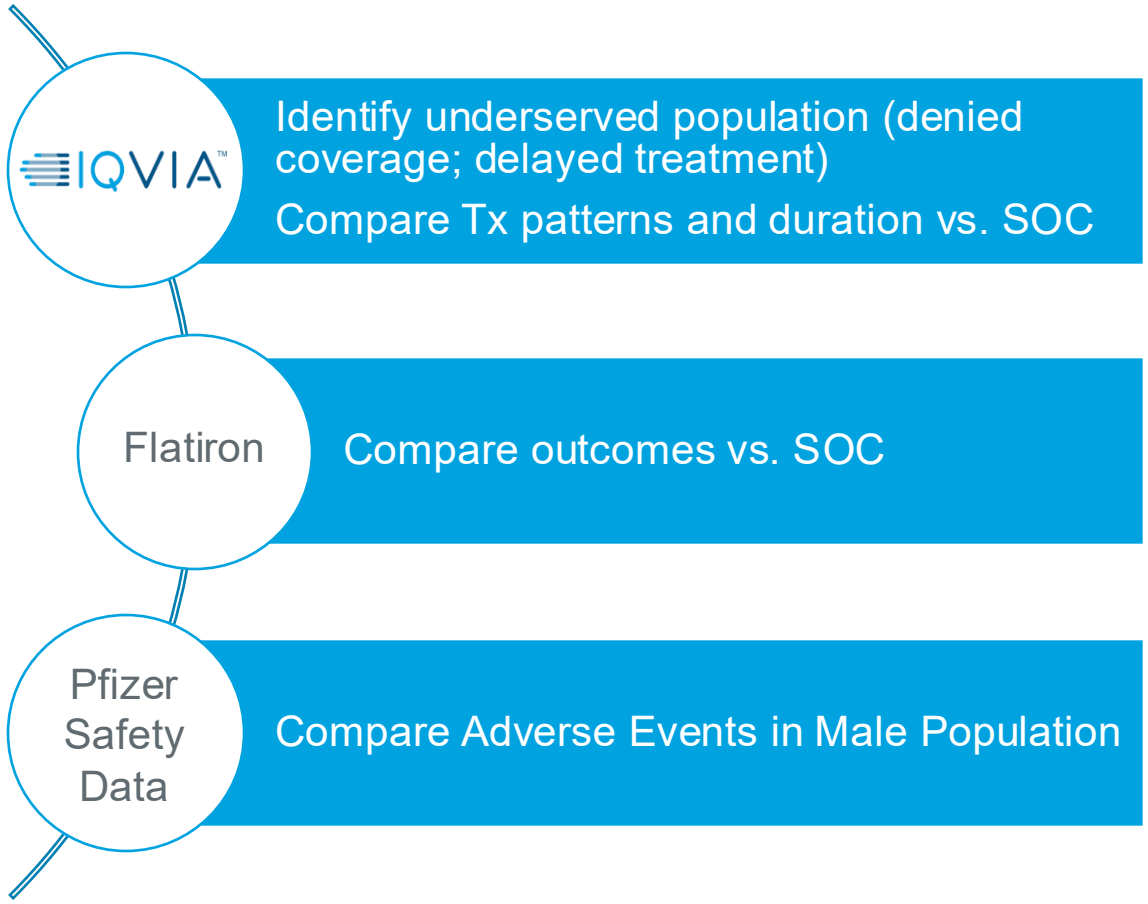
Male Breast Cancer Label Extension/ Ibrance

Pfizer's Challenge

- **Hard to find patient population** would make a traditional RCT time consuming and expensive
- **Male Patients comprise 1% of Breast cancer patients**

Real-World Data Approach

- Off-label prescription of the research drug **robustly captured in IQVIA RWD** enabled a database study approach with following value proposition.
- Three data sources were compiled independently by Pfizer and integrated to provide the FDA broad evidence of the treatment patterns and hurdles experienced by the male population as well as data points on safety and efficacy



IQVIA has a key role in the industry with its experience of executing and advancing the delivery of external comparator programs

>80

Projects to support External Comparator programs

>25

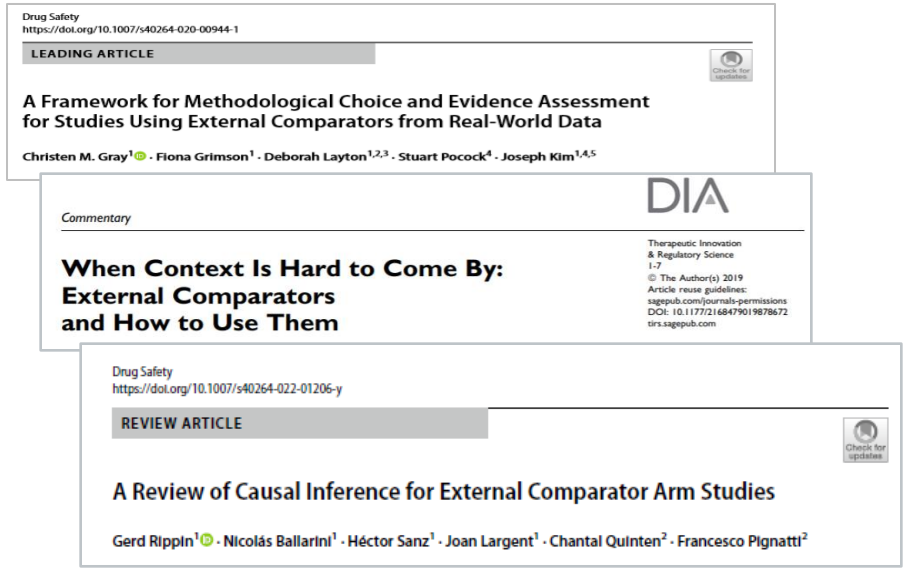
External Comparator studies executed or ongoing

with Regulatory, Payers and Operational expertise from IQVIA real-world teams on the ground in 100+ countries

>30

Peer reviewed publications, editorials, posters, articles

Developing standards for external comparator design



Drug Safety
https://doi.org/10.1007/s40264-020-00944-1

LEADING ARTICLE

A Framework for Methodological Choice and Evidence Assessment for Studies Using External Comparators from Real-World Data

Christen M. Gray[1] · Fiona Grimson[1] · Deborah Layton[1,2,3] · Stuart Pocock[4] · Joseph Kim[1,4,5]

Commentary

DIA

When Context Is Hard to Come By: External Comparators and How to Use Them

Therapeutic Innovation & Regulatory Science
1-7
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Drug Safety
https://doi.org/10.1007/s40264-022-01206-y

REVIEW ARTICLE

A Review of Causal Inference for External Comparator Arm Studies

Gerd Rippin[1] · Nicolás Ballarini[1] · Héctor Sanz[1] · Joan Largent[1] · Chantal Quinten[2] · Francesco Pignatti[2]

Collaborating with agencies and industry to set RWD standards

ENEPP

Sentinel Initiative

REAL-WORLD EVIDENCE ALLIANCE

FRIENDS of CANCER RESEARCH

Duke MARGOLIS CENTER for Health Policy

GETREAL INSTITUTE

Key takeaways

1

RWD is one of the important issues to solve drug loss in Japan

- Japanese health authorities are striving to reduce drug loss issues
- RWD could contribute to drug approval

2

Change in regulatory environment and future direction

- The regulatory environment allows RWD data for both registry and medical information purposes.
- The use of pseudonymized data for regulatory submission and data linkage at the national level.

3

IQVIA's expertise in external comparator programs around the world

- External comparator programs will be a key of using RWD for regulatory decision making in pediatric and rare indications

ご清聴ありがとうございました

PHSSRサミット「より強靭な保健医療システムの共創」ー すべての人のためのトランスフォーム・ケア@大阪・関西万博 2025年06月30日(月)　14:00～19:45

- イベントでは、国内外の専門家が集い、がんや糖尿病、循環器疾患、呼吸器疾患などの非感染性疾患（NCDs）に対する早期対応の重要性に加え、医療DXの進展による医療の質向上やアクセス改善、さらにエビデンスに基づく政策立案の実現について広く議論します。