ISPOR Europe 2022
6-9 November 2022
Vienna, Austria and Virtual

USE OF REAL-WORLD EVIDENCE TO SUPPORT HEALTH TECHNOLOGY ASSESSMENT IN UNITED STATES, EUROPE AND JAPAN

8 NOVEMBER, 2022

Session Goals & Objectives

- To provide an overview of current use of RWE in HTA processes in Europe, United States, and Japan
- To share results from analysis to evaluating the use of RWE in HTA processes globally using HTA accelerator®
- To highlight opportunities to increase use of RWE in HTA processes

Today's Speakers

Shirley Wang, PhD, MSc

Associate Professor of Medicine at Harvard Medical School and in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital, US

Massoud Toussi, MD, PhD, MBA

Global Category Lead, Evidence from Secondary Data, Real World Evidence

Solutions, IQVIA, France

Eric Yu, MPharm, MSc, LLM

Real World Evidence

Solutions, IQVIA, Japan

Jasmanda Wu, PhD, MPH

Global Health Economics and Outcomes Research & Real-World Evidence, Insmed, US

Presentation Topics

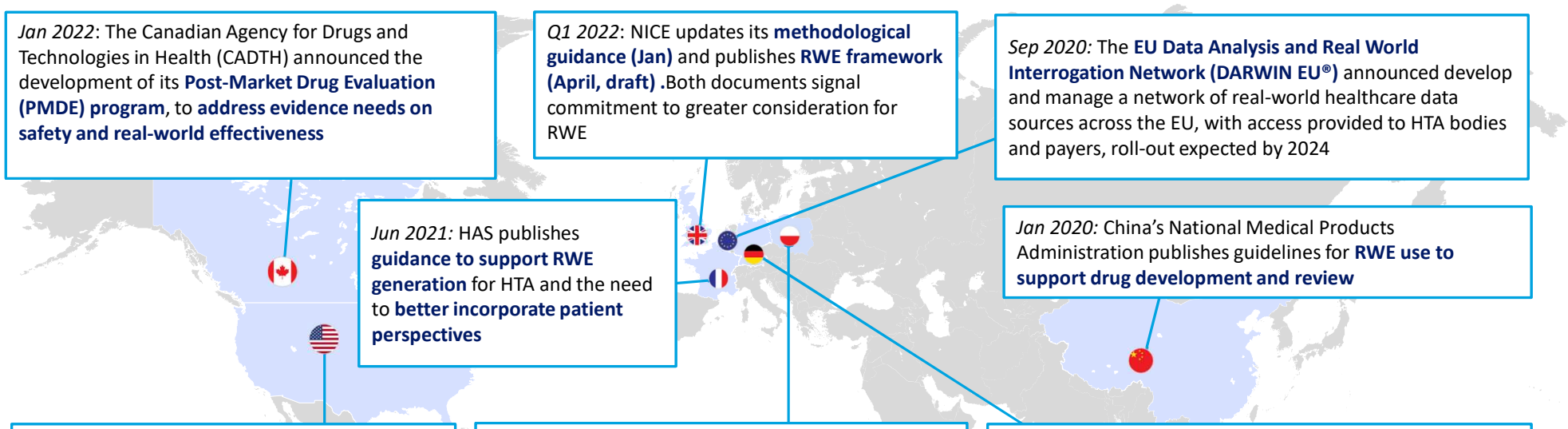
- Use of RWE to support HTA in United States, Europe and Japan – A brief analysis – by Eric Yu, MPharm, MSc, LLM
- Literature review of the use of RWE in HTA processes in United States, Europe and Japan – by Jasmanda Wu, PhD, MPH
- Dynamics, drivers and barriers of use of RWE in HTA – by Massoud Toussi, MD, PhD, MBA
- Supporting HTA by strengthening transparency and reproducibility of real-world evidence studies – by Shirley Wang, PhD, MSc

Use of Real-World Evidence to Support Health Technology Assessment in United States, Europe and Japan – A brief analysis

ISPOR Vienna 8 November 2022

Eric Yu, MPharm MSc LLM
Principal, Global HEOR HTA – Tokyo

Health Technology Assessment (HTA) and regulatory bodies worldwide recognize the importance of real world evidence (RWE)



Jan 2022: The Canadian Agency for Drugs and Technologies in Health (CADTH) announced the development of its **Post-Market Drug Evaluation (PMDE) program**, to **address evidence needs on safety and real-world effectiveness**

Q1 2022: NICE updates its **methodological guidance (Jan)** and publishes **RWE framework (April, draft) .**Both documents signal commitment to greater consideration for RWE

Sep 2020: The **EU Data Analysis and Real World Interrogation Network (DARWIN EU®)** announced develop and manage a network of real-world healthcare data sources across the EU, with access provided to HTA bodies and payers, roll-out expected by 2024

Jun 2021: HAS publishes **guidance to support RWE generation** for HTA and the need to **better incorporate patient perspectives**

Jan 2020: China's National Medical Products Administration publishes guidelines for **RWE use to support drug development and review**

Jan 2020: ICER updates its methods and procedures for Value Assessment Framework:

- **Augmented use of RWE**, through new collaborative partnerships (e.g. with Aetion)
- **Re-review of drugs** approved under accelerated approval **after 24 months, informed by RWE**

Oct 2020: **Innovative treatments in oncology and rare diseases** may be reimbursed via accelerated procedure with **further data collection in registries** according to the 'Act on the Medical Fund'

- So far, only 2 products are covered: **Oxlumo** for primary hyperoxaluria type 1 (PH1) and **Givlari** for acute hepatic porphyria

Jul 2019: Concept report on RWE use in HTA suggests the **use of high-quality patient registries in comparative settings**, randomised or not

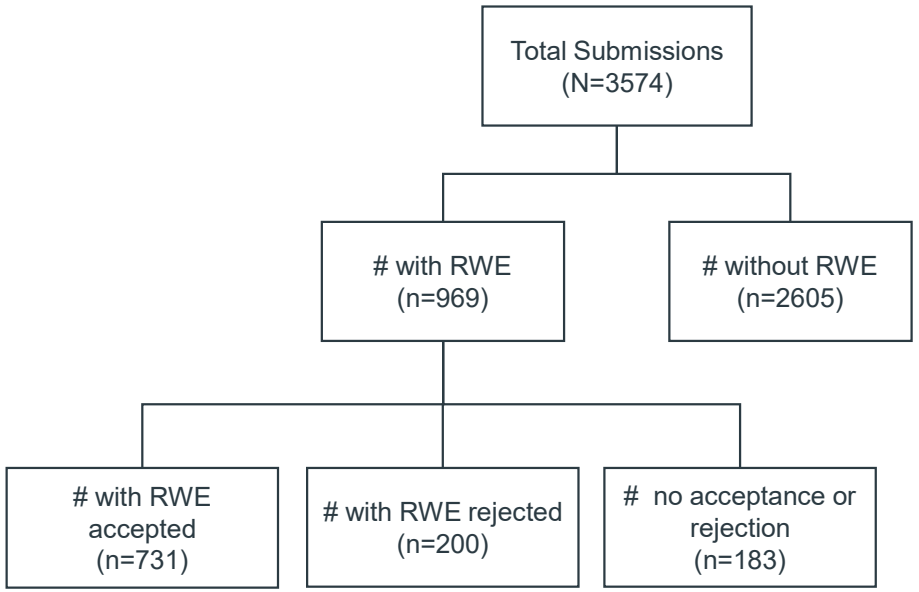
Feb 2021: GBA mandate that **Novartis must complete a registry-based study** for Zolgensma, additional products are under consideration

2017-2021

Published submissions with RWE included

Country	#submissions 2017-2021
Brazil	152
Canada	816
China	4
France	728
Germany	749
Italy	153
Japan	13
Spain	269
United Kingdom	678
United States of America	12
Total	**3574**

Published submissions with RWE 2017-2021

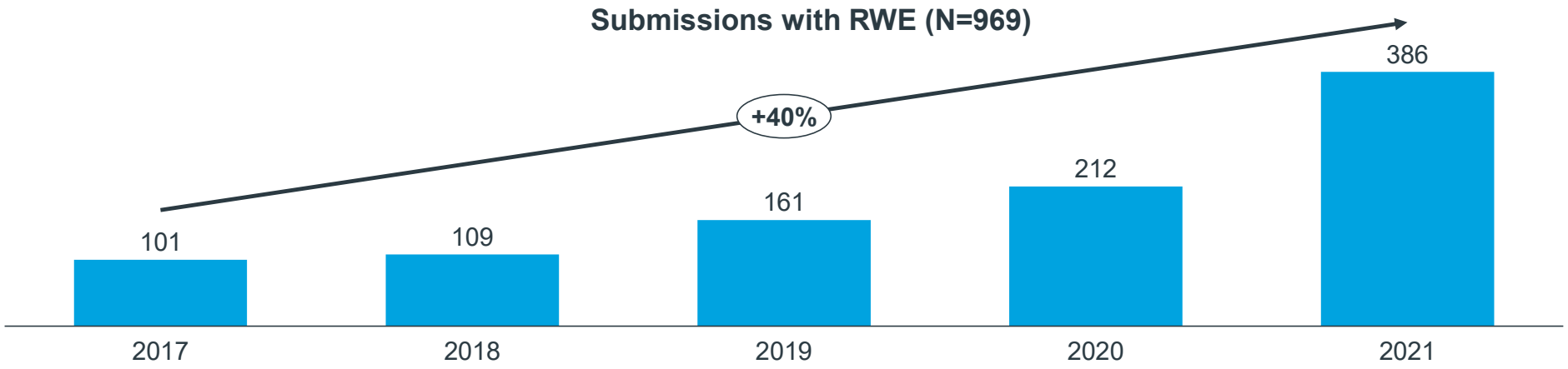


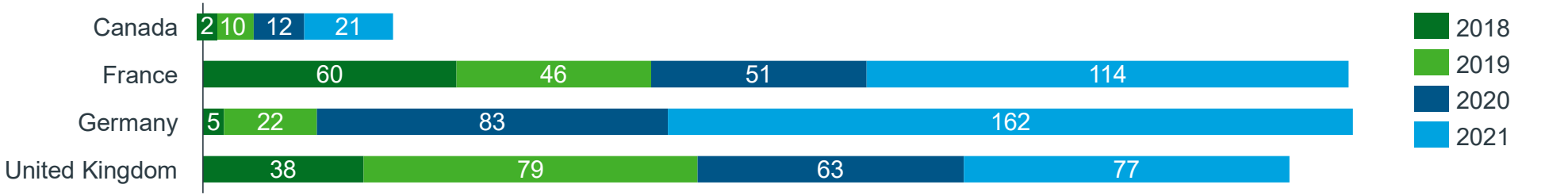
Note: Numbers not mutually exclusive

Source: IQVIA HTA Accelerator
Single Technology Assessment; original submissions, indication extensions and resubmissions between Jan 1st 2017- 31st Dec 2021 with RWE included and published by bodies
Counts reflect multiple sources of RWE contained in a submission with some being accepted whilst others not

2017-2021

Submissions with RWE are accelerating



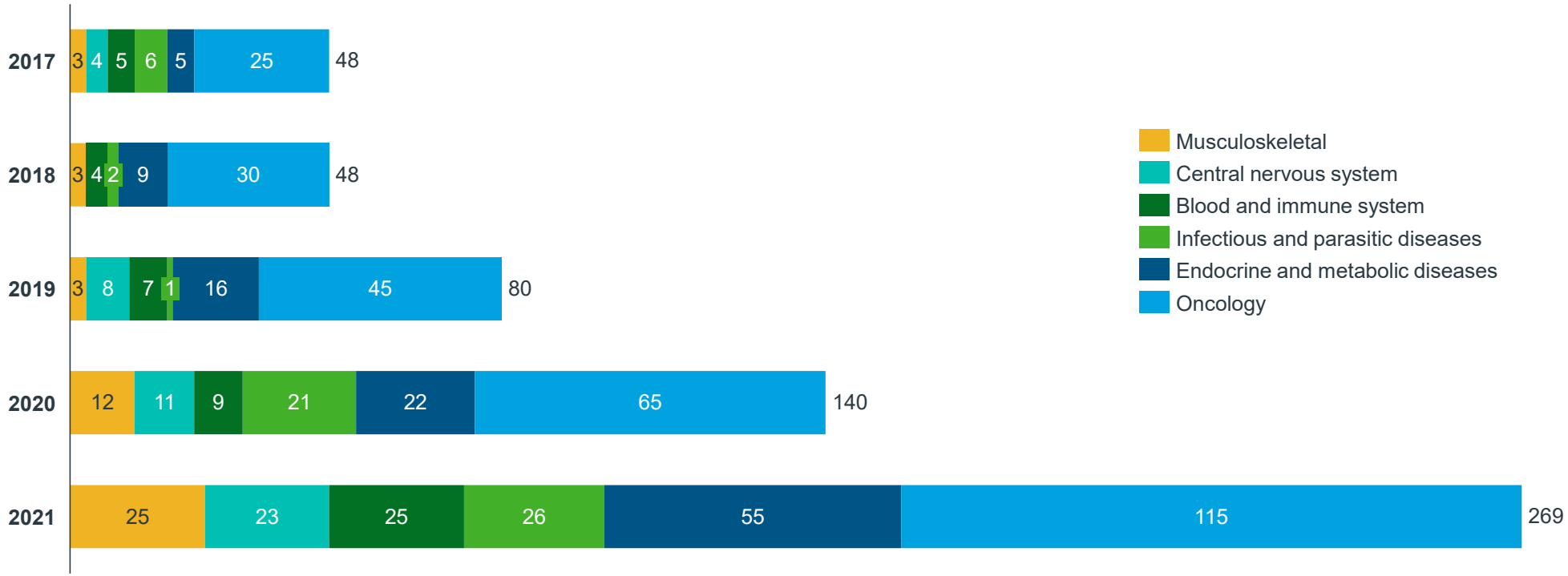


Brazil, China, Italy, Japan, Spain, US – omitted due to low numbers & scaling

Source: IQVIA HTA Accelerator
Single Technology Assessment; original submissions, indication extensions and resubmissions between Jan 1st 2017- 31st Dec 2021 with RWE included and published by bodies

2017-2021

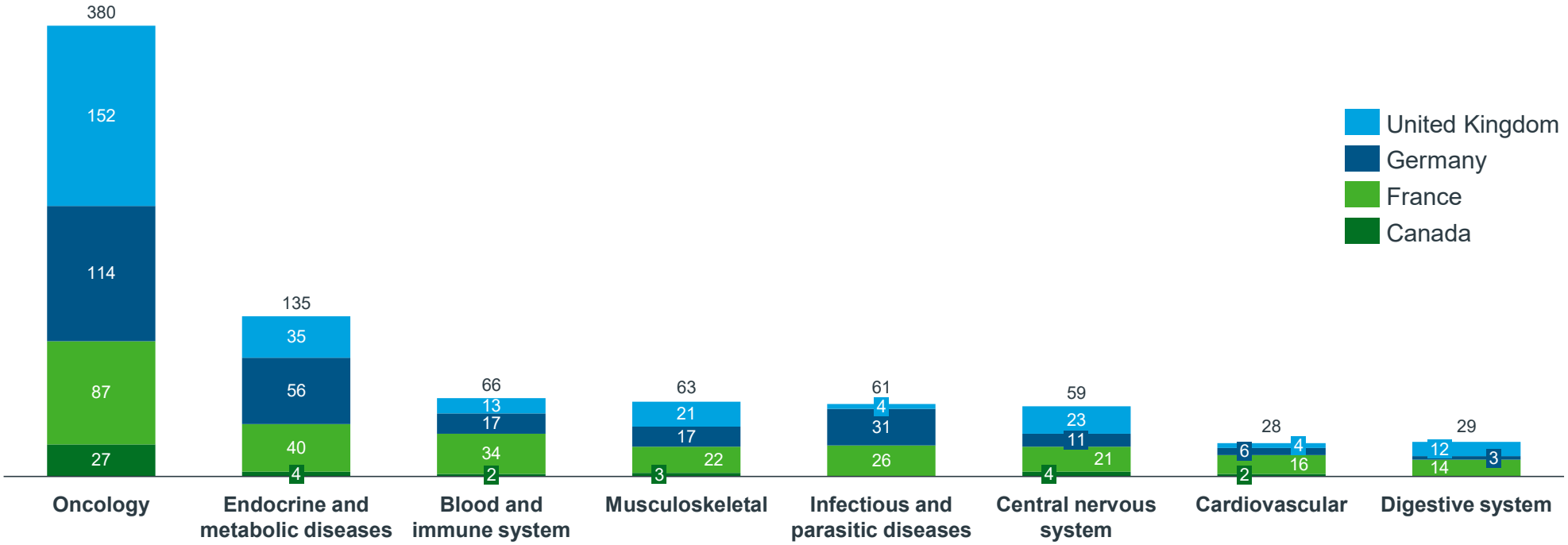
Submissions accepted containing RWE by year and therapeutic area



Source: IQVIA HTA Accelerator
Single Technology Assessment; original submissions, indication extensions and resubmissions between Jan 1st 2017- 31st Dec 2021 with RWE included and published by bodies

2017-2021

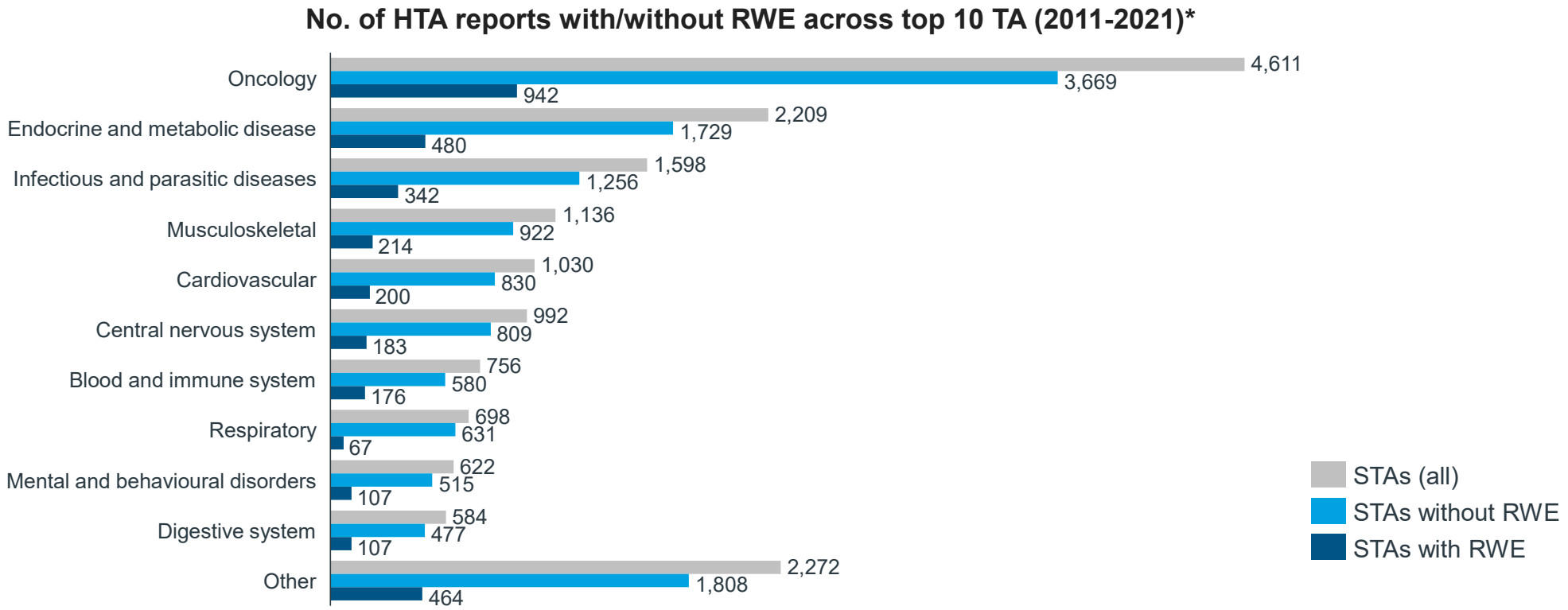
Submissions accepted containing RWE by therapeutic area & country



Source: IQVIA HTA Accelerator
Single Technology Assessment; original submissions, indication extensions and resubmissions between Jan 1st 2017- 31st Dec 2021 with RWE included and published by bodies

2011-2021

RWE has been mostly submitted as part of oncology HTAs, however RWE has also been used for other TAs



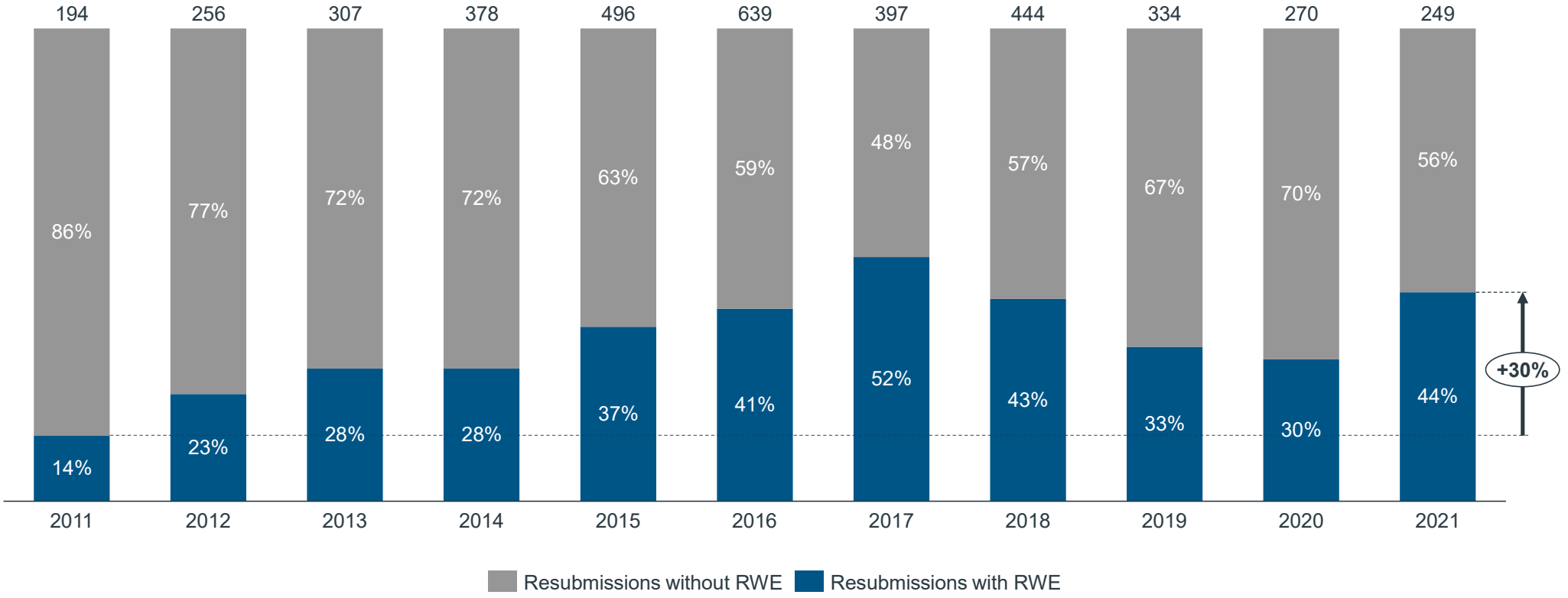
Source: IQVIA HTA Accelerator. HTA reports (single drug assessments) published January 1st, 2011 until December 31st, 2021
*Count reflects number of RWE used in all HTA reports including single submission and re-submission and as such one RWE study may have supported different areas and multiple RWE sources may have been considered in the same reports
Other therapeutic areas include dermatology, ophthalmology, gynecology, urogenital, ENT and other.
ISPOR Europe 2022 – Vienna: Use of Real-World Evidence to Support Health Technology Assessment in United States, Europe and Japan – A brief analysis

2011-2021

Using RWE is more common in resubmissions and there was an increase in the last 10 years observed as well

Resubmissions only

Number of HTA resubmissions where RWE was used (2011-2021)*



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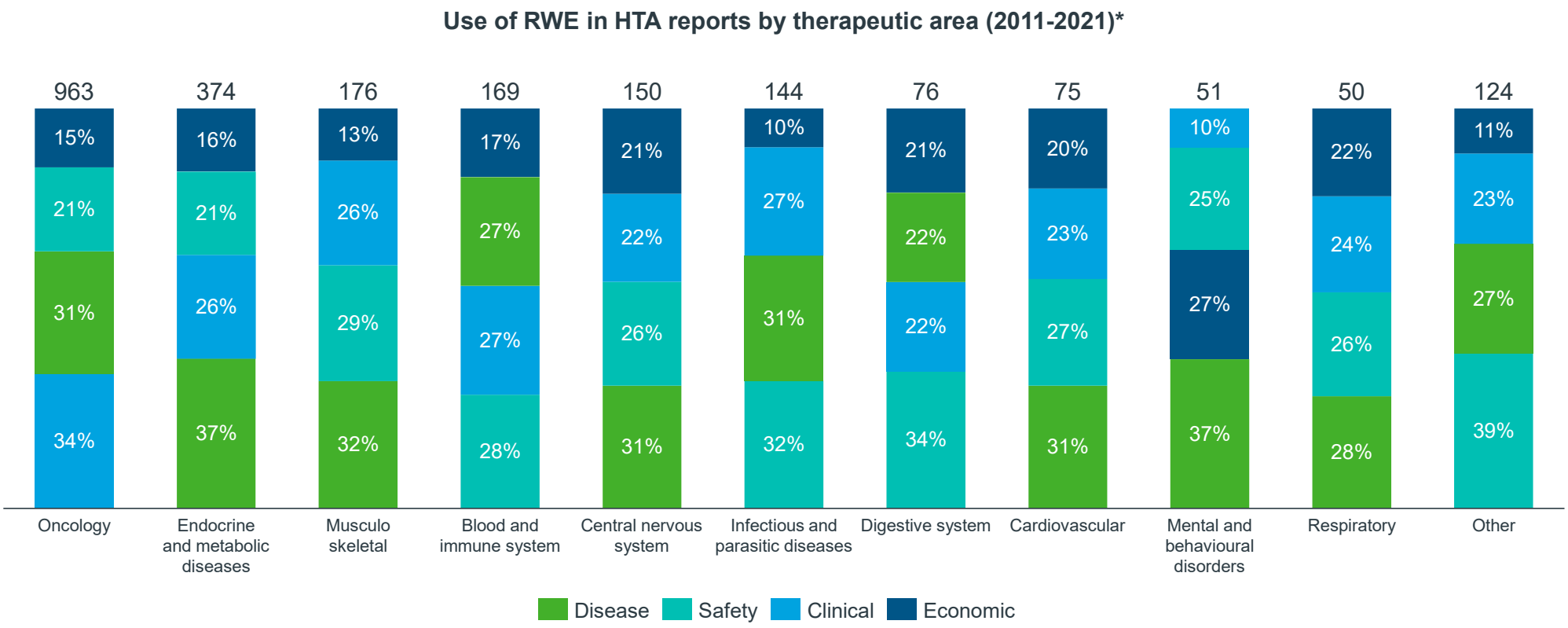
2011-2021

With the exception of oncology, RWE is mostly used to supplement evidence on disease background and safety



Source: IQVIA HTA Accelerator. HTA reports (single drug assessments) published January 1st, 2011 until December 31st, 2021, for which details of submitted RWE were available (n=1,508 HTA reports)
*Count reflects number of RWE used in all HTA reports including single submission and re-submission and as such one RWE study may have supported different areas and multiple RWE sources may have been considered in the same reports. Other therapeutic areas include dermatology, ophthalmology, gynecology, urogenital, ENT and other.

2017-2021

What is successfully accepted and why?

Top 15 areas where RWE is submitted and source in accepted submissions

Area submitted in accepted submission(N=725)	
Safety	349
Epidemiology	233
Effectiveness	149
Patient population	60
QoL	51
Utility	46
Treatment patterns	43
Burden of illness	35
Resource utilisation	33
Extrapolation of outcome	33
Extrapolation of OS	25
Natural history of disease	23
Treatment costs	23
Proxy comparator	20
Economic analysis	20

Source submitted in accepted submission (N=545)	
Patient disease registry	206
Observational study	172
Retrospective cohort study	90
Pharmacovigilance data	86
Administrative data	54
Insurance claim	48
Prospective cohort study	42
Electronic patient record	29
Retrospective chart review	25
Population health survey	21
Cross-sectional study	20
Systematic physician survey/interview	17
Prescription	16
Hospitalization	14
Systematic patient survey/interview	13

Rationale for rejection (N=103)	
Bias/risk	57
Differences in patient populations	25
Insufficient data	17
Study population not well defined	17
Small population	13
Study design not well defined	4

Source: IQVIA HTA Accelerator
Single Technology Assessment; original submissions, indication extensions and resubmissions between Jan 1st 2017- 31st Dec 2021 with RWE included and published by bodies
Counts reflect multiple sources of RWE contained in a submission with some being accepted whilst others not – numbers not mutually exclusive

Takeaways & thoughts

1 **RWE continues to play an increasingly important role with volumes and rates of submissions with RWE increasing**

- Managing and tracking evidence generation becomes a greater challenge for industry
- For payers more evidence to sift through

2 **Understanding what RWE is meaningful to industry and HTA bodies and payers will become evermore complex to manage for all stakeholders**

- Knowing & predicting what evidence to generate – role for new decision support tools utilising ML and
- Early engagement with payers
- Integrated evidence planning around a product

3 **Diversification of accepetable RWE and TAs supported**

- Added layer of complexity to source & assessing suitability of new sources e.g. representativeness and inclusiveness
- Attendant methodological considerations
- Continuing necessity for transparency and local context

Literature Review of Use of RWE in HTA Processes in Europe, United States and Japan

Jasmanda Wu, PhD, MPH, FISPE

8 November, 2022

OUTLINE

- Use of RWE in HTA processes in Europe
- Use of RWE in HTA processes in US
- Use of RWE in HTA processes in Japan
- Summary

EU Payers and HTA Authorities

Country	Key agencies	Details
 UK	• NICE • SMC • AWMSG	• Clinical and cost-effectiveness are assessed • Cost-effectiveness is assessed using QALYs; the key threshold is about £30,000 per QALY • The SMC reviews all new products before launch (it is typically the first formal HTA to be completed)
 France	• TC • CEPS • HAS	• A dossier is submitted to the TC after marketing authorization. TC strongly prefers head-to-head data • Incremental therapeutic benefit (ASMR) is assessed and the reimbursed population is identified. • Prices are negotiated with CEPS on the basis of the ASMR and SMR ratings, and may include price–volume agreements with payback clauses • HAS is typically responsible for developing treatment and prescribing guidelines

Country	Key agencies	Details
 Germany	• G-BA • IQWiG	• Free pricing applies for the first 12 months; the price is negotiated after the benefit assessment • The AMNOG legislation introduced in 2011 requires submission of a benefit dossier to the G-BA
 Italy	• AIFA • UVEF	• A file is submitted to AIFA • Products are reimbursed on Class H or A list • Budget impact and head-to-head data are important • Risk-sharing agreements are extensively used, particularly in oncology • Regional autonomy: UVEF is responsible for HTAs in the Veneto region
 Spain	• Ministry of Health • Regional HTA agencies	• Central HTA agency assesses clinical profile and daily cost • HTAs occur mostly at the regional level, with increasing use of cost-effectiveness and coordination at the hospital level • Cost-effectiveness is likely to be required in future

Courtesy of Dr Driss Berdai, EURORDIS Summer School, 2015

Comparison of Submission Requirements

Work stream	Comments
Therapeutic benefit	• Prefer hard efficacy endpoints; however, surrogate endpoints if supported by guidelines/KOLs
CE modeling	• Cost per QALY gained is preferred ICER. UK threshold usually £30,000 but rises to £50,000 for EoL treatments €
Budget impact modeling	• Price–volume agreements or caps in some countries • Clear ability to define the eligible patient population
HRQoL data	• Utilities are used • HRQoL data may have an impact particularly in chronic diseases and EoL considerations
Head-to-head data vs SOC	• Establishing the SOC or comparator important
Real-world observational data	• Real-world data may help achieve market access
Innovation	• Innovation is a key factor in P&R and can have a significant impact on price

Key requirement Nice to have Not required

UK

Italy

Germany

Spain

France

Courtesy of Dr Driss Berdai, EURORDIS Summer School, 2015

Real-world evidence use in assessments of cancer drugs by NICE

Ash Bullement[1], Tanja Podkonjak[2], Mark J. Robinson[2], Eugene Benson[2], Ross Selby[3], Anthony J. Hatswell[1,4] and Gemma E. Shields[5,6]

[1]Delta Hat, Nottingham, UK; [2]Takeda UK Ltd, London, UK; [3]Global Oncology Business Unit, Takeda Pharmaceuticals International Co., London, UK; [4]Department of Statistical Science, University College London, London, UK; [5]Manchester Centre for Health Economics, The University of Manchester, Manchester, UK and [6]Azurite Research Ltd, Sheffield, UK

Objective. To establish how real-world evidence (RWE) has been used to inform single technology appraisals (STAs) of cancer drugs conducted by the National Institute for Health and Care Excellence (NICE).

Methods. STAs published by NICE from April 2011 to October 2018 that evaluated cancer treatments were reviewed. Information regarding the use of RWE to directly inform the company-submitted cost-effectiveness analysis was extracted and categorized by topic. Summary statistics were used to describe emergent themes, and a narrative summary was provided for key case studies.

Results. Materials for a total of 113 relevant STAs were identified and analyzed, of which nearly all (96 percent) included some form of RWE within the company-submitted cost-effectiveness analysis. The most common categories of RWE use concerned the health-related quality of life of patients (71 percent), costs (46 percent), and medical resource utilization (40 percent). While sources of RWE were routinely criticized as part of the appraisal process, we identified only two cases where the use of RWE was overtly rejected; hence, in the majority of cases, RWE was accepted in cancer drug submissions to NICE.

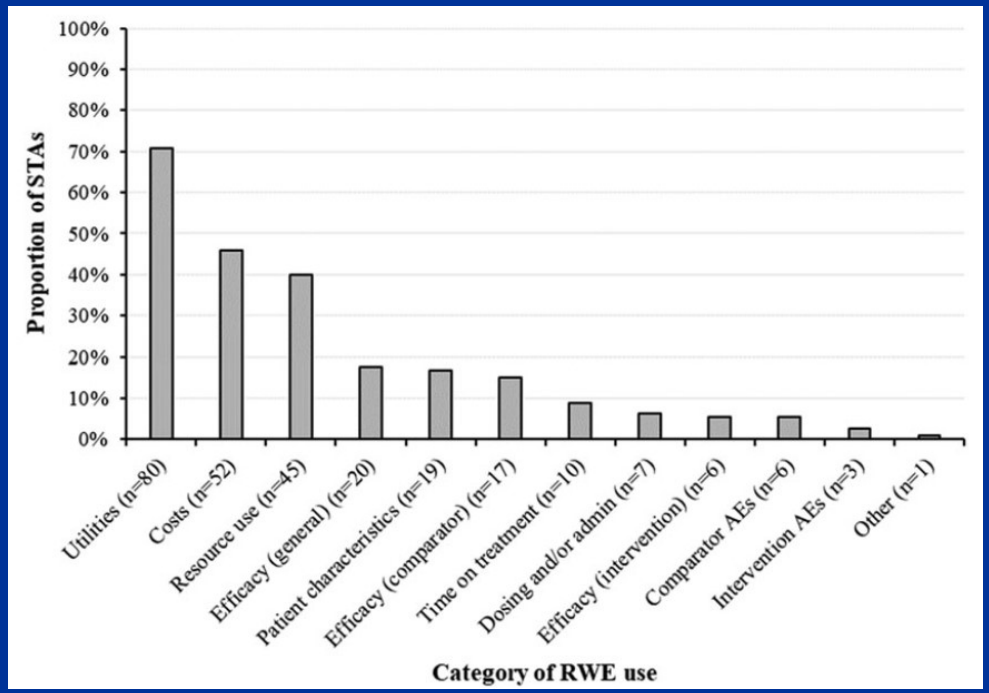
Discussion. RWE has been used extensively in cancer submissions to NICE. Key criticisms of RWE in submissions to NICE are seldom regarding the use of RWE in general; instead, these are typically concerned with specific data sources and the applicability of these to the decision problem. Within an appropriate context, RWE constitutes an extremely valuable source of information to inform decision making; yet the development of best practice guidelines may improve current reporting standards.

- Evidence submissions from companies to NICE typically include
  - analysis of clinical trial data, economic modeling, and the synthesis of other relevant information, such as clinical expert opinion and epidemiological data
- This study focused on the use of RWE to inform the company's cost-effectiveness analysis only
- Single technology appraisals (STAs) published by NICE from April 2011 to October 2018 that evaluated cancer treatments were reviewed
- Extraction form was designed to capture data regarding the use of RWE to inform cost-effectiveness modeling
- Categories of RWE use were extracted to establish which aspects of submitted information is most frequently supported, e.g. quantification of costs, patient outcomes, HRQoL

International Journal of Technology Assessment in Health Care 2020;36:388-394

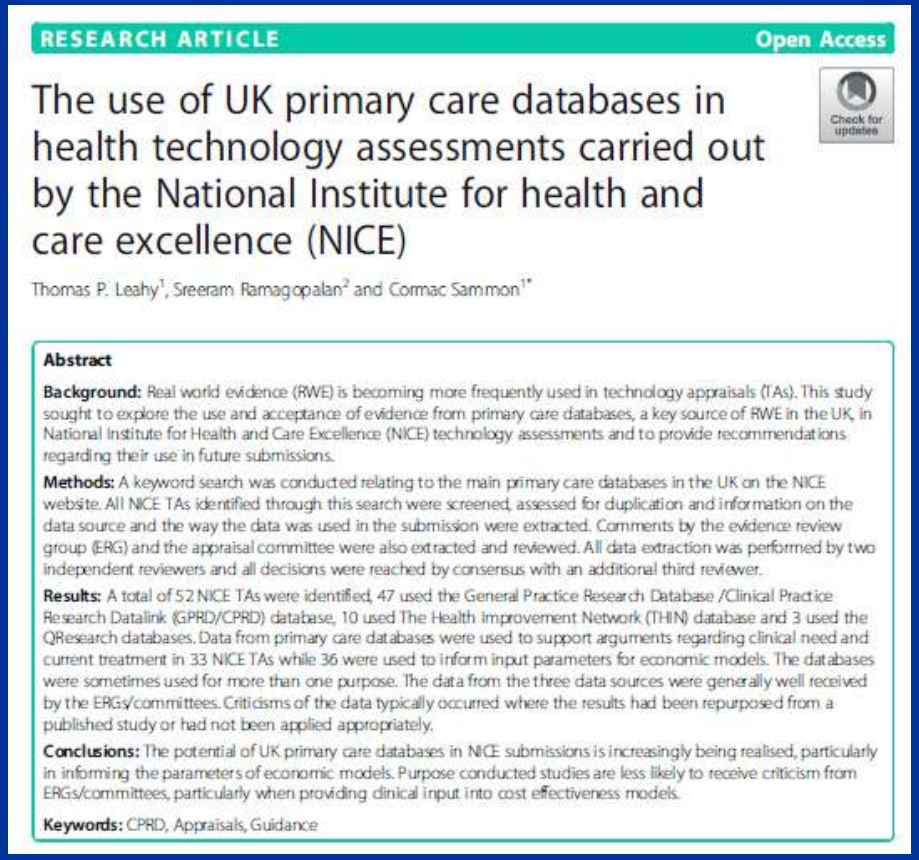
Real-world Evidence Use in Assessments of Cancer Drugs by NICE

- Materials for a total of 113 STAs were identified and analyzed
  - Nearly all (96 percent) included some form of RWE within the company submission
- The most common categories of RWE use were HRQoL (71%), costs (46%), and medical resource utilization (40%)
- RWE has been used extensively in cancer submissions to NICE
- The key criticisms raised by NICE that should be addressed prior to submission
  - providing a clear justification of the similarities between the trial population and patients considered within the RWE



Case Studies of RWE Use in NICE Appraisals

Appraisal	Data gap	Company approach (uses of RWE)	Perception by ERG/ NICE committee	Implications
TA269 Vemurafenib Melanoma (2012)	Survival outcomes and health-related quality of life	The company presented survival extrapolations using data from the Surveillance, Epidemiology, and End Results (SEER) registry to inform modeled hazard of death beyond duration of clinical trial follow-up period (8). Utility values from a standard gamble study were also used (9)	While the Committee accepted the idea of using external evidence to support decision making, each of the preferred sources was disputed by the ERG and Committee. More specifically, data from an observational study by Balch et al. (10) were preferred over the SEER registry data as the Balch data allowed for adjustment according to staging of disease, and utility values from another study were preferred over the standard gamble study (10;11)	Check for alternative RWE sources, in particular where alternative analytical approaches may be taken across different sources (e.g. matching). Ensure alignment of utility values with NICE reference case
TA378 Ramucirumab Gastro-esophageal cancer (2016)	Treatment patterns and medical costs	The company included findings from a chart review to quantify the costs associated with best supportive care, and a costing study of UK patients receiving palliative care to capture the costs incurred by patients towards the end of life (12). The company also conducted a survey to establish real-world treatment patterns in order to determine relevant comparator treatments used in UK clinical practice	The costing studies were accepted as appropriate for informing decision making. However, the ERG commented that the survey regarding treatment patterns was based on data from June to July 2013 (FAD published in November 2015); and that since this time favorable results from another clinical study of currently used docetaxel (COUGAR II) may have led to increased real-world use of taxanes in general. The ERG undertook a number of analyses to incorporate comparators excluded by the company on the basis of this survey, which was considered to be outdated	Assess the relevance of historical RWE to current practice, especially when there has been published documentation that may influence treatment patterns. If changes have occurred, ensure these are described with associated implications



RESEARCH ARTICLE Open Access

The use of UK primary care databases in health technology assessments carried out by the National Institute for health and care excellence (NICE)

Thomas P. Leahy[1], Sreeram Ramagopalan[2] and Cormac Sammon[1*]

Abstract

Background: Real world evidence (RWE) is becoming more frequently used in technology appraisals (TAs). This study sought to explore the use and acceptance of evidence from primary care databases, a key source of RWE in the UK, in National Institute for Health and Care Excellence (NICE) technology assessments and to provide recommendations regarding their use in future submissions.

Methods: A keyword search was conducted relating to the main primary care databases in the UK on the NICE website. All NICE TAs identified through this search were screened, assessed for duplication and information on the data source and the way the data was used in the submission were extracted. Comments by the evidence review group (ERG) and the appraisal committee were also extracted and reviewed. All data extraction was performed by two independent reviewers and all decisions were reached by consensus with an additional third reviewer.

Results: A total of 52 NICE TAs were identified, 47 used the General Practice Research Database /Clinical Practice Research Datalink (GPRD/CPRD) database, 10 used The Health Improvement Network (THIN) database and 3 used the QResearch databases. Data from primary care databases were used to support arguments regarding clinical need and current treatment in 33 NICE TAs while 36 were used to inform input parameters for economic models. The databases were sometimes used for more than one purpose. The data from the three data sources were generally well received by the ERGs/committees. Criticisms of the data typically occurred where the results had been repurposed from a published study or had not been applied appropriately.

Conclusions: The potential of UK primary care databases in NICE submissions is increasingly being realised, particularly in informing the parameters of economic models. Purpose conducted studies are less likely to receive criticism from ERGs/committees, particularly when providing clinical input into cost effectiveness models.

Keywords: CPRD, Appraisals, Guidance

- This study evaluated the use and acceptance of evidence from primary care databases, a key source of RWE in NICE technology assessments
- A keyword search was conducted relating to the main primary care databases in UK on the NICE website
- Among 52 NICE TAs were identified, 47 used the GPRD/CPRD database, 10 used The Health Improvement Network (THIN) database and 3 used the QResearch databases
- The data from the three data sources were generally well received the evidence review group (ERG) and the appraisal committee
- Purpose conducted studies are less likely to receive criticism from ERGs/committees, particularly when providing clinical input into cost effectiveness models
  - Criticisms of the data typically occurred where the results had been repurposed from a published study

OUTLINE

- Use of RWE in HTA processes in Europe
- **Use of RWE in HTA processes in US**
- Use of RWE in HTA processes in Japan
- Summary

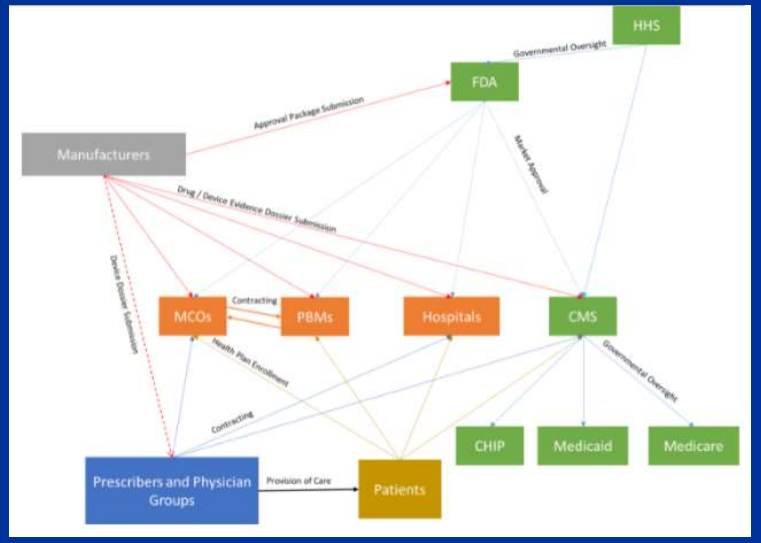
Institute for Clinical and Economic Review

- Founded in 2006, ICER is an independent non-profit non-government organization that conduct evidence-based reviews of health care interventions
- ICPE produces reports, known as “cost effectiveness analyses” or “value assessments” on how much it thinks new drugs should cost
  - Independent pricing watchdog for US
- In the US, decisions around drug pricing and patient access have historically been made based on limited evidence and without patients in the room
  - ICER use comparative clinical effectiveness, which weighs the benefits and harms / burdens of one treatment option versus another through a systematic review of all available evidence
  - Feedback from patients and families in addition to input from clinicians, manufacturers, and payers is used to frame the questions that an ICER comparative effectiveness review attempts to answer

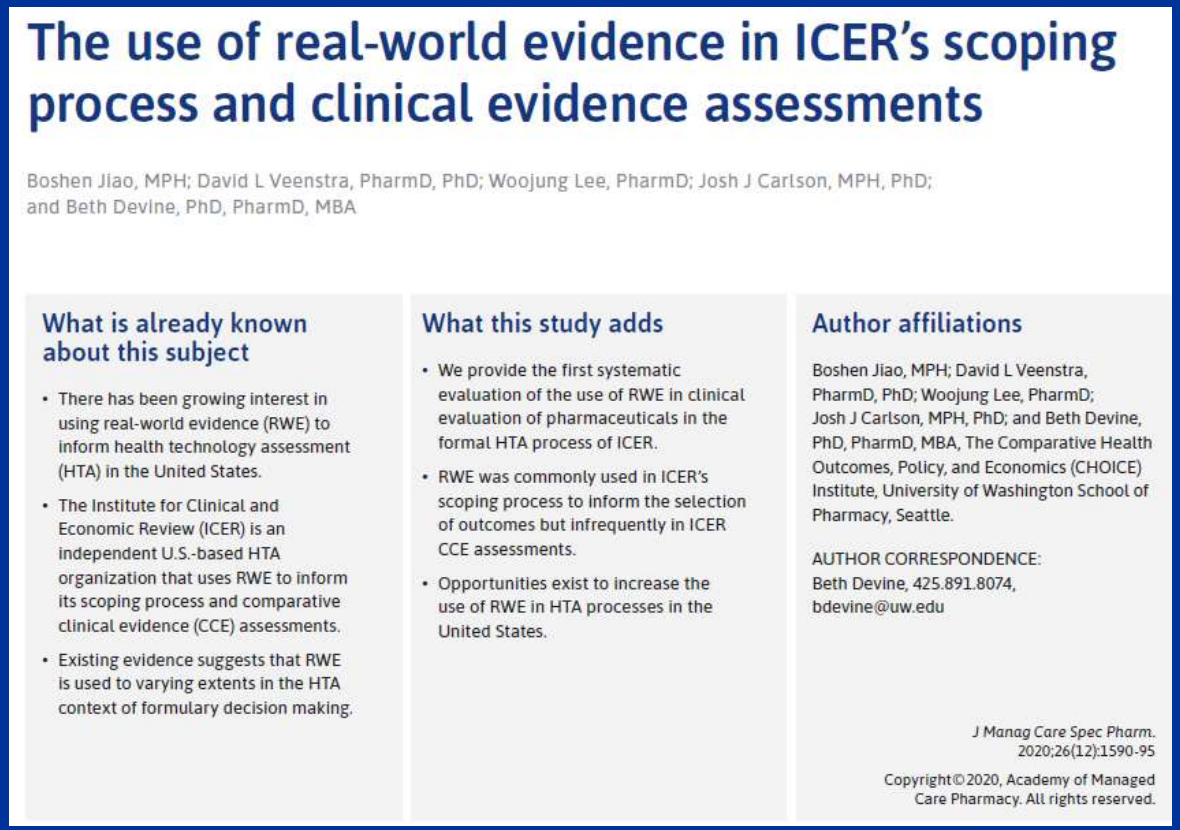
https://icer.org/who-we-are/history-impact/

Key Healthcare Decision Makers in the US

- The Managed Care Organizations (MCO), Pharmacy Benefit Managers (PBM), Centers for Madicare & Medicaid Services (CMS), and hospital organizations make a coverage determination based on the evidence dossier submitted by the manufacturer
  - **Pharmacy and Therapeutics Committee (P&T):**
    - Make coverage decisions for therapies in particular facility or insurance plans
  - **Value Analysis Committee:**
    - Similar to a P&T Committee, these groups focus on medical diagnostics and devices in a health system



https://www.ispor.org/heor-resources/more-heor-resources/us-healthcare-system-overview/united-states-healthcare-system-overview-decision-makers-and-influencers-page-2



The use of real-world evidence in ICER's scoping process and clinical evidence assessments

Boshen Jiao, MPH; David L Veenstra, PharmD, PhD; Woojung Lee, PharmD; Josh J Carlson, MPH, PhD; and Beth Devine, PhD, PharmD, MBA

What is already known about this subject

- There has been growing interest in using real-world evidence (RWE) to inform health technology assessment (HTA) in the United States.
- The Institute for Clinical and Economic Review (ICER) is an independent U.S.-based HTA organization that uses RWE to inform its scoping process and comparative clinical evidence (CCE) assessments.
- Existing evidence suggests that RWE is used to varying extents in the HTA context of formulary decision making.

What this study adds

- We provide the first systematic evaluation of the use of RWE in clinical evaluation of pharmaceuticals in the formal HTA process of ICER.
- RWE was commonly used in ICER's scoping process to inform the selection of outcomes but infrequently in ICER CCE assessments.
- Opportunities exist to increase the use of RWE in HTA processes in the United States.

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J Manag Care Spec Pharm.
2020;26(12):1590-95

- The authors reviewed all ICER reports published between 01/2014 and 06/ 2019, including RWE use
  - in the scoping documents to inform the population, intervention, comparator, outcome, setting, or timing (PICOTS) elements of the appraisal
  - In the CCE assessments to inform effectiveness, safety, or treatment patterns
  - in clinical guidelines that were cited in the CCE assessments

J Manag Care Spec Pharm, 2020:26:1590-95

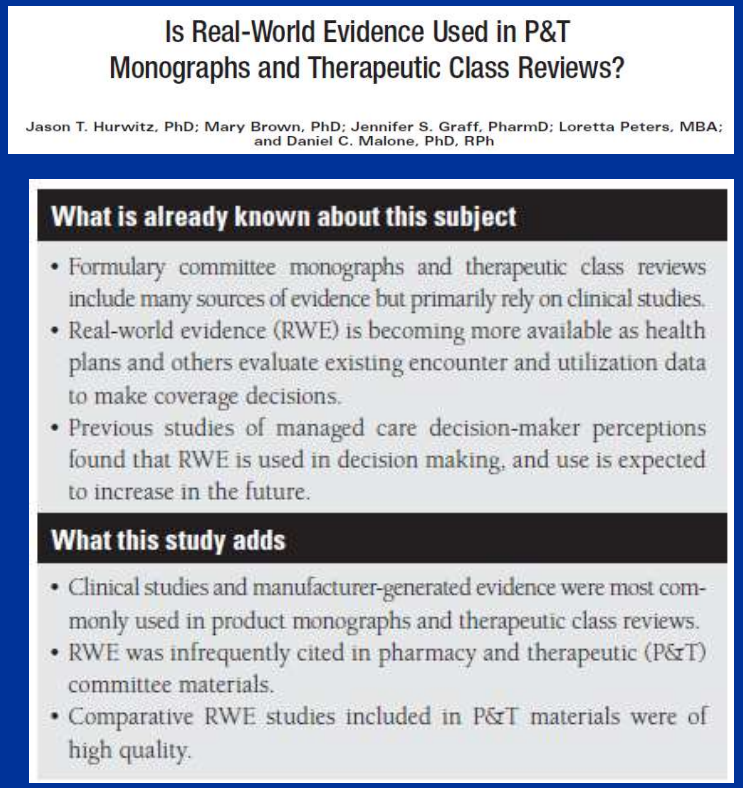
Use of RWE in ICER's Scoping Process and Clinical Evidence Assessments

- RWE was frequently used in the ICER scoping process, particularly to inform selection of outcomes
- RWE was used infrequently in ICER comparative clinical effectiveness (CCE) assessments, while more often used to inform effectiveness, safety, and treatment patterns in relevant clinical guidelines
- RWE was not used frequently in the setting of oncology
- RWE has played an important role in rare diseases
  - clinical trials are often impractical
- There are opportunities to increase the use of RWE in US HTA processes

J Manag Care Spec Pharm, 2020:26:1590-95

Use of RWE in P&T Monographs and Therapeutic Class Reviews

- Individuals employed by MCOs, PBMs, health care systems who agreed to participate provided 3 product monographs and 2 therapeutic class reviews presented to P&T committee within prior 24 months
- Two investigators examined and grouped references into multiple subcategories (e.g., product label, clinical trials, RWE, systematic reviews)
- Overall, the most frequently cited evidence came from clinical trials (n = 174/565, 31%)
  - Followed by manufacturer-provided information (n = 136/565, 24%; e.g., product labels).
  - Systematic reviews, FDA reports, and expert consensus statements each comprised 5%-9% of the 565 references.
  - Published RWE accounted for 4% of references (n = 21/565)



Is Real-World Evidence Used in P&T Monographs and Therapeutic Class Reviews?

Jason T. Hurwitz, PhD; Mary Brown, PhD; Jennifer S. Graff, PharmD; Loretta Peters, MBA; and Daniel C. Malone, PhD, RPh

What is already known about this subject

- Formulary committee monographs and therapeutic class reviews include many sources of evidence but primarily rely on clinical studies.
- Real-world evidence (RWE) is becoming more available as health plans and others evaluate existing encounter and utilization data to make coverage decisions.
- Previous studies of managed care decision-maker perceptions found that RWE is used in decision making, and use is expected to increase in the future.

What this study adds

- Clinical studies and manufacturer-generated evidence were most commonly used in product monographs and therapeutic class reviews.
- RWE was infrequently cited in pharmacy and therapeutic (P&T) committee materials.
- Comparative RWE studies included in P&T materials were of high quality.

J Manag Care Spec Pharm, 2020:26:1590-95

Use of RWE in P&T Monographs and Therapeutic Class Reviews

- The authors concluded that clinical studies and manufacturer-generated evidence were most commonly used in product monographs and therapeutic class reviews
- RWE was infrequently cited in P&T committee materials
- Given the timeliness of P&T decisions, it is not surprising that RWE was less cited in single-product monographs
  - as RWE is not typically available at the time of product approval
- Available staff resources may be an important barrier
  - conducting reviews of existing literature can be time consuming for organizations with limited staff time and resources.
  - research methods applied to deal with potential biases and confounding in RWD can be complex and requires new skills to evaluate RWE results
  - To this end, tools and training are needed to improve staff confidence in their ability to evaluate RWE studies and incorporate these studies in decision making

J Manag Care Spec Pharm, 2020:26:1590-95

OUTLINE

- Use of RWE in HTA processes in Europe
- Use of RWE in HTA processes in US
- **Use of RWE in HTA processes in Japan**
- Summary

Japan Health Insurance System

National Health Insurance System

Every citizen is covered by the national health insurance.

Same Fees for Treatment

Almost treatments except for OTC drugs are covered the national health insurance. The fee for each treatment is the same across the country. The fee is revised every year(from 2021). Co-payment ratio is normally 30% of the total medical cost.

Free Access

There is no primary doctor system in Japan. Every citizen can visit any medical facility at anytime.

Mandatory Annual Health Check Up

Annual health check up is mandatory for citizens age 40 and older.

No Refill System

There is no refill system in Japan. Patients need to see doctors to get prescriptions.

Type of payers (JMDC Data Source)	Operator	# of operator	Member type	# of member	Age
(1) Health Insurance Associations	Private Company	1,431	Salaried workers and their families (Mainly large-middle size companies)	29 million	0-74
(2) Japan Health Insurance Association	Japan Health Insurance Association	1	Salaried workers and their families (Mainly middle-small size companies	35 million	
(3) Fraternal Health Insurance Associations	Mutual aid association	85	Public officer/ Teachers and their families	9 million	
(4) National Health Insurance Society	Local governments	1,771 (each city)	Self employee Retired employee	35 million	
(5) Elderly Healthcare System	Local governments	47 (each prefecture)	People aged 75 or older	15 million	75 or older

All Japanese are covered by one of the insurance associations listed above, they are classified by their age and the type of occupation

HTA in Japan

- The Center for Outcomes Research and Economic Evaluation for Health (C2H) –
  - Japan's official HTA organization established within the National Institute of Public Health
- In April 2019, Japan formally introduced HTA, specifically, a cost-effectiveness analysis, to inform decision making on pricing of new technologies
- In Japan, the CE analysis has been used to inform price adjustments, not yet been used for decision making on insurance coverage
  - Precedent: in UK, cost-effectiveness results are used in negotiations over price for some new drugs
- Not all drugs and medical devices could be evaluated owing to a shortage of experts

Cost-effectiveness Evaluation in Japan

- Selection criteria for target projects in Japan HTA system are based on financial effect on healthcare insurance expenditure
  - Not all drugs and devices subjected to a CE evaluation owing to a shortage of experts in Japan

Table 1. Five categories of selection criteria in a cost-effectiveness evaluation

Classification		Selection Criteria
Newly listed products* (meaning listed on health insurance after formal implementation)	H1[†]	Estimated peak annual sales are ¥10 billion or more
	H2[†,‡]	Estimated peak annual sales are between ¥5 billion and ¥10 billion
	H3	Products with notably high prices[§] Products requiring re-evaluation because robust new evidence with a major effect on evaluation has been discovered after completion of cost-effectiveness evaluation
Already listed products[‖] (meaning listed before formal implementation)	H4	Products with annual sales of ¥100 billion or greater Products with notably high prices[§] Products requiring re-evaluation because robust new evidence with a major effect on evaluation has been discovered after the completion of cost-effectiveness evaluation
Similar products	H5	Products whose prices are calculated comparatively against those categorized in the H1 to H4 classifications

*Products with premiums in the similar efficacy (category) comparison method, or products with premiums or disclosure rates of 50% in the cost calculation method are prerequisite conditions for the targets of scope in the cost-effectiveness evaluation. In addition, if these products meet any of the following criteria, they are selected as target products, and are classified into 3 categories: (1) estimated peak annual sales of ¥10 billion or more ("H1 classification"), (2) estimated peak annual sales of between ¥5 billion and ¥10 billion ("H2 classification"), and (3) products requiring re-evaluation or products with notably high unit prices ("H3 classification").
[†]Even if a product does not meet the selection criteria in terms of estimated peak sales at the time of listing, it will be sorted as falling into a particular classification if the annual market size exceeds the criteria due to market expansion. In this case, the product will be sorted into the H1 or H2 classifications according to their annual market size.
[‡]Products of H2 classification are initially chosen as candidate products for evaluation; they are subsequently selected as targets.
[§]Notably high price is not defined explicitly, but at least a product whose unit price is JPY a few million or higher is considered to meet this criterion.
[‖]Regardless of the pricing methods, products with annual sales of ¥100 billion or more owing to market expansion, or products with notably high unit prices, are selected as the scope of target in the cost-effectiveness evaluation, provided that the products have premiums ("H4 classification").

Value in Health 2020;23:43-51

Challenges and Future Perspectives of RWD/RWE in Japan

Application examples of use RWD/RWE in Japan

Categories	Purpose of use
Development strategy	1. Selection of the target disease 2. Incidence and prevalence of disease 3. Natural course of the disease 4. Background incidence of interesting safety events 5. Pattern of disease treatment 6. Disease burden of patients and caregivers 7. Identifying unmet needs of current therapy
Clinical trial design	1. Identifying unmet needs of current therapy 2. Understanding of potential confounders 3. Supporting documentation for the clinical trial protocol 4. Feasibility study
Promotion of enrolment of study subjects	1. Recruitment of the study subjects to clinical trials
Application dossier	1. Historical control data [14, 96] 2. Supplementary materials
Drug price calculation	1. Cost and health data to support drug pricing decisions
Expansion of indications	1. Application based on public knowledge

- The key challenges for RWD and RWE use in Japan
  - Restricted access and linkage of RWD
  - A lack of universally accepted methodological approaches

These challenges are not unique to Japan and similar challenges exist for countries in Europe and US

SUMMARY

Current literature findings show:

- In the UK, RWE has been used extensively in NICE appraisals, especially to inform cost-effectiveness modeling
- The use of RWE from UK primary care databases is becoming more common in NICE technology assessment submissions
- In the US, although RWE was frequently used in the ICER scoping process, RWE was used infrequently in ICER comparative clinical effectiveness (CCE) assessments
- RWE was also infrequently cited in P&T committee materials
- In Japan, the cost-effectiveness analysis has been used to inform price adjustments, not yet been used for decision making on insurance coverage

Thank You

- First-line melanoma therapy
- Evidence evaluated:
  - 2 retrospective single-arm observational studies using licensed dose of ipilimumab 3 mg/kg
  - Pooled analysis from RCTs using unlicensed dose of ipilimumab 10 mg/kg

Agency	Date	Decision
HAS	June 2017	ASMR 4
IQWiG	May 2014	No additional benefit
G-BA	June 2014	No additional benefit
pCODR	Dec 2014	✓
SMC	Oct 2014	✓
NICE	July 2014	✓

✓ Recommend.

ASMR, age-standardized mortality rate; RCT, randomized controlled trial.

YERVOY™ (ipilimumab)

- HTA agencies that did not accept RWE:
  - HAS – subject to bias and low-quality evidence source
  - G-BA/IQWiG – no comparative evidence versus appropriate comparator
- HTA agencies focused on RCT data even though in unlicensed dose:
  - NICE discussed RCTs and RWE and made decisions based on RCTs in the unlicensed dose
- HTA agencies that accepted RWE as a main evidence source with positive decisions:
  - SMC
  - pCODR

HTAi

Drug (Disease Condition)	Year	Orphan Drug	Use of RWE	HTA Agency	Data Viewpoint
Ipilimumab (Melanoma)	2014	No	Efficacy	NICE, HAS, SMC, IQWiG, pCODR	Viewed only as supplemental data, even when main evidence source for the approved dosage
Belimumab (Lupus)	2016	No	Economic modeling	NICE	Accepted approach of using RWE to link short-term outcomes to long-term outcomes
Brentuximab vedotin (NHL)	2014	Yes	Efficacy data for comparator treatment	PBAC	No direct evidence was available; PBAC accepted manufacturer-submitted indirect comparison using registry data for comparator treatment evidence
Montelukast (Asthma)	2015	No	Efficacy data in reassessment	HAS	Accepted evidence from observational data used as primary efficacy evidence in 1 indication, though limitations were noted
Etravirine (HIV)	2012	No	Efficacy data in reassessment	HAS	RWE was used to maintain market access by confirming previous clinical evidence in a routine reassessment
Rituximab (RA)	2017	No	Efficacy data in reassessment	HAS	Requested follow-up study did not meet needs of the Transparency Committee; however, there were no real consequences for the drug - ASMR score remained a 2

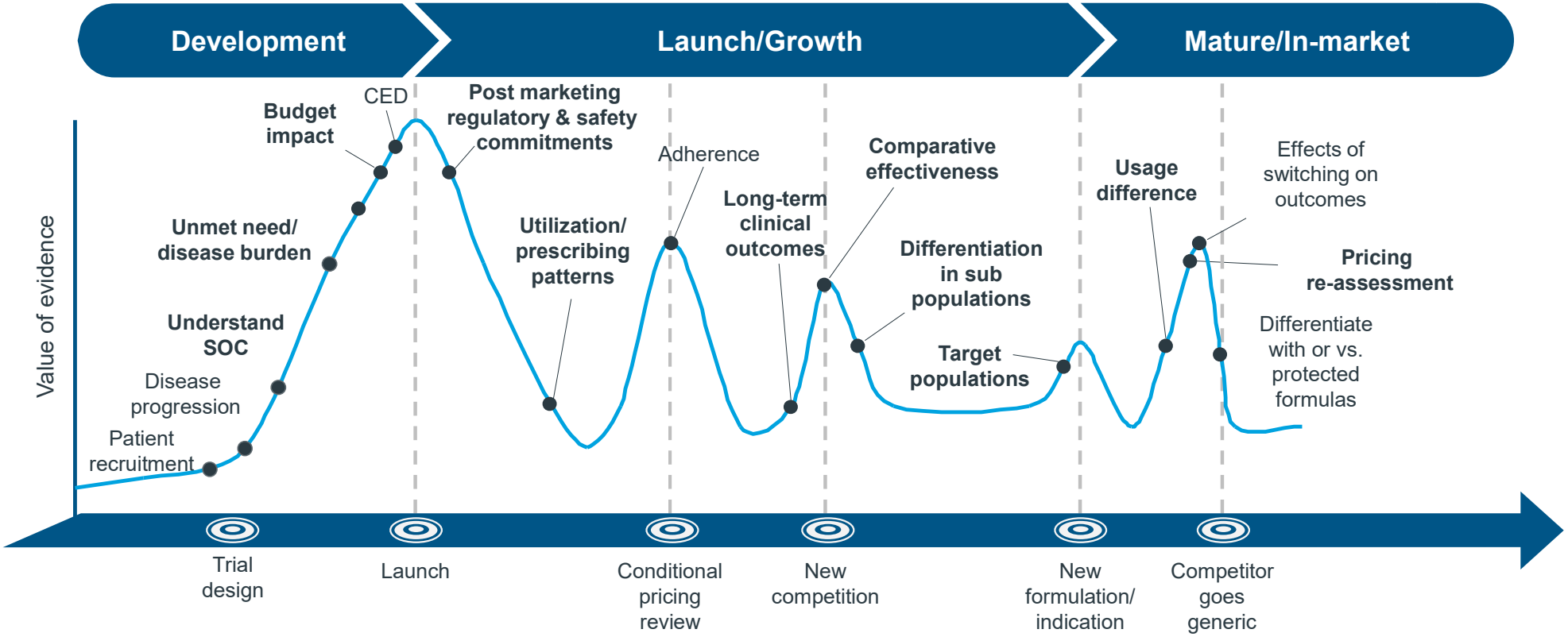
Courtesy of Dr Ashley Jaksa, HTA 2018 Annual Meeting, Vancouver, BC, Canada

RWE use in HTA: Dynamics, drivers and barriers of

ISPOR Vienna, 8 December 2022

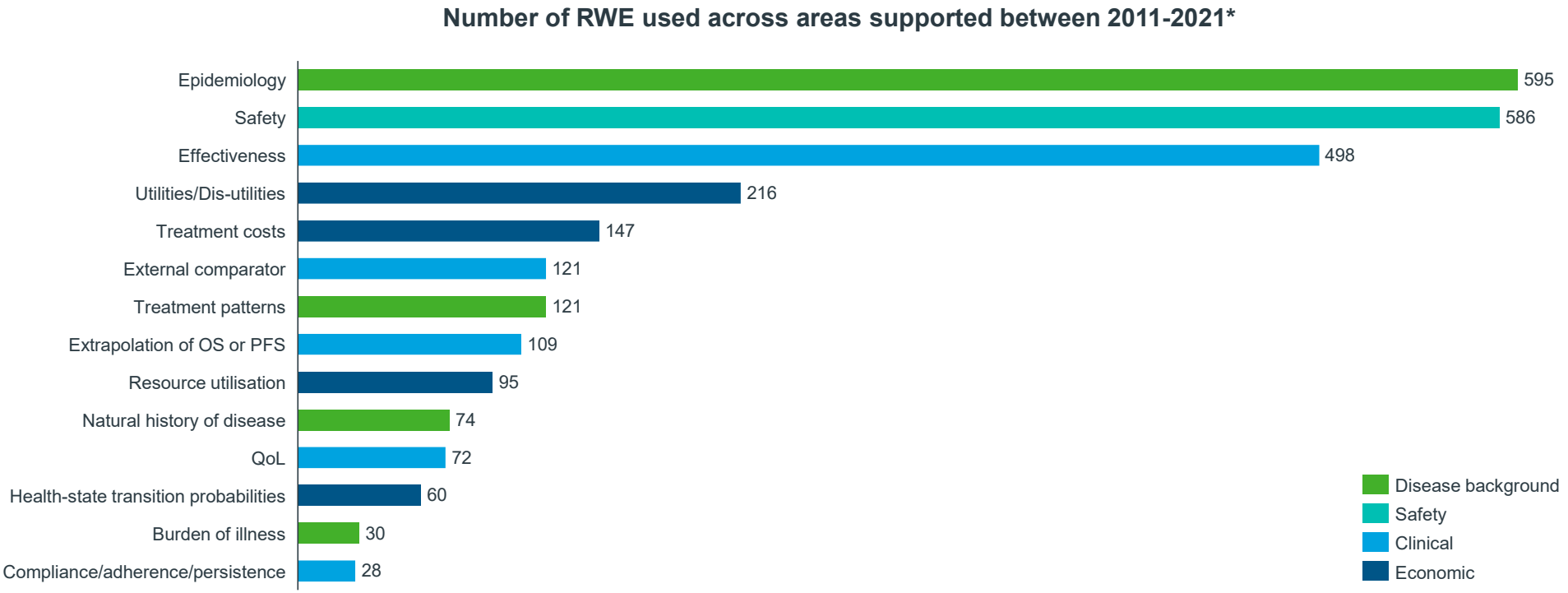
Massoud Toussi, Global Category Lead, Evidence from Secondary Data, IQVIA

When do we use RWE?



SOC: Standard of care; CED: Continued evidence development; Source: IQVIA expertise

Which types of studies are used to support HTA?

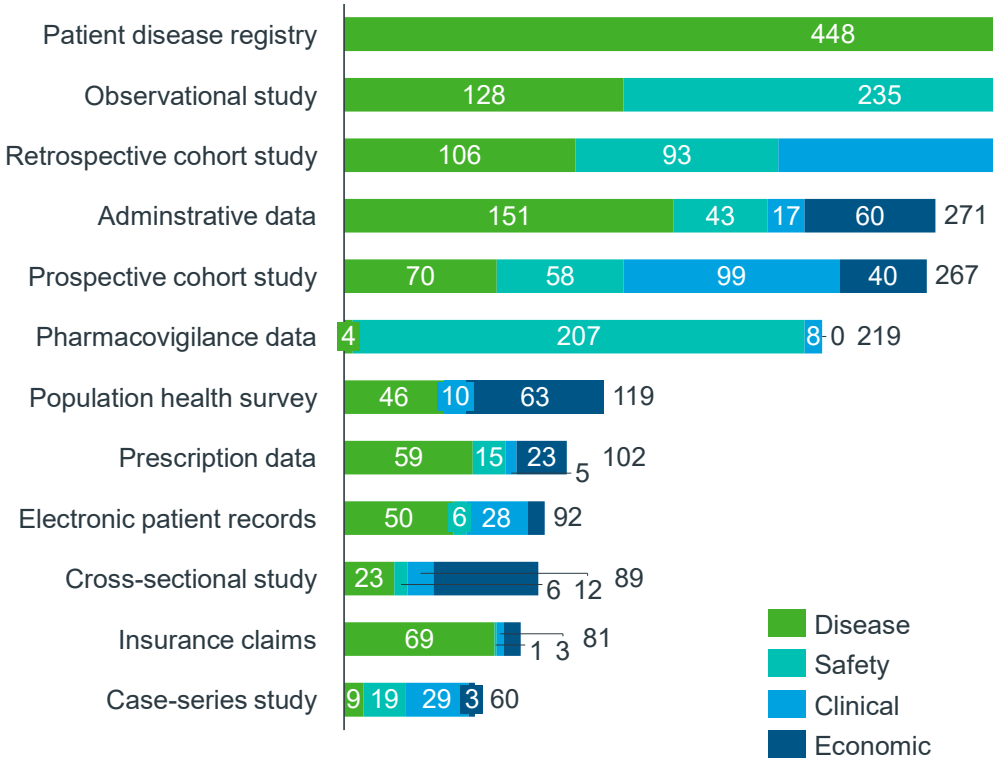


The high use of RWE for safety and epidemiology may be caused by the requirements for pharmacovigilance safety data in France and the necessity to estimate the patient population size in many countries, e.g. Germany (IQWiG)

Source: IQVIA HTA Accelerator. HTA reports (single drug assessments) published January 1st, 2011 until December 31st, 2021, for which details of submitted RWE were available (n=1,508 HTA reports)
*Count reflects number of RWE used in all HTA reports including single submission and re-submission and as such one RWE study may have supported different areas and multiple RWE sources may have been considered in the same reports

Which types of RWD is used for RWE generation in HTA?

Type of RWE data sources used in HTA reports over 2011-2021*

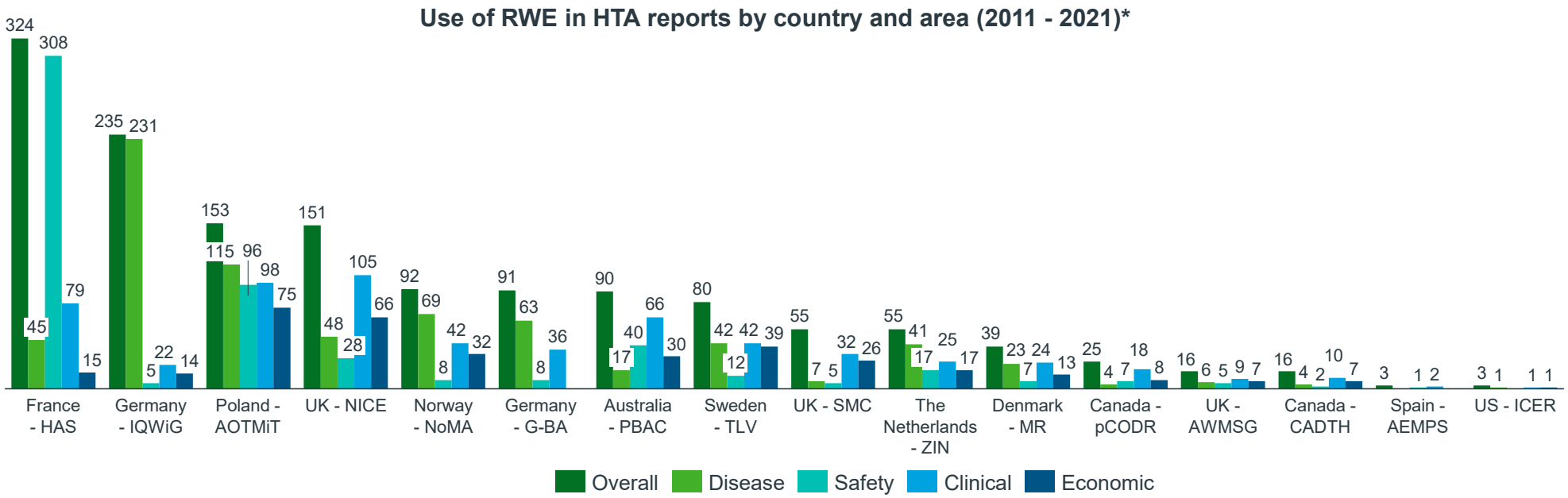


Other data sources used in HTA submissions are shown below and illustrate the variety of these data sources

- Retrospective chart review
- Uncontrolled study
- Post-marketing study
- Systematic patient surveys and interviews
- Vignette study
- Non-randomized controlled trial
- Case-control study
- Hospitalization data
- Supplements to registrational RCTs
- Systematic physician surveys/interviews
- Pragmatic trial

Source: IQVIA HTA Accelerator. HTA reports (single drug assessments) published January 1st, 2011 until December 31st, 2021, for which details of submitted RWE were available (n=1,508 HTA reports)
*Count reflects number of RWE used in all HTA reports including single submission and re-submission and as such one RWE study may have supported different areas and multiple RWE sources may have been considered in the same reports

Which countries use RWE to support HTA?

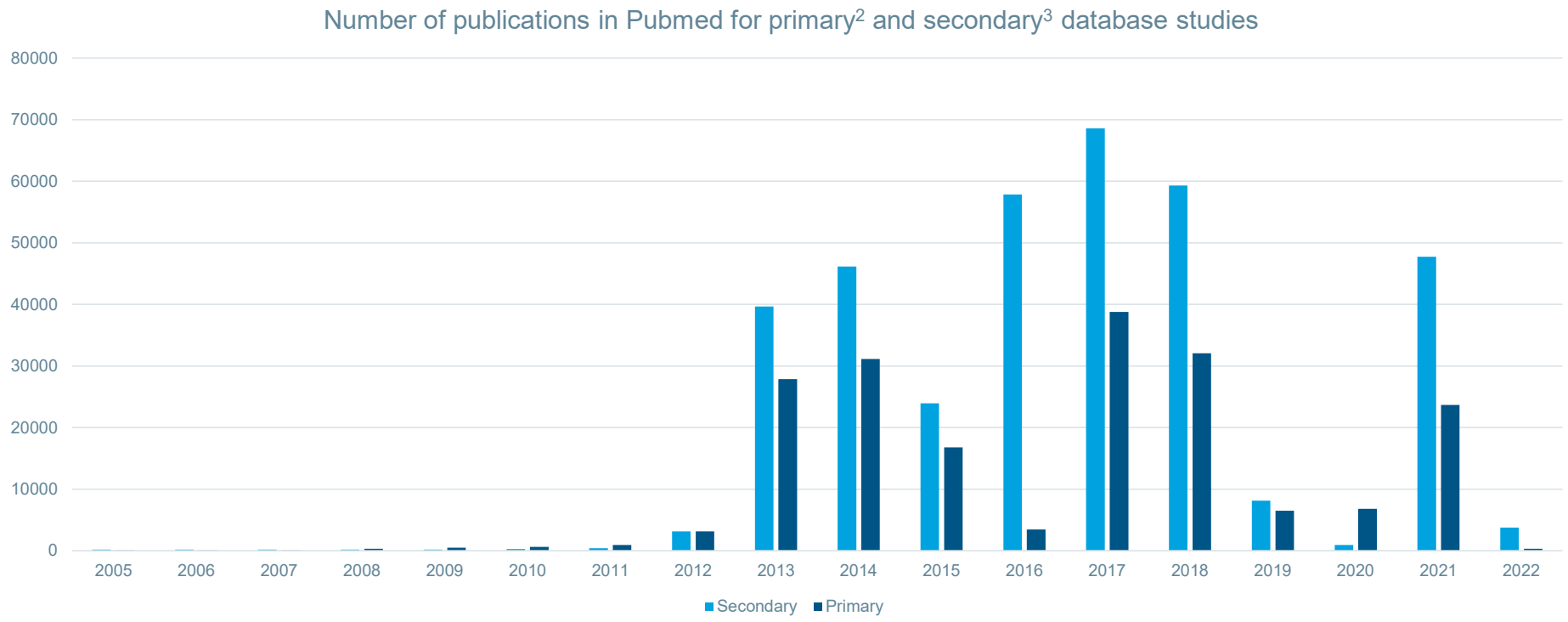


- HTA reports from HAS included the highest number of RWE data sources. This may be due process and requirements of in France whereby products are reassessed frequently, providing manufacturers with the possibility to submit additional evidence; the majority consisting of safety data.
- In Germany, RWE sources are frequently submitted to support sizing of the population.
- Poland requires conducting a systematic literature review of RWE for effectiveness of the assessed interventions
- Higher use of RWE for economic inputs is seen in cost-effectiveness markets as RWE may be needed to inform the model inputs

Source: IQVIA HTA Accelerator. HTA reports (single drug assessments) published January 1st, 2011 until December 31st, 2021, for which details of submitted RWE were available (n=1,508 HTA reports)
*Count reflects number of RWE used in all HTA reports including single submission and re-submission and as such one RWE study may have supported different areas and multiple RWE sources may have been considered in the same reports

Growth of RWD supply push for RWE generation

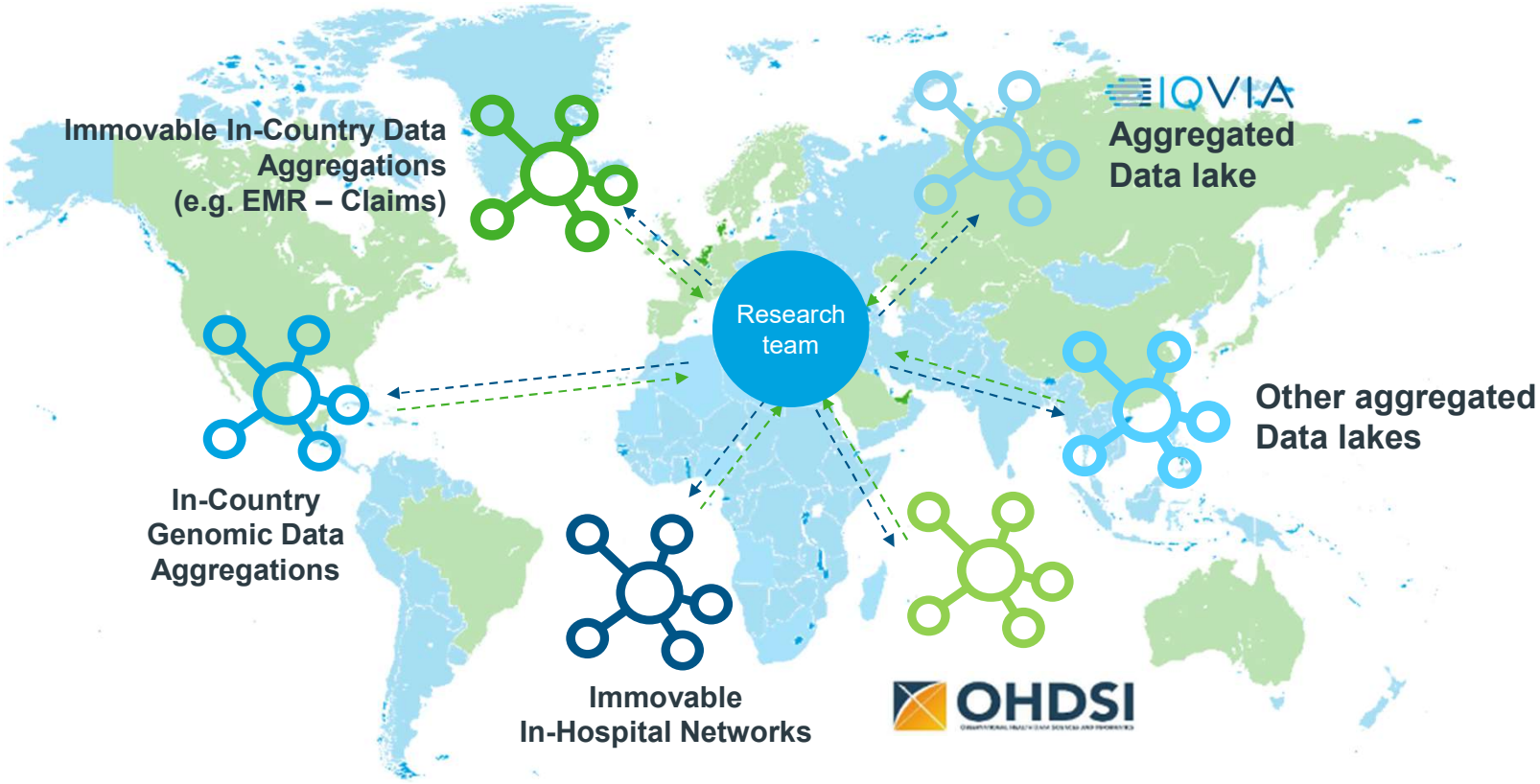
Healthcare data grew from 2 to 97 zetabytes from 2010 to 2022[1]



1) Source: Statistica 2022; 2) Research terms: « secondary data » OR « database » OR « retrospective »; 3) Research terms: « primary data » OR « prospective »

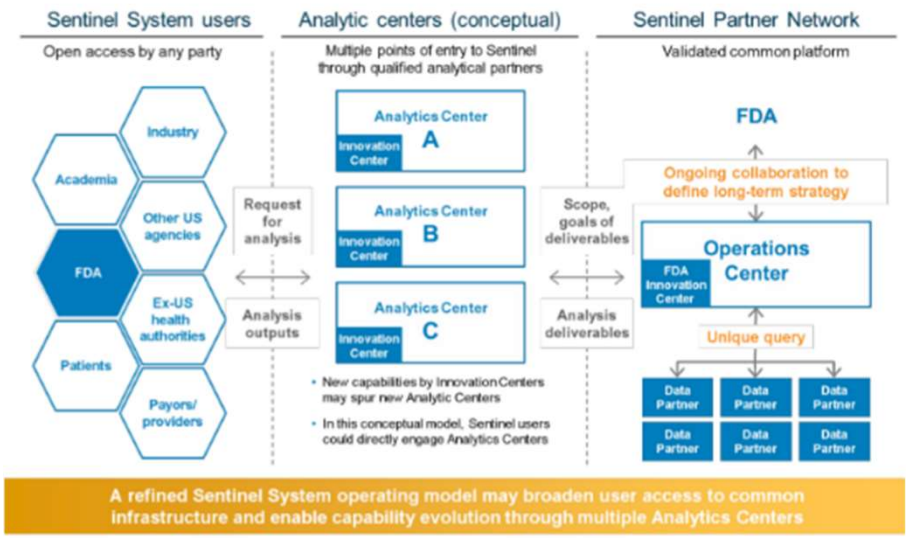
Federated data access models accelerate RWD supply

Providing access to data and analytics in a homogeneous and compliant manner wherever it is

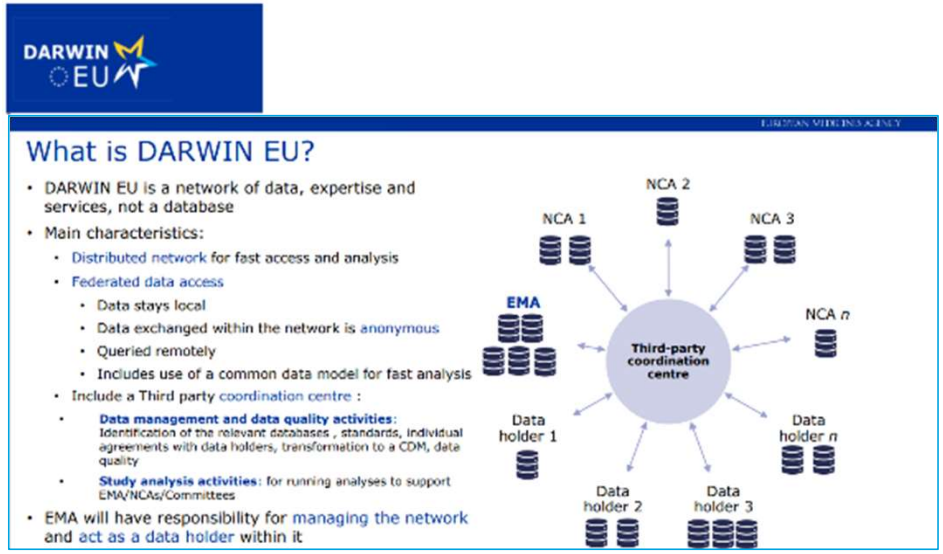


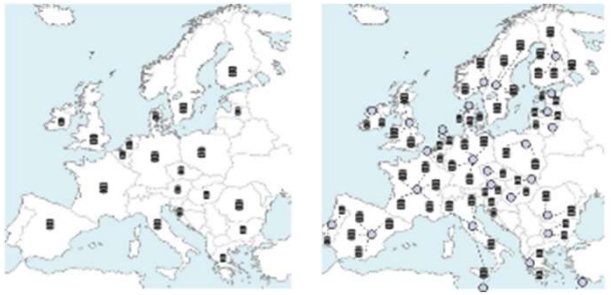
Common data models and analytic centers facilitate RWE supply

Similar strategic plans by FDA (Sentinel) and EMA (Darwin EU®) for a distributed network of real world data using a common data model, and analytic centres, accessible to a variety of stakeholders.



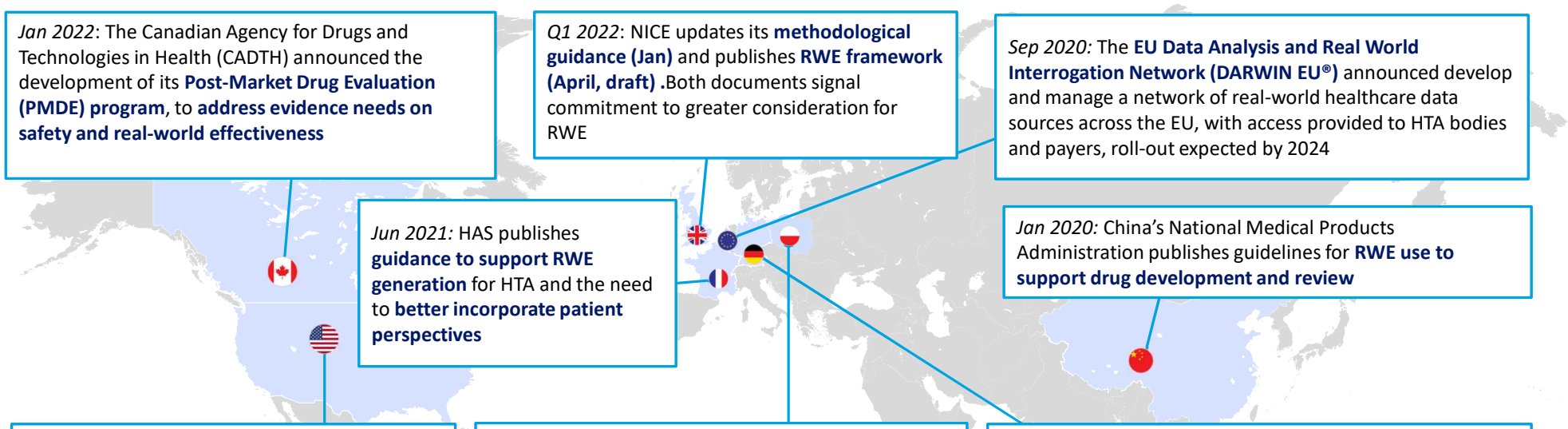
FDA Sentinel Strategic Plan (2019- 2023)





EMA Darwin EU Vision (2021-2024)

Regulators and HTA bodies' guidance and initiatives improve generation and use of RWE



Jan 2022: The Canadian Agency for Drugs and Technologies in Health (CADTH) announced the development of its **Post-Market Drug Evaluation (PMDE) program**, to **address evidence needs on safety and real-world effectiveness**

Q1 2022: NICE updates its **methodological guidance (Jan)** and publishes **RWE framework (April, draft) .**Both documents signal commitment to greater consideration for RWE

Sep 2020: The **EU Data Analysis and Real World Interrogation Network (DARWIN EU®)** announced develop and manage a network of real-world healthcare data sources across the EU, with access provided to HTA bodies and payers, roll-out expected by 2024

Jun 2021: HAS publishes **guidance to support RWE generation** for HTA and the need to **better incorporate patient perspectives**

Jan 2020: China's National Medical Products Administration publishes guidelines for **RWE use to support drug development and review**

Jan 2020: ICER updates its methods and procedures for Value Assessment Framework:

- **Augmented use of RWE**, through new collaborative partnerships (e.g. with Aetion)
- **Re-review of drugs** approved under accelerated approval **after 24 months, informed by RWE**

Oct 2020: **Innovative treatments in oncology and rare diseases** may be reimbursed via accelerated procedure with **further data collection in registries** according to the 'Act on the Medical Fund'

- So far, only 2 products are covered: **Oxlumo** for primary hyperoxaluria type 1 (PH1) and **Givlari** for acute hepatic porphyria

Jul 2019: Concept report on RWE use in HTA suggests the **use of high-quality patient registries in comparative settings**, randomised or not

Feb 2021: GBA mandate that **Novartis must complete a registry-based study** for Zolgensma, additional products are under consideration

Are we using RWE at its best?

Mainly traditional types of data analysis are used in HTA

Descriptive

- **What happened?**
- How many patients went to the hospital last month?

Diagnostic

- **Why did it happen?**
- Why these patients went to the hopsital?

Predictive

- **What will happen?**
- Which patients will go the hospital next month?

Prescriptive

- **How can we make it (not) happen?**
- We shall give treatmetn X to these patients to prevent hospitalisation.

- Artificial intelligence is becoming increasingly an important topic in discussions around RWE in HTA.

Barriers of use of RWE in HTA

Technical

Lack of expertise and capacity in the HTA agency
Lack of available resources for using and administrating RWE

Regulatory

Lack of appropriate guidelines
Lack of cooperation standards and data integration
Requirements for using only local evidence in HTA
Lack of a governance framework related to using RWE
Frequently changing regulations on RWE

Clinical and scientific

Differences in epidemiological data across countries
Differences in predefined criteria for evaluation of the effectiveness of medicines
Lack of **transparency** in the design, execution and report of studies using RWD
Lack of established methodological standards for RWE generation

Perception

Uncertainty in the quality of RWE
Limited trust in RWE due to lack of access to the underlying RWD
Variability, heterogeneity and lack of **reproducibility of RWE**
Lack of access to the study **protocols** before data collection

Source: Kamusheva et.al: Using real-world evidence in healthcare from Western to Central and Eastern Europe: a review of existing barriers. DOI: 10.2217/cer-2022-0065

Supporting HTA by strengthening transparency and reproducibility of real-world evidence studies

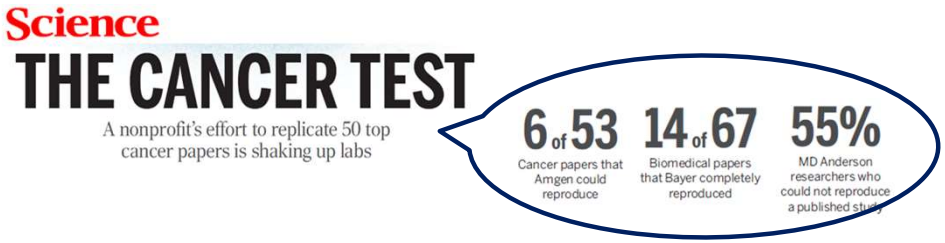
Shirley V Wang
Division of Pharmacoepidemiology and Pharmacoeconomics
Brigham and Women's Hospital, Harvard Medical School

Disclosures

- REPEAT Initiative work was funded by:
  - Arnold Ventures (non-profit foundation)
- I am principal investigator on grants from FDA and NIH (NHLBI, NIA, NICHD)

Reproducibility is a cornerstone of the scientific method

- Concerns about irreproducible research across many scientific fields
  - *Biomedical:* Pre-clinical, Clinical
  - *Other:* Psychology, economics…



Reproducibility is closely related to clear reporting

- Unambiguous scientific process increases understanding of
  - How evidence is generated
  - Validity of methods
  - Reasons for divergence in results

- Credibility of RWE from RWD has suffered from apparent divergence between…

Database studies (apparently) investigating the same question

Reanalysis of two studies with contrasting results on the association between statin use and fracture risk: the General Practice Research Database

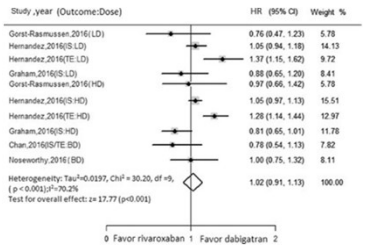
Frank de Vries Corinne de Vries Cyrus Cooper Bert Leufkens Tjeerd-Pieter van Staa

International Journal of Epidemiology, Volume 35, Issue 5, October 2006, Pages 1301–1308, https://doi.org/10.1093/ije/dyl147

Rivaroxaban Versus Dabigatran or Warfarin in Real-World Studies of Stroke Prevention in Atrial Fibrillation

Systematic Review and Meta-Analysis

Ying Bai, PhD; Hai Deng, PhD; Alena Shantsila, PhD; Gregory Y.H. Lip, MD



Database studies and trials

RESEARCH

Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey

Lars G Hemkens,[1,2] Despina G Contopoulos-Ioannidis,[3,4] John P A Ioannidis[1,4-6]

Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease

Miguel A. Hernán[1,2], Alvaro Alonso[3], Roger Logan[1], Francine Grodstein[1,4], Karin B. Michels[1,4,5], Meir J. Stampfer[1,4,6], Walter C. Willett[1,4,6], JoAnn E. Manson[1,4,7], and James M. Robins[1,8]

A hurdle to get over

Lack of clarity in reporting is a barrier to use of RWE for decision making

- Need unambiguous methods to assess validity/relevance

HARPER

HARmonized Protocol Template to Enhance Reproducibility

ispe ISPOR *Improving healthcare decisions*

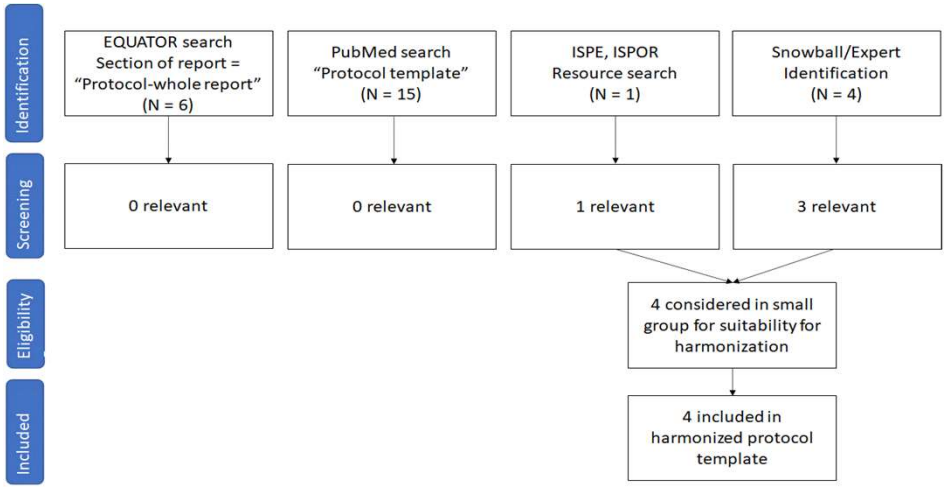


Figure 1. PRISMA Diagram

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Tables and figure

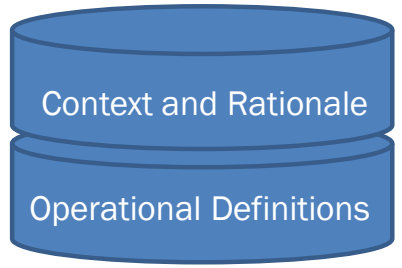

Table of contents

7.1 Study Design
7.2 Study Design Diagram

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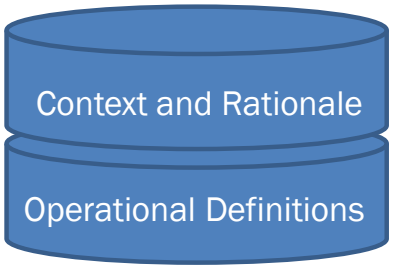
Figure



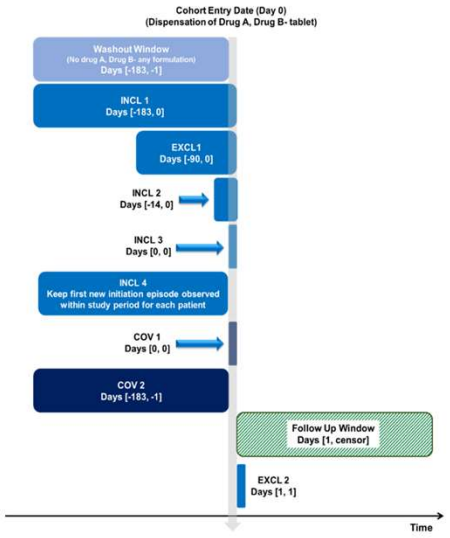
7.1 Study design

Research design (e.g. cohort, case-control, etc.): <Text>

Rationale for study design choice: <Text>

7.2 Study design diagram

New initiator, active comparator cohort design evaluating risk of outcome Y for Drug A vs Drug B



INCL/EXCL = Inclusion/Exclusion Assessment Window

INCL1
Medical and Drug coverage (45 day gaps allowed)

INCL2
Community acquired pneumonia diagnosis and chest radiography

INCL3
Age between 18-65

INCL4
Keep first new initiator episode

EXCL1
Inpatient hospitalization

EXCL2
Censored on day follow up starts

Censoring
183 days
30-Sep-15
Discharged dead
Disenroll medical or drug coverage (45 day gaps allowed)

COV = Covariate Assessment Window

COV1
Age (continuous)
Gender

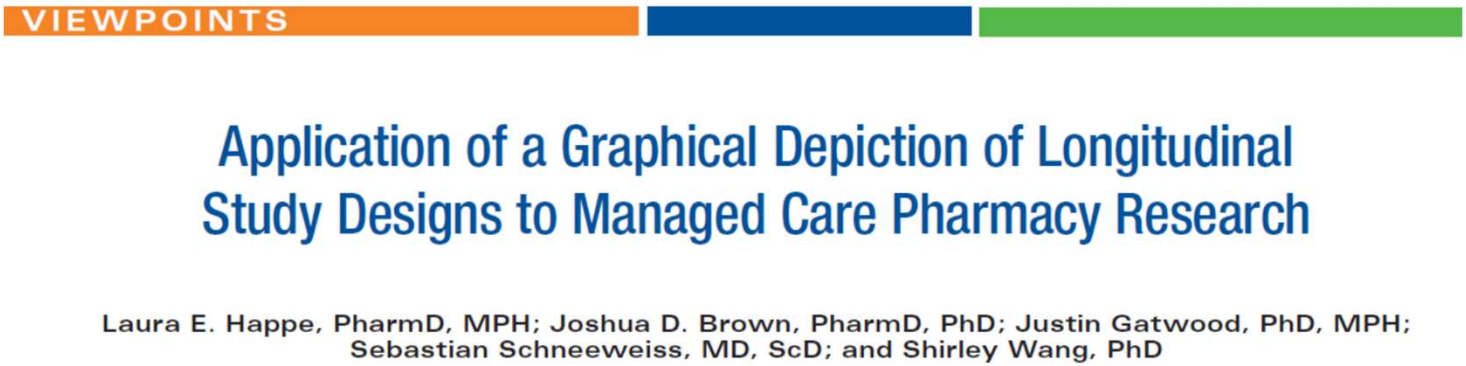
COV2
Metastatic cancer
Tumor
Arrhythmia
Congestive heart failure
Dementia
Renal failure
Weight loss
Hemiplegia
Alcohol abuse
Number of inpatient hospitalizations
Number of outpatient visits
Number of emergency department visit
Number of unique generics
Prior prescription of penicillins
Prior prescription of cephalosporins
Prior prescription of sulfonamides
Prior prescription of tetracyclines
Prior prescription of aminoglycosides
Pregnancy at time of initiation

“A picture is worth a thousand words…” Fred Barnard

Planning
Reporting
Evaluation

- 42% of database studies in JMCP included design diagram
- Tried diagramming 2 published studies and noticed ambiguity and inconsistency in text

J Manag Care Spec Pharm 2020 Mar;26(3):268-274. doi: 10.18553/jmcp.2020.26.3.268.


VIEWPOINTS

Application of a Graphical Depiction of Longitudinal Study Designs to Managed Care Pharmacy Research

Laura E. Happe, PharmD, MPH; Joshua D. Brown, PharmD, PhD; Justin Gatwood, PhD, MPH; Sebastian Schneeweiss, MD, ScD; and Shirley Wang, PhD

7.3.1 Time 0

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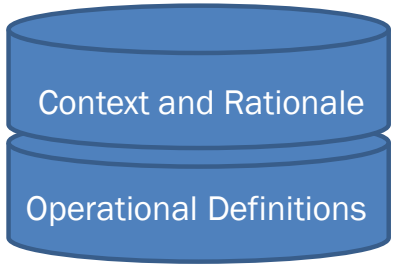
Table



7.3.1 Context and rationale for definition of time 0 for entry to the study population

<Text>

Table 1 Operational Definition of Time 0 (index date)

Study population name(s)	Day 0 Description	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics /validation	Source of algorithm
<Text>	<Text>	<drop down>	<drop down>	Number range	<Text>	<Text>	<drop down>	<Text>	<Text>	<Text>
Exposure	*Date of incident dispensation for Drug A (tablets only)*	*Single*	*Incident*	*[-183, 0]*	*n/a*	*NDC*	*n/a*	*Drug A or B (any formulation)*	*Unknown*	*Investigator review of generic names*
Comparator	*Date of incident dispensation for Drug B (tablets only)*	*Single*	*Incident*	*[-183, 0]*	*n/a*	*NDC*	*n/a*	*Drug A or B (any formulation)*	*Unknown*	*Investigator review of generic names*

IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2]See appendix for listing of clinical codes for each study parameter

7.5 Sensitivity Analyses

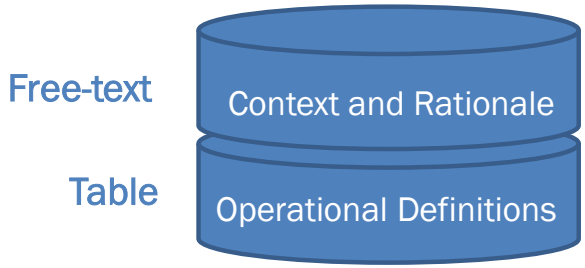
7.5.1 Context and rationale for analysis plan

<Text>

Table 11. Sensitivity analyses – rationale, strengths and weaknesses

	What/how is the parameter being varied?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Weaknesses of the sensitivity analysis compared to the primary
Sensitivity Analysis 1	We change the prior enrolment, covariate and inclusion/exclusion windows from 180 days to 365 days	We learn whether a longer assessment window to more fully capture baseline conditions results in similar estimated effect	Potentially more complete capture of baseline conditions used for inclusion-exclusion or covariate adjustment	Loss of sample size due to turnover in enrollment with health plan
Sensitivity Analysis 2	We analyse a negative control outcome (hospitalization for X) instead of the outcome of interest, myocardial infarction What is varied?	We learn the magnitude of association for an outcome that is not expected to be differentially affected by Drug A and Drug B, except through confounding Why?	The presumed true null relationship between Drug A, Drug B and hospitalization for X means that observed effects are due to bias or random chance. If results are null, this could strengthen the argument for the causal effect of Drug A vs. Drug B and myocardial infarction. If results are not null, the magnitude of observed effect could be used to calibrate the effect of Drug A vs. Drug B and myocardial infarction.	The confounding structure may not be the same for hospitalization for X as for myocardial infarction. If that is the case, a null effect from the analyzing the negative control, provides less reassurance of the casual effect for Drug A vs. Drug B on myocardial infarction and could increase bias is used to calibrate the effect size.

7.6 Data Sources



7.6.1 Context and rationale for data sources

Reason for selection: <Text>

Strengths of data source(s): <Text>

Limitations of data source(s): <Text>

Data source provenance/curation: <Text>

Table 12. Metadata about data sources and software

	Data 1	Data 2	Data 3	Data 4
Data Source(s):	XYZ database version 5.1.2	XYZ database version 5.1.2	n/a	n/a
Study Period:	January 1, 2003 - September 30, 2015	January 1, 2012 – December 31, 2020		
Eligible Cohort Entry Period:	January 1, 2003 - September 30, 2015	January 1, 2012 - September 30, 2015		
Data Extraction Date/Version:	January 1, 2018	January 1, 2021		
Data sampling/extraction criteria:	All enrollees in data source between January, 2003 - September 30, 2015	All enrollees with <1 month Part A, B, D coverage between Jan 2012 and Dec 2020 and <1 diabetes diagnosis		
Type(s) of data:	Commercial claims	Commercial claims		
Data linkage:	None	Linkage to National Death Index. See appendix for details		
Data conversion:	ABC Common Data Model version 7.0	ABC Common Data Model version 7.0		
Software for data management:	Statistical software version 9.4	Statistical software version 9.4		

Sections on data management plans and quality control procedures not shown.

HARPER

Why?

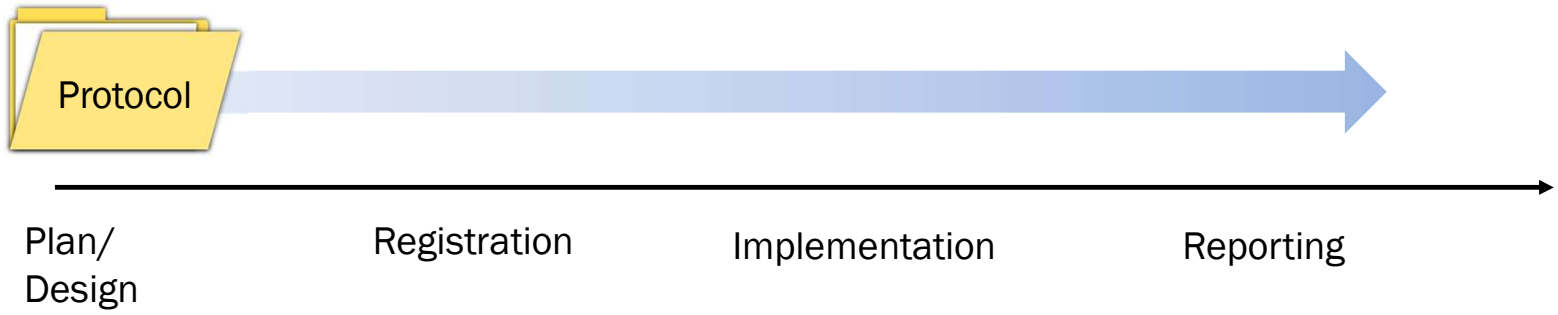
- Current ambiguity can limit utility of database studies in healthcare decision-making

How?

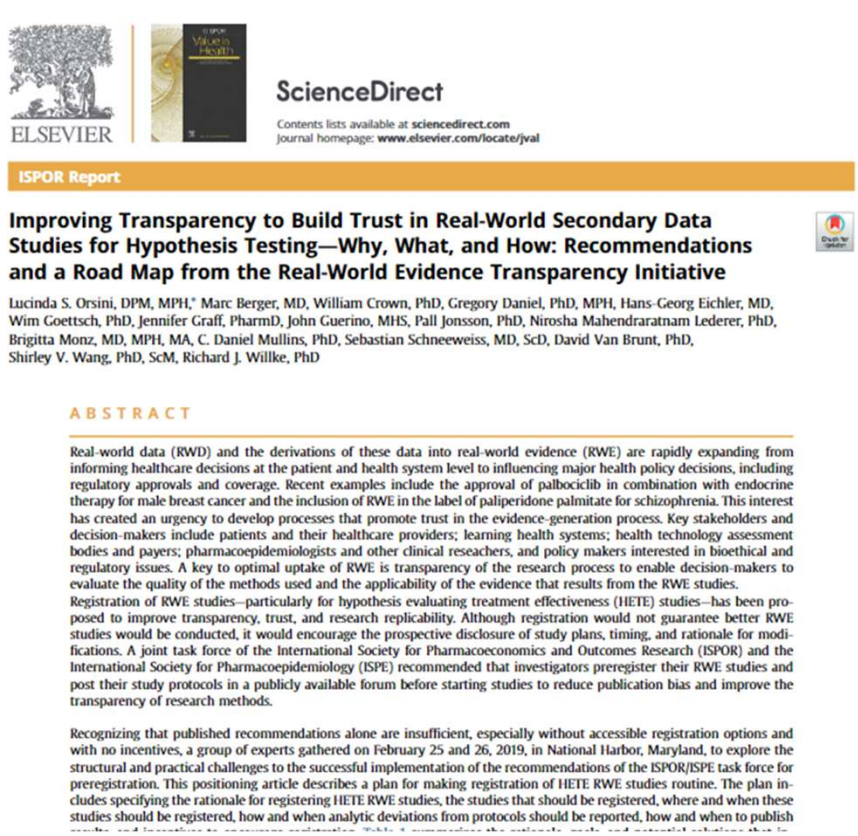
- Build on existing efforts
- Incorporate insights on detail needed for reproducibility
- Shared understanding through common text, tabular and visual framework
- Know what to look for and where to find it

What?

- A template tool for unambiguous communication about study implementation



Transparency and registration



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ISPOR Report

Improving Transparency to Build Trust in Real-World Secondary Data Studies for Hypothesis Testing—Why, What, and How: Recommendations and a Road Map from the Real-World Evidence Transparency Initiative

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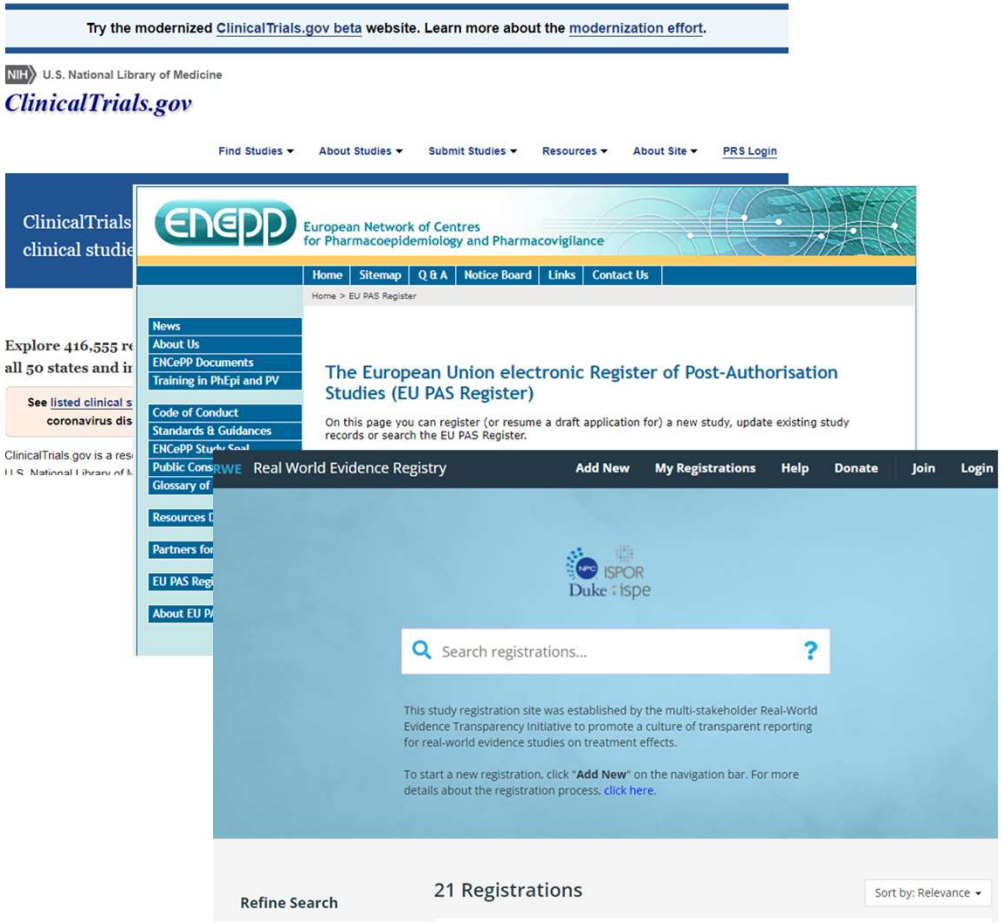
ABSTRACT

Real-world data (RWD) and the derivations of these data into real-world evidence (RWE) are rapidly expanding from informing healthcare decisions at the patient and health system level to influencing major health policy decisions, including regulatory approvals and coverage. Recent examples include the approval of palbociclib in combination with endocrine therapy for male breast cancer and the inclusion of RWE in the label of paliperidone palmitate for schizophrenia. This interest has created an urgency to develop processes that promote trust in the evidence-generation process. Key stakeholders and decision-makers include patients and their healthcare providers; learning health systems; health technology assessment bodies and payers; pharmacoepidemiologists and other clinical reseachers, and policy makers interested in bioethical and regulatory issues. A key to optimal uptake of RWE is transparency of the research process to enable decision-makers to evaluate the quality of the methods used and the applicability of the evidence that results from the RWE studies. Registration of RWE studies—particularly for hypothesis evaluating treatment effectiveness (HETE) studies—has been proposed to improve transparency, trust, and research replicability. Although registration would not guarantee better RWE studies would be conducted, it would encourage the prospective disclosure of study plans, timing, and rationale for modifications. A joint task force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) recommended that investigators preregister their RWE studies and post their study protocols in a publicly available forum before starting studies to reduce publication bias and improve the transparency of research methods.

Recognizing that published recommendations alone are insufficient, especially without accessible registration options and with no incentives, a group of experts gathered on February 25 and 26, 2019, in National Harbor, Maryland, to explore the structural and practical challenges to the successful implementation of the recommendations of the ISPOR/ISPE task force for preregistration. This positioning article describes a plan for making registration of HETE RWE studies routine. The plan includes specifying the rationale for registering HETE RWE studies, the studies that should be registered, where and when these studies should be registered, how and when analytic deviations from protocols should be reported, how and when to publish

https://www.sciencedirect.com/science/article/pii/S109830152030190X



Real World Evidence Registry (mainly non-PASS)

Real World Evidence Registry

Real world evidence studies can be used for hypothesis evaluation of treatment effects including safety (HETE studies). However these studies can also be perceived as less rigorous than clinical trials especially when not pre-registered in a public setting such as ClinicalTrials.gov or the EU-PAS register.

ISPOR and our partners ISPE, NPC and Duke Margolis have developed a simplified registration site especially for RWE HETE studies using secondary data. This searchable site provides a place for pre-registration of studies that may not require registration for regulatory purposes but benefit from the rigor of transparent study methods and also provide a reference (such as a URL or doi) to share with peer reviewers, assessors, or other decision making bodies. Get started 'here' by creating a profile on the Open Sciences Framework and registering your study on the RWE study registration site.

GO TO THE REGISTRY

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Improving healthcare decisions

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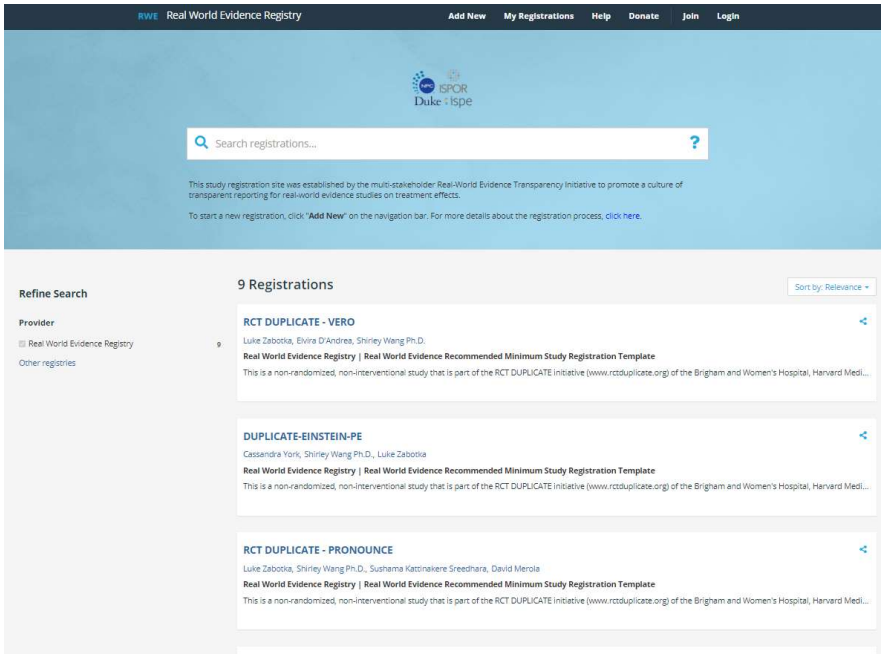

https://osf.io/registries/rwe/discover

Study Transparency ≠ Study Quality