Real-World Evidence: Tools to Support Innovation

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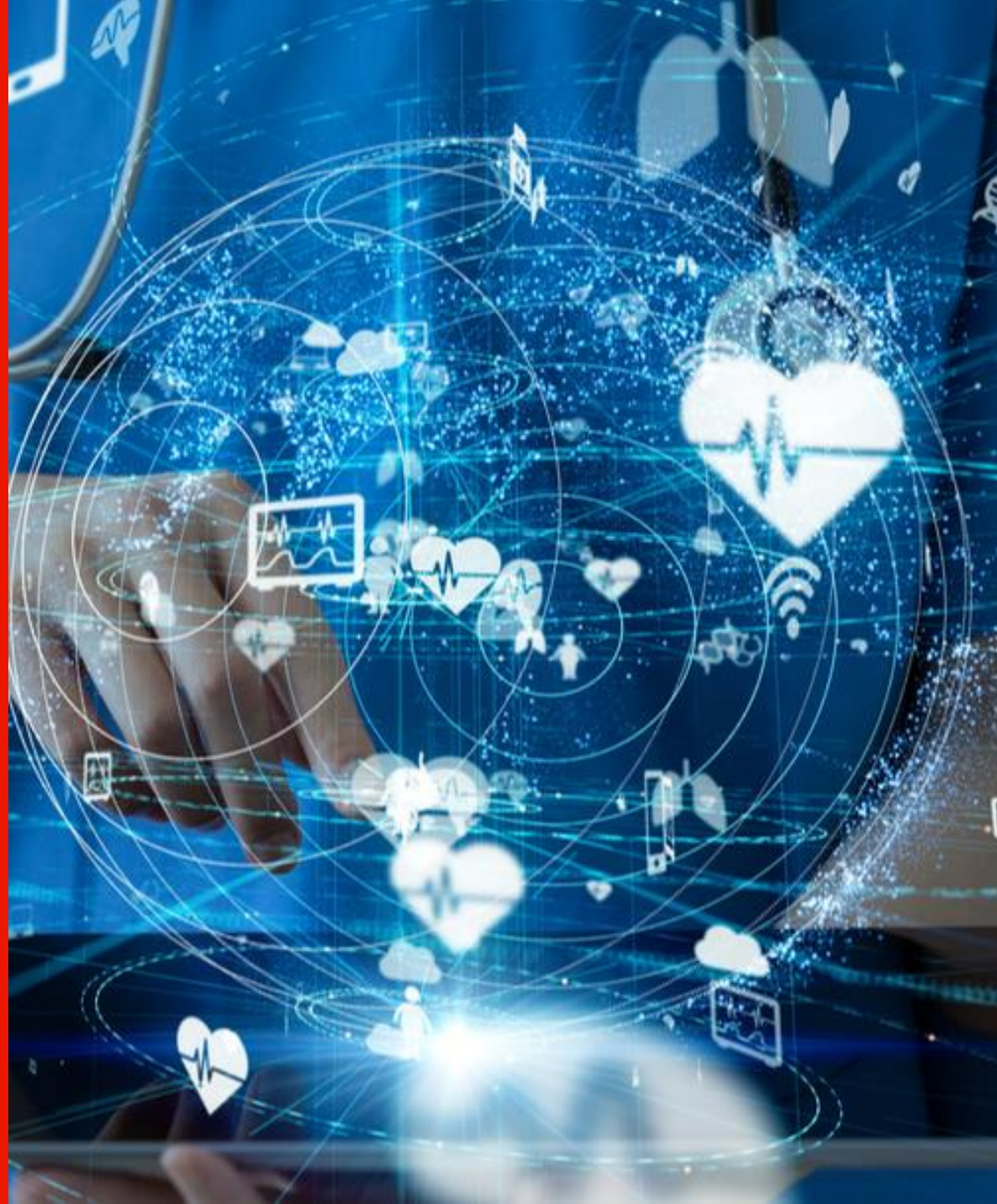


Topics

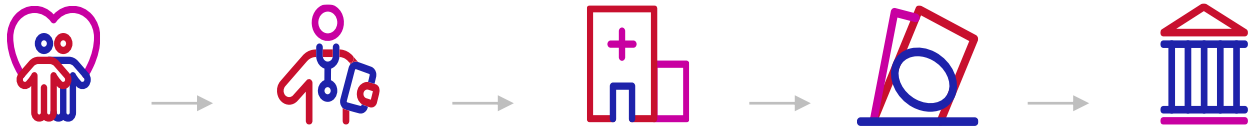
- Fundamental of Real-World Data and Real-World Evidence for Regulatory Activities
- Global Real-World Evidence Instructure and Guidance Development
- Approaches to Advance the Acceptance of Real-World Evidence

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

Transparency

- Posting/registering protocol
- Interactions between sponsor and authority
- Documenting data provenance
- Process for protocol changes
- Criteria for submitting an IDE or similar requirements

Uses of RWD/RWE

- Pre, Post market
- Submission types (e.g., High to Low Risk, implantables, humanitarian/rare/orphan, pediatrics)
- Accepted uses (e.g., supplemental, primary clinical evidence)

Data Quality

Data Collection

- Allowable data sources
- Data set characterization
- Extraction, curation practices
- Data governance/ethics (e.g., consent)
- Define relevance and/or reliability

Study Design

- Research question guidance
- Data methods (e.g., Common Data Model, data dictionary requirements, linkages between different sources)
- Analytical methodology (e.g., weighting, bias)

Regulatory Bar Has Not Changed

Determining RWD “Fit-for-Purpose”

Data Relevance + **Data Quality** = **Fit-for-Purpose Data**

- 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

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Source: Duke-Margolis Center for Health Policy White Paper: Characterizing RWD Quality and Relevancy for Regulatory Purposes (October 1, 2018). Available at https://healthpolicy.duke.edu/sites/default/files/atoms/files/characterizing_rwd.pdf); Janssen Epidemiology Presentation

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

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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.

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Reference: https://nestcc.org/data-quality-and-methods/

Importance of Transparent Research & Reporting

Received: 21 July 2017 | Revised: 26 July 2017 | Accepted: 28 July 2017

DOI: 10.1002/pds.4297

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

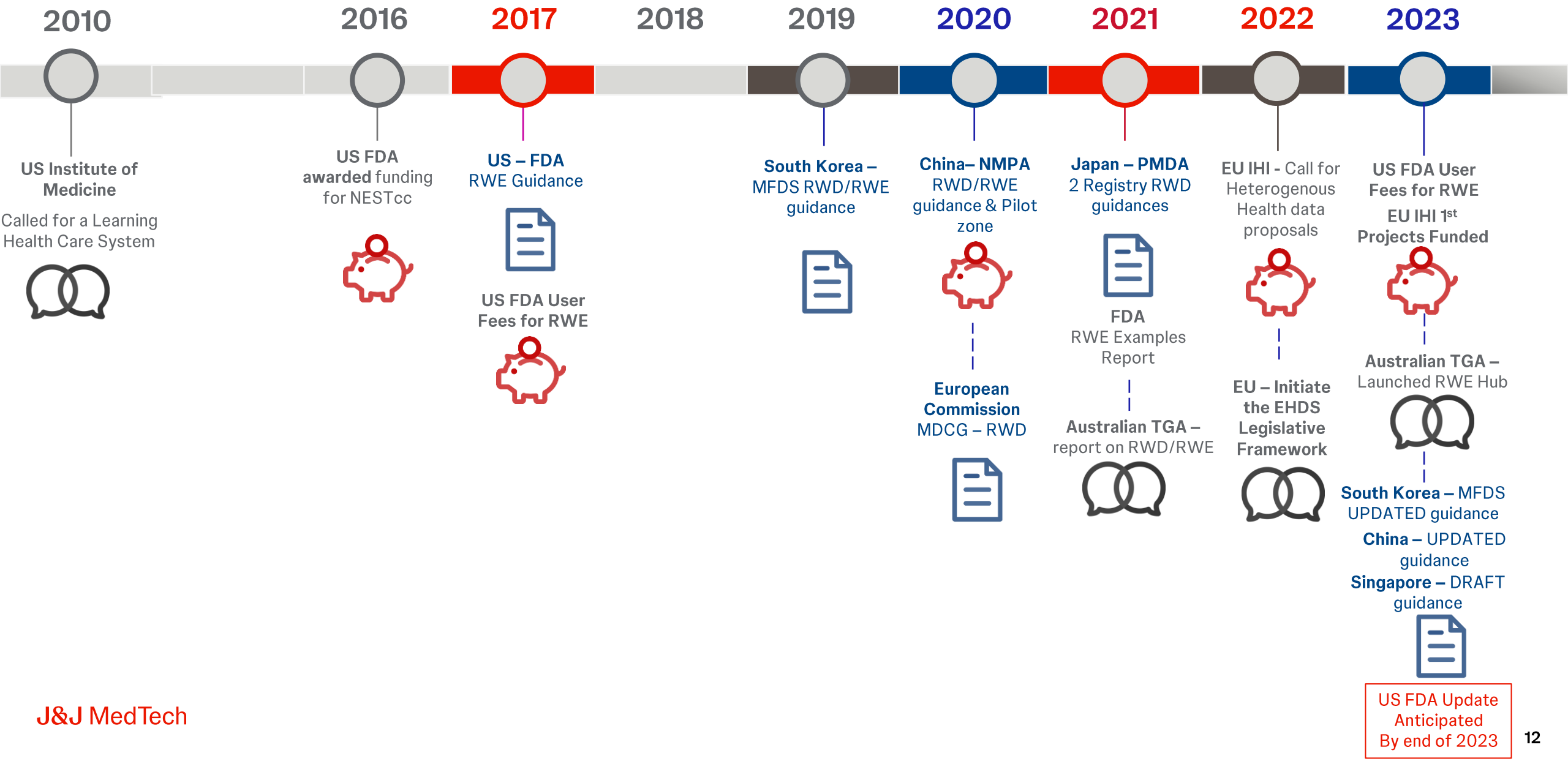
The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology

(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 Instructure & Guidance Development

Timeline of Medical Device RWE Activities & Guidances



Building on Related Global Harmonization Efforts

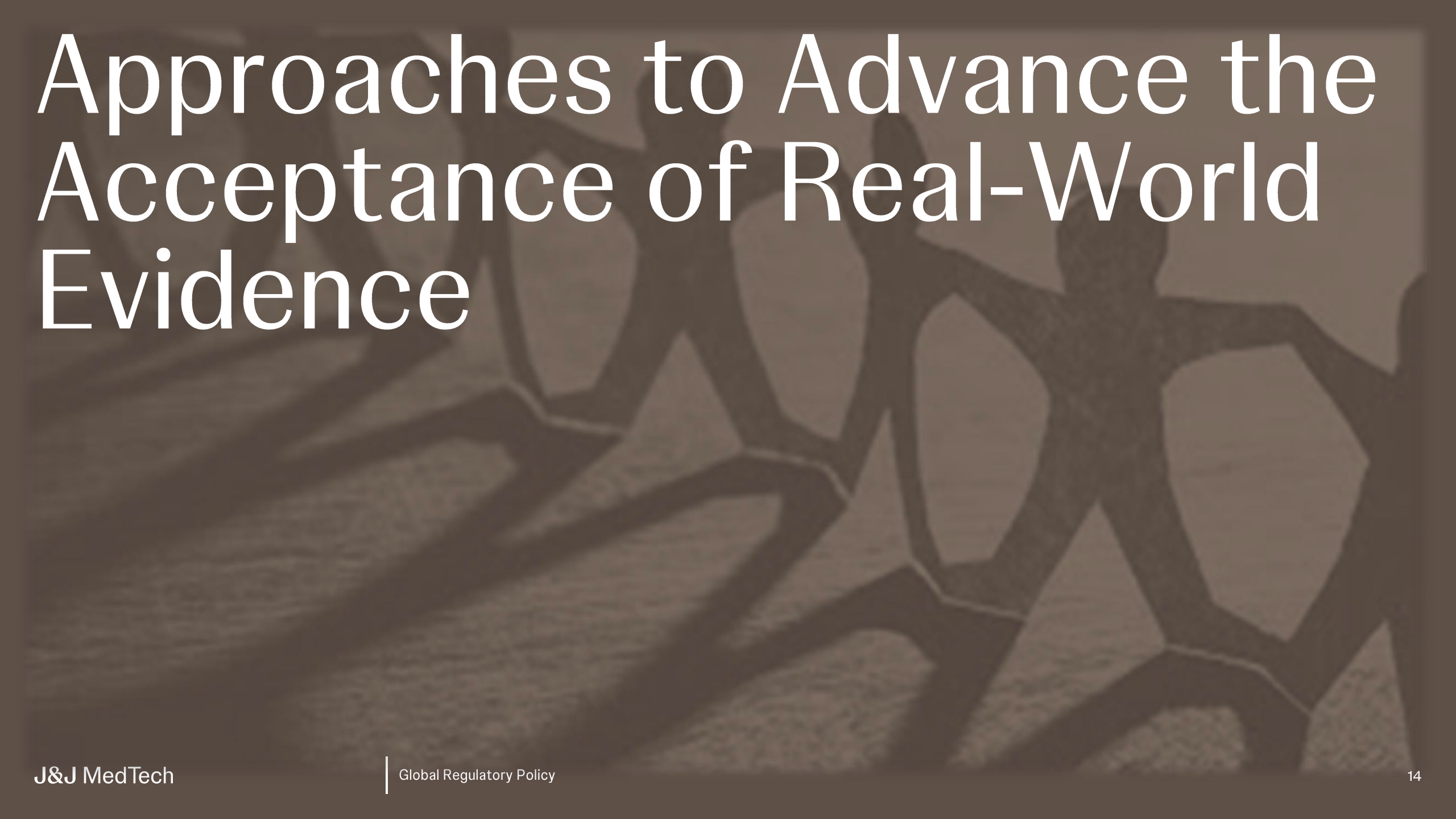
IMDRF International Medical Device Regulators Forum

- 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)

ICH harmonisation for better health

- 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

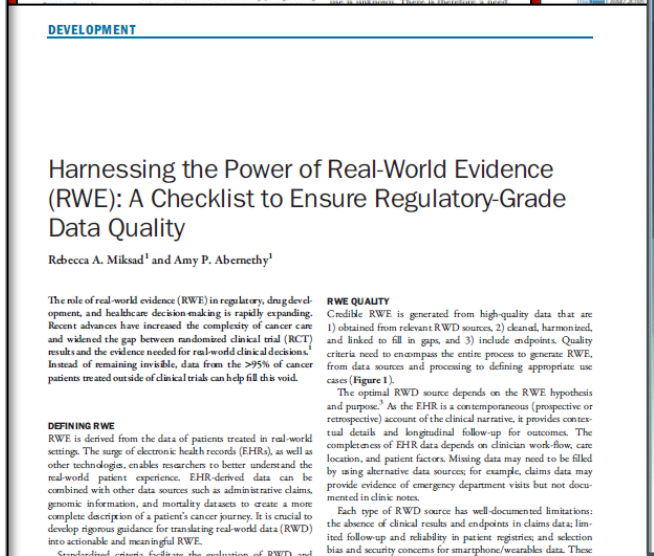
Approaches to Advance the Acceptance of Real-World Evidence

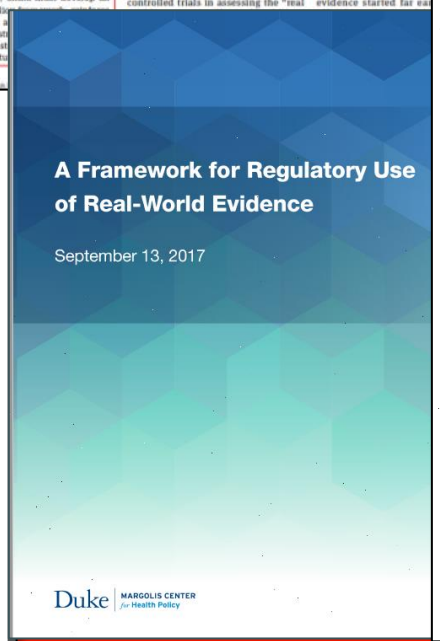


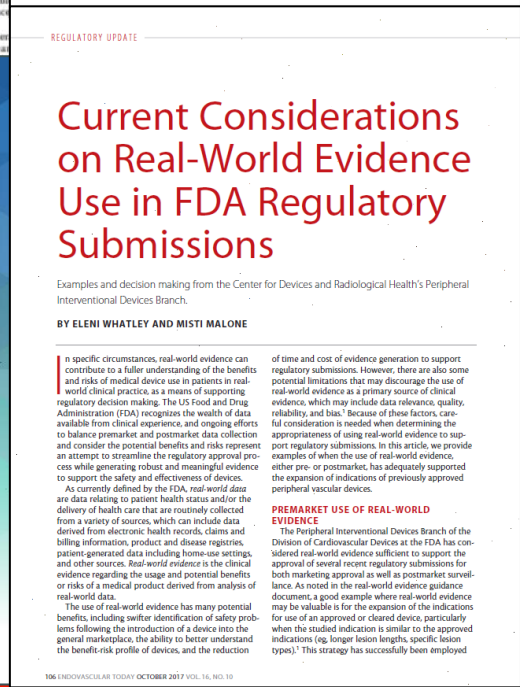
Collaborations Pave the Way to Advance RWE Acceptance

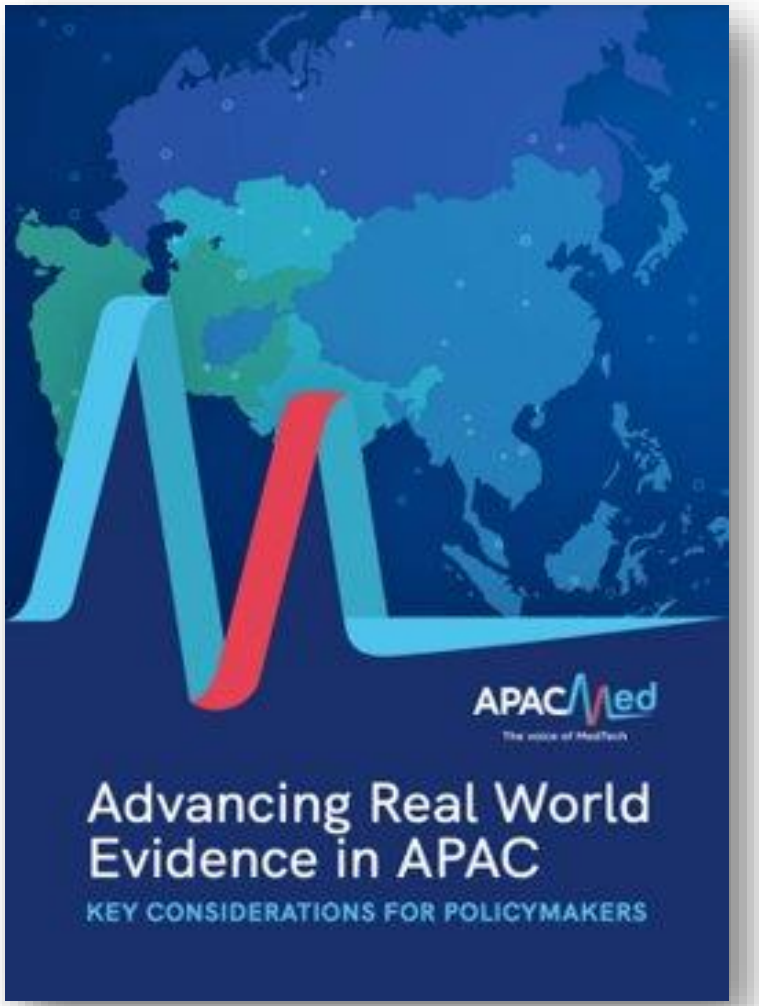
Clinical Societies
Patient Organizations
Public-Private Partnerships
Trade Associations
Academics

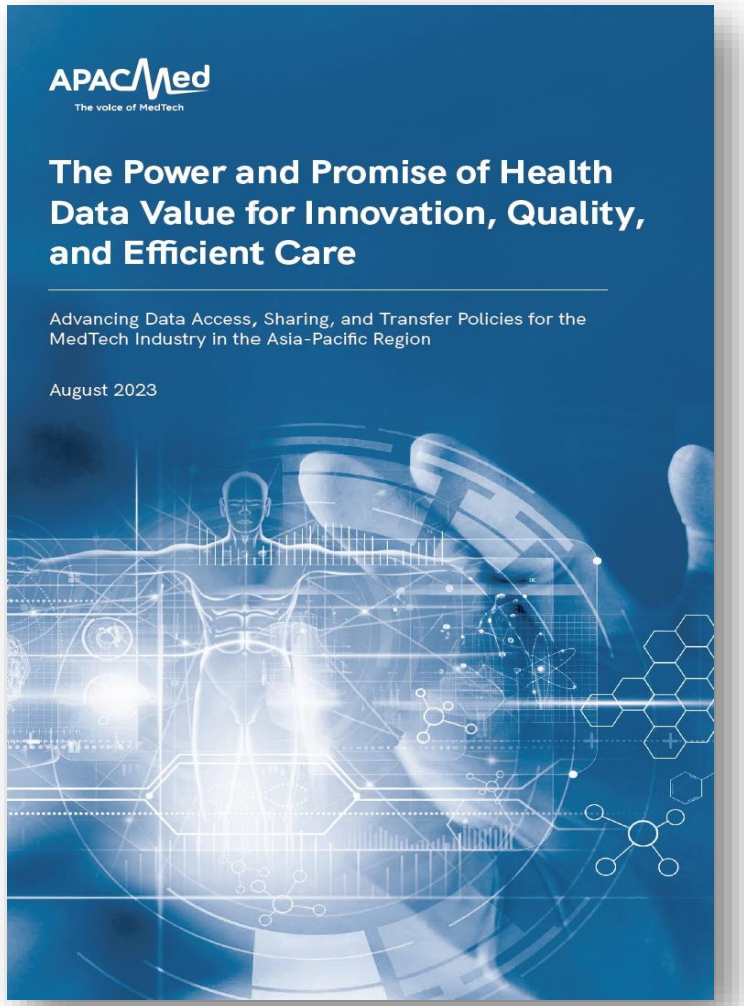
Johnson&Johnson
MedTech











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

Multi-Stakeholder Partnerships and Collaborations

HBD

CIN
Clinical Innovation Network

海南自由贸易港
博鳌乐城国际医疗旅游先行区
HAINAN FREE TRADE PORT
BOAO HOPE CITY

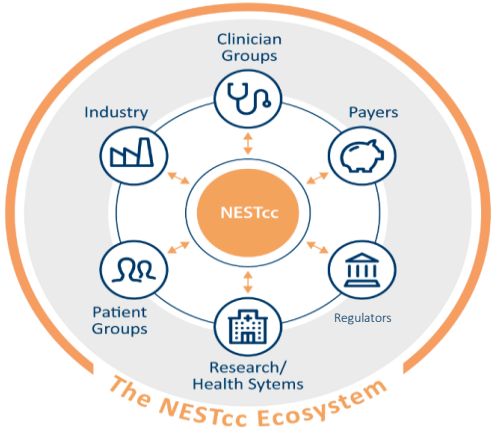
RWD
海南乐城真实世界研究院

innovative health initiative

IDERHA
integrating health data

South Korea

- NHISS: 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



MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM

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
obrigado
Thank You
Köszönöm
Tack
Спасибо
Dank
Gracias
谢谢
Merci
Seé
ありがとう