

Real-World Evidence: Tools to Support Innovation

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Topics

- Fundamental of Real-World Data and Real-World Evidence for Regulatory Activities
- Global Real-World Evidence Instructure and Guidance Development
- Approaches to Advance the Acceptance of Real-World Evidence

Growing Need for Evidence

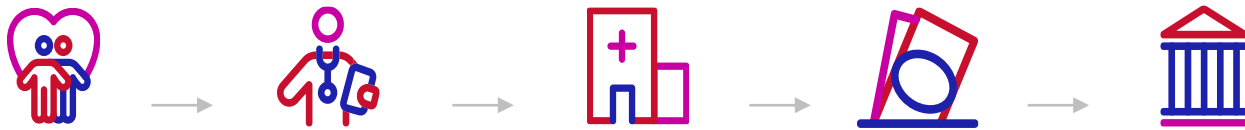
Evolution of Medical Products



Expanding Sources of Clinical Data & Evidence



Emerging Needs of Decision Makers







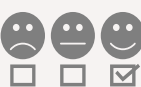




Fundamentals of Real-World Data and Real-World Evidence for Regulatory Activities

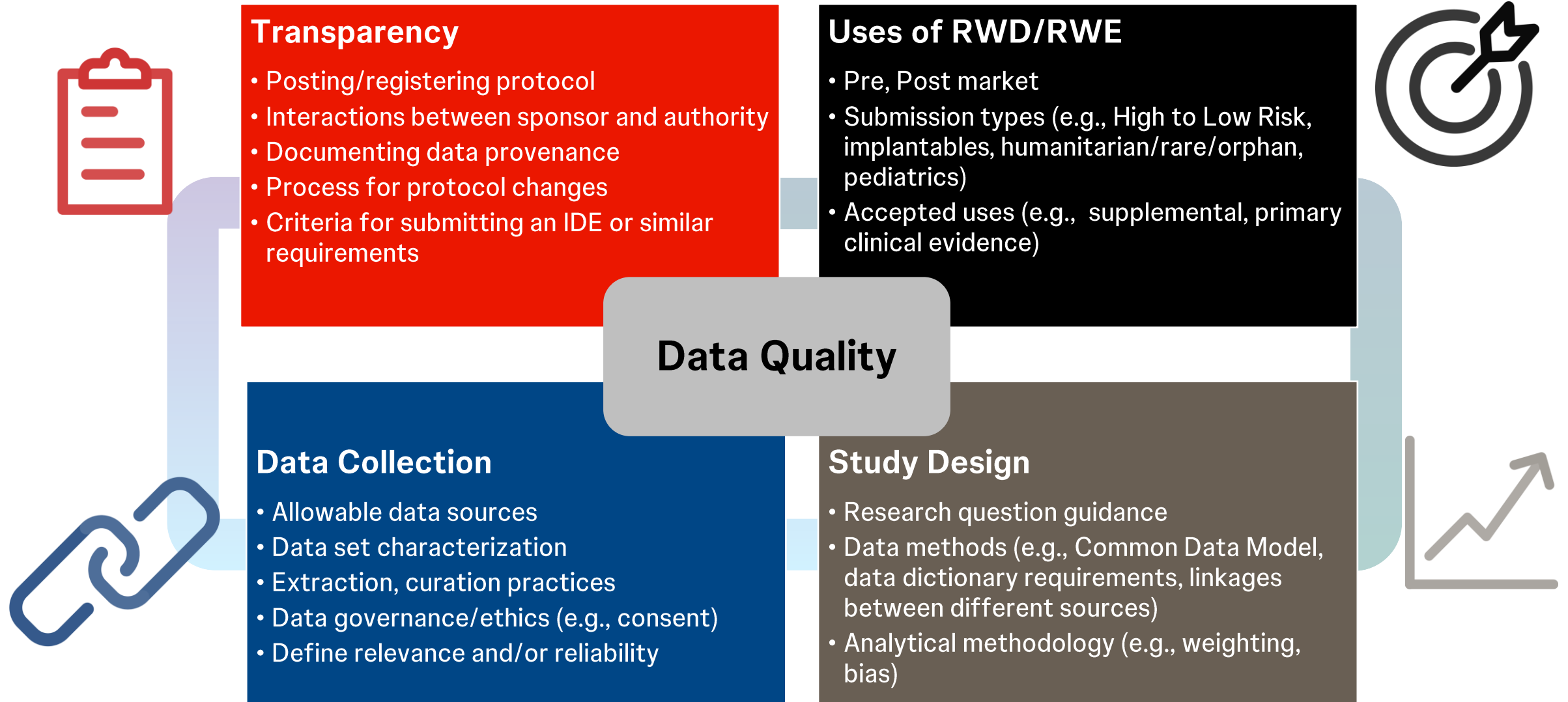
Real-World Data

“Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.”

“...sources other than traditional clinical trials”

	Complaints: MAUDE, Eudramed, and Company Databases
	Hospital Databases
	Electronic Health Records
	Claims
	Registries
	Registries linked to claims/EHR
	Patient surveys, Surgeon surveys, PROs, Patient Preferences, wearables, sensors, social media
	Device generated data
	Imaging, video, AI

Components of Real-World Evidence Guidances



Determining RWD “Fit-for-Purpose”



- Availability of key data elements
 - Exposure
 - Outcome
 - Covariate
 - Patient-level linking (if applicable)
- Representativeness
- Sufficient patients
- Continuity of coverage is adequate/longitudinal
- Follow-up period is long enough for outcomes to develop
- Coding standardization and ease of extraction

- Accuracy
 - Validity
 - Conformance
 - Plausibility
 - Consistency
- Completeness
- Provenance
- Transparency of data processing
- Auditability
- Understand impact of data errors

- Within the given clinical and regulatory context, the real-world dataset is of sufficient quality, as well as relevant, robust, and representative

Slide Courtesy of Shumin Zhang, MedTech Epi

Design Considerations Using RWE for Regulatory Decisions

General Principles

- Get alignment with FDA on study design and analysis plan
- Separate analytic design from outcome analysis and use **2-stage outcome-free analytic design process** to maintain objectivity
- Pre-specification
- Address potential confounding using propensity score methods
- Conduct pre-specified sensitivity analyses to show consistent and robust results

Pre-submission

- Develop study protocol and analysis plan and get alignment with FDA

Analytic Design

- **2-Stage outcome-free design**
 - Stage 1
 - Estimate sample size
 - Pre-specify all study components such as baseline covariates, covariate balancing methods, endpoints, outcome analysis methods, non-inferiority margin, and success criteria.
 - Identify an independent statistician with no access to outcomes for conducting covariate balancing between the study groups
- Stage 2
 - Perform covariate balancing using pre-specified baseline covariates and propensity score methods by the independent statistician
 - Achieve acceptable covariate balance

Outcome Analysis

- Perform outcome analysis by different data analysts using covariate-balanced data

Slide Courtesy of Shumin Zhang, MedTech Epi

References: Yue, Lu, and Xu. J Biopharm Stat. 2014;24(5):994–1010.; Lu N, Xu Y, Yue LQ. Stat Biopharm Res. 2020;12(2):155–163.

Research Methods Framework

A pragmatic research methods framework in designing, implementing, and evaluating RWE studies of medical devices

Outline an RWE medical device **study protocol's key components** and **general principles to follow** and provide examples

- Background: Disease, Available Therapies, and Device Risk
- Device Description
- Study Specific Objectives
- Target Population, Patient Selection, and Source for Patient Recruitment
- Outcomes: Primary, Secondary, Procedural, and Device
- Patient Exposure to the Device
- Study Design
- Study Procedures
- Required Sample Size
- Study Registration
- Monitoring Plan
- Statistical Analysis Plan (SAP)

Emphasize **two key principles**

- Pre-specification of study design and analysis
- Justification for control of confounders.

Importance of Transparent Research & Reporting

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WILEY

ORIGINAL REPORT

Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making

EMA/95098/2010 Rev.11

The European Network of Centres for
Pharmacoepidemiology and Pharmacovigilance (ENCePP)
Guide on Methodological Standards in
Pharmacoepidemiology
(Revision 11)

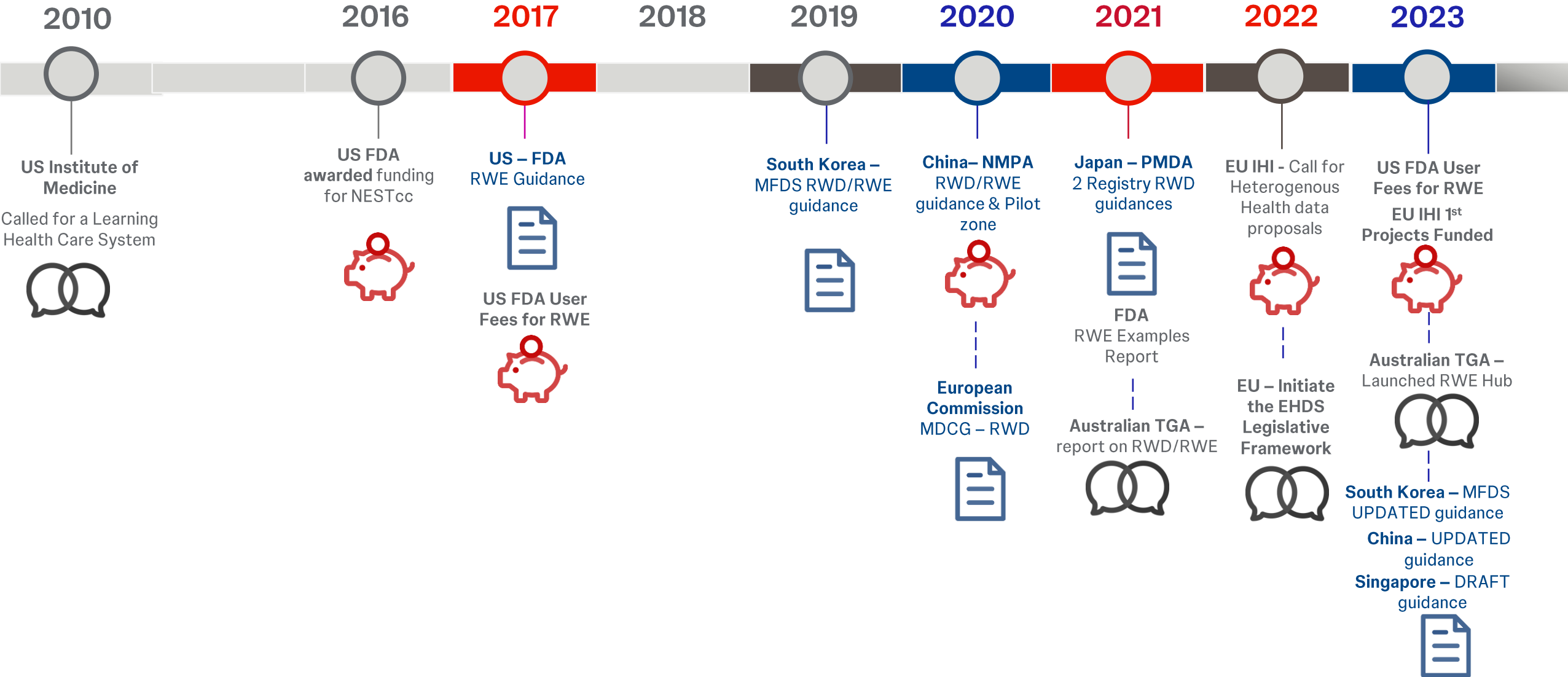
ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ISPOR/ISPE: International Society for Pharmacoeconomics and Outcomes Research / International Society for Pharmacoepidemiology

Global Real-World Evidence Infrastructure & Guidance Development



Timeline of Medical Device RWE Activities & Guidances



US FDA Update Anticipated By end of 2023

Building on Related Global Harmonization Efforts



- Integrating patient registries and innovative tools for enhanced medical device evaluation and tracking (Closed)
- Medical Device Clinical Evaluation (Closed)
- Clinical Evidence for IVD Medical Devices (Closed)
- Unique Device Identification (UDI) Application Guide & the Roadmap for implementation of UDI system (Closed)



- International Harmonisation of Real-World Evidence Terminology and Convergence of General Principles Regarding Planning and Reporting of Studies Using Real-World Data, with a Focus on Effectiveness of Medicines

Approaches to Advance the Acceptance of Real-World Evidence

A dark, monochromatic background image showing a group of people from behind, holding hands in a circle. The image is slightly out of focus and serves as a backdrop for the title text.

Collaborations Pave the Way to Advance RWE Acceptance

Clinical Societies
Patient Organizations
Public-Private Partnerships
Trade Associations
Academics

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Original Report
Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making

Marc L. Berger^{1,2*}, Harold Sox³, Richard J. Willy⁴, Diana L. Brimer⁵, Hans Georg Eckert⁶, Wim Gerrits⁷, David Madigan⁸, Amy Mahoney⁹, Sebastian Schneider¹⁰, Joanna Turkovic¹¹, Shirley Y. Wang¹², John Wharton¹³, G. David Wolfe¹⁴

ABSTRACT
Purpose: Real-world evidence (RWE) includes data from retrospective or prospective observational studies and observational inquiries and provides insights beyond those addressed by randomized controlled trials. RWE studies aim to improve health care decision making. Methods: The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoeconomics and Outcomes Research (ISPE) formed a task force to make recommendations regarding good practices for real-world evidence studies. Results: The task force considers data from single-arm clinical trials as RWE as stated in a 2007 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force report. Evidence is generated according to a research plan and interpreted accordingly, whereas data that use components of the research plan, but do not use any component of the research plan, are non-representative. RWE can inform the application of evidence from RCTs to health care decision making and provide insights beyond those addressed by RCTs. RWE studies assess both the care and health outcomes of patients in routine clinical practice and produce RWE in contrast to RCTs, patients and their clinicians choose treatments on the basis of the patient's clinical characteristics and preferences. However, since the factors that influence treatment choice in clinical practice may also influence clinical outcomes, RWE and

Introduction
Real-world evidence (RWE) is obtained from analyzing real-world data (RWD). RWE is defined here broadly as data obtained outside the context of randomized controlled trials (RCTs) generated during routine clinical practice (1). This includes data from retrospective or prospective observational studies and observational inquiries, some consider data from single-arm clinical trials as RWE as stated in a 2007 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force report. Evidence is generated according to a research plan and interpreted accordingly, whereas data that use components of the research plan, but do not use any component of the research plan, are non-representative. RWE can inform the application of evidence from RCTs to health care decision making and provide insights beyond those addressed by RCTs. RWE studies assess both the care and health outcomes of patients in routine clinical practice and produce RWE in contrast to RCTs, patients and their clinicians choose treatments on the basis of the patient's clinical characteristics and preferences. However, since the factors that influence treatment choice in clinical practice may also influence clinical outcomes, RWE and

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1098-3018/18 - see front matter © 2017 Published by Elsevier Inc. on behalf of International Society for Pharmacoeconomics and Outcomes Research (ISPOR).
http://dx.doi.org/10.1016/j.pec.2017.08.003

BMJ Open EU-funded initiatives for real world evidence: descriptive analysis of their characteristics and relevance for regulatory decision-making

Kelly Phuschke,¹ Patricia McGettigan,^{1,2} Alexandra Paccurari,^{1,3} Xavier Kurr,⁴ Alison Cave⁵

ABSTRACT
Introduction: A review of European Union (EU)-funded initiatives linked to Real World Evidence (RWE) was performed to determine whether their outputs could be used for the generation of real-world data able to support the European Medicines Agency (EMA)'s regulatory decision-making on medicines.
Methods: The initiatives were identified from publicly available websites. These topics were categorized into five areas: Data source, Methodology, Governance model, Analytical model and Infrastructure. To assess their immediate relevance for medicines evaluation, their therapeutic areas were compared with the products recommended for EU approval in 2016 and those included in the (EMA pharmaceutical business pipeline).
Results: Of 171 originally identified EU-funded initiatives, 63 were selected based on their primary and secondary objectives (35 Data source initiatives, 11 'Methodology', 10 'Governance model', 17 'Analytical model' and 25 'Infrastructure'). These 63 initiatives received over 734 million Euros of public funding. At the time of evaluation, the published outputs of the 63 completed initiatives did not always match their original objectives. Overall, public information was limited, data sources did not support their sustainability and the methods used were not always appropriate for the intended purposes. The topics matched 8 of 14 therapeutic areas of the products recommended for approval in 2016 and 11 therapeutic areas in the 2017-2019 pharmaceutical business pipeline. Haematology, gastroenterology or cardiovascular systems were poorly represented.
Conclusion: This landscape of EU-funded initiatives linked to RWE which started before 21 December 2014 highlighted that the immediate utilization of their outputs to support regulatory decision-making is limited, often due to insufficient available information and to discrepancies between objectives and objectives. Furthermore, the restricted sustainability of the initiatives impacts on their downstream utility. Multiple projects focusing on the same therapeutic areas increase the likelihood of duplication of both efforts and resources. These issues contribute to gaps in generating

Strengths and limitations of this study
► This is the first comprehensive evaluation of European Union funded initiatives linked to Real World Evidence that looks at their confidence to support regulatory decision-making on medicines.
► The analysis is based on reviews of the publicly available information provided by each initiative on their English language websites.
► The internet search was based on a list of internally agreed keywords which might not be fully exhaustive.
► The follow-up period to perform the second and third steps of our analysis was 6 months (January to June 2017). This might not have been long enough to cover the time lag between the finalisation of some of the initiatives and the publication of their final reports, therefore our analysis may not have taken into account their final outputs.
► The analysis of each initiative was reviewed by individual European Medicines Agency staff members. However, in some cases, there were (1) limited editorial input on the websites, (2) broken links and (3) both limited accumulated information on access to data, which made it difficult to determine the appropriateness of the initiatives' attributes for inclusion in the summary and constitute on their general applicability to regulatory science.

INTRODUCTION
The clinical evidence collected for the marketing authorisation of new medicines is rapidly changing. From the immediate utilisation of clinical trials (RCTs) but it is recognised that RCT data have limitations including limited representation of subjects and populations, highly selected populations and, in some scenarios, small sample sizes. As a result, their applicability to the safety and efficacy of medicines in postauthorisation use cases is unknown. There is therefore a need

DEVELOPMENT

Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure Regulatory-Grade Data Quality

Rebecca A. Miksad¹ and Amy P. Abernethy²

The role of real-world evidence (RWE) in regulatory, drug development, and healthcare decision making is rapidly expanding. Recent advances have increased the complexity of cancer care and widened the gap between randomized clinical trial (RCT) results and the evidence needed for real-world clinical decisions.¹ Instead of remaining invisible, data from the >95% of cancer patients treated outside of clinical trials can help fill this void.

DEFINING RWE
RWE is derived from the data of patients treated in real-world settings. The surge of electronic health records (EHRs), as well as other technologies, enables researchers to better understand the real-world patient experience. EHR-derived data can be combined with other data sources such as administrative claims, genomic information, and mortality datasets to create a more complete description of a patient's cancer journey. It is crucial to develop rigorous guidance for translating real-world data into actionable and meaningful RWE.

MEDICAL RESEARCH IN CHINA

Real world evidence: experience and lessons from China

Xin Sun and colleagues discuss the development of real world evidence in Chinese health care and propose strategies to improve its quality and usefulness

Worldwide, real world evidence has become a topic of broad interest in healthcare. Its definitions, however, has not achieved wide consensus.² As an umbrella term, real world evidence comes from a spectrum of studies that apply various epidemiological methods to data collected from real world settings.³ Real world data can be derived from a wide range of sources, such as routine healthcare (eg, electronic medical records), traditional epidemiological studies (eg, classical cohort studies), surveillance (eg, spontaneous adverse drug events monitoring), administrative databases (eg, death registers, medical claims), or personal devices (eg, regular blood pressure measured with mobile devices). Study designs are generally classified into three categories: pragmatic clinical trials, which may or may not be randomised; observational studies involving prospective collection of data; and observational studies using retrospective administrative databases (box 1).
Real world evidence can be used for developing medical products and informing healthcare practice and policy making. Examples of its uses include support for identification of unmet medical needs,⁴ design of registered clinical trials,⁵ post-approval drug safety assessment

- Box 1: Classification and data sources of real world studies**
- Pragmatic clinical trials**
- Varying, may include multiple sources (as below)
 - Observational studies involving prospective data collection
 - Disease registries
 - Patient surveys
 - Traditional cohort studies
 - Data collected from mobile devices
- Observational studies using existing administrative data**
- Electronic medical records
 - Medical claims data
 - Birth or death registers
 - Surveillance databases
 - Spontaneous adverse drug events databases
- and pharmacovigilance,⁶ payment and coverage decisions,⁷ healthcare quality improvement,⁸ new indications of medical products,⁹ assessment of healthcare technologies,¹⁰ and clinical practice guideline development.¹¹ In addition, the abundance and diversity of data allows exploration of clinical research questions other than healthcare interventions, such as disease burden, prognosis, and clinical predictions.
A common misunderstanding is that traditional randomised controlled trials do not reflect the real world setting, and that all observational studies are real world. In fact, randomised controlled trials may include components of real world settings (eg, broad eligibility criteria and pragmatic trials),¹² and real world studies may have elements that are not part of regular care (eg, intensified follow-up). Instead of a dichotomy there is a continuum in that study features of traditional randomised controlled trials and real world studies, with external validity increasing as more real world features are included in the design.
Some also argue that observational studies have advantages over randomised controlled trials in assessing the 'real

- KEY MESSAGES**
- Real world evidence has gained wide attention in China in the past few years
 - Disease registries and retrospective databases are the two main types of real world studies in China. Limited resources are available for pragmatic clinical trials
 - Use of real world evidence for healthcare practice and policy decisions is limited at present, although there are a few important governmental initiatives
 - To advance the real world evidence movement, China must develop an explicit policy to ensure consistent data standards, safety, and security, and access to data

A Framework for Regulatory Use of Real-World Evidence

September 13, 2017

In specific circumstances, real-world evidence can contribute to a fuller understanding of the benefits and risks of medical device use in patients in real-world clinical practice, as a means of supporting regulatory decision making. The US Food and Drug Administration (FDA) recognizes the wealth of data available from clinical experience, and ongoing efforts to balance premarket and postmarket data collection and consider the potential benefits and risks represent an attempt to streamline the regulatory approval process while generating robust and meaningful evidence to support the safety and effectiveness of devices.
As currently defined by the FDA, real-world data are data relating to patient health status and/or the delivery of health care that are routinely collected from a variety of sources, which can include data derived from electronic health records, claims and billing information, product and disease registries, patient-generated data including home-use settings, and other sources. Real-world evidence is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data.
The use of real-world evidence has many potential benefits, including swifter identification of safety problems following the introduction of a device into the general marketplace, the ability to better understand the benefit-risk profile of devices, and the reduction



Mobilizing mHealth Innovation for Real-World Evidence Generation

REGULATORY UPDATE

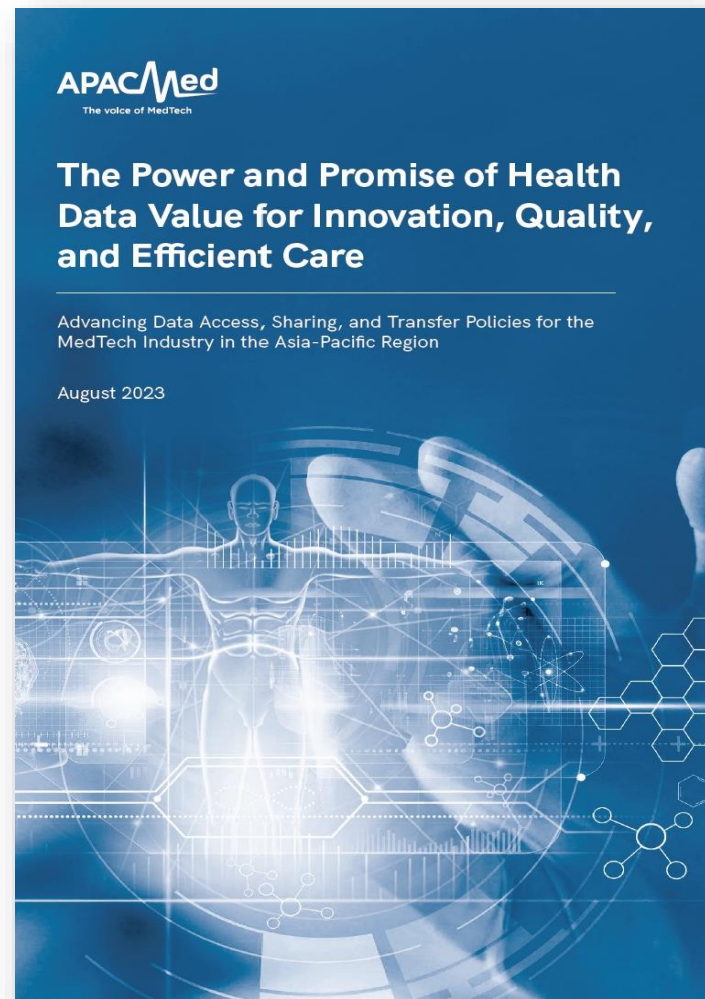
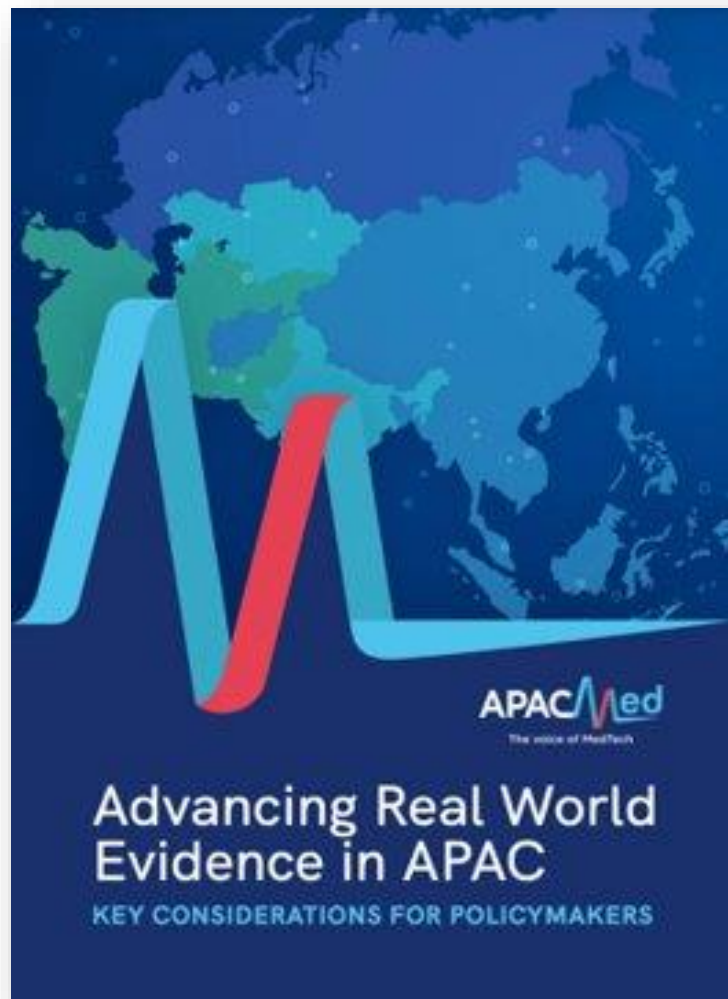
Current Considerations on Real-World Evidence Use in FDA Regulatory Submissions

Examples and decision making from the Center for Devices and Radiological Health's Peripheral Interventional Devices Branch.

BY ELENI WHATLEY AND MISTI MALONE

The Peripheral Interventional Devices Branch of the Division of Cardiovascular Devices at the FDA has considered real-world evidence sufficient to support the approval of several recent regulatory submissions for both marketing approval as well as postmarket surveillance. As noted in the real-world evidence guidance document, a good example where real-world evidence may be valuable for the organization is in the use of an approved or cleared device, particularly when the studied indication is similar to the approved indications (eg, longer lesion lengths, specific aneurysm types).¹ This strategy has successfully been employed

PREMARKET USE OF REAL-WORLD EVIDENCE
The Peripheral Interventional Devices Branch of the Division of Cardiovascular Devices at the FDA has considered real-world evidence sufficient to support the approval of several recent regulatory submissions for both marketing approval as well as postmarket surveillance. As noted in the real-world evidence guidance document, a good example where real-world evidence may be valuable for the organization is in the use of an approved or cleared device, particularly when the studied indication is similar to the approved indications (eg, longer lesion lengths, specific aneurysm types).¹ This strategy has successfully been employed



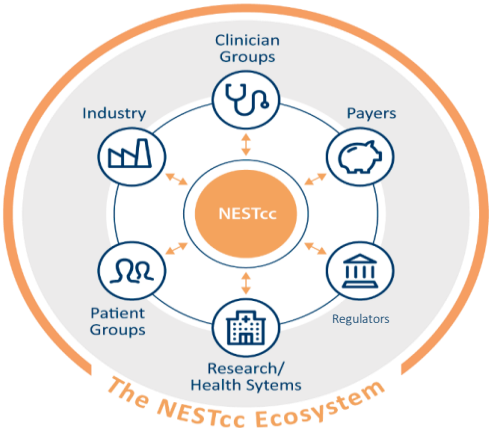
APACMed policy position paper: <https://apacmed.org/content/uploads/2022/03/Advancing-Real-World-Evidence-in-APAC.pdf> *

Multi-Stakeholder Partnerships and Collaborations



South Korea

- NHIS** Used national public health data
- Published guideline of RWE application on MD
- Designated 5 "Health Care Data Central Hospital"
- Established "Big Data Center" with high quality health data
- Conducted RWE projects



Advancing Regulatory Science and Evidence Drives Innovation



Innovation in Evidence Generation is Critical

- Global market quickly evolving
- Capturing the patient's experience and care pathway
- Improving the evidence portfolio to be more diverse and representative of all our patients



Importance of Appropriate Access to Real-World Data

- Conduct robust research
- Development of Digital Health Innovations



Real-World Evidence is an Enabling Tool

- Innovative Regulatory Pathways: Orphan, Pediatric and Rare diseases
- Innovation in clinical care and technology



감사합니다 Natick

Grazie

Danke Ευχαριστίες Dalu

Thank You

Köszönöm

Tack

Спасибо Dank

Gracias

谢谢

Merci

Seé

ありがとう

Obrigado