IMDRF
International Medical Device Regulators Forum

EU2023
EUROPEAN UNION Chair

European Commission

European Union

11:40 – 13:00

Session 2:
Real World Evidence

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11:40 – 11:50

Status of Global Acceptance of RWD/RWE in regulatory activities and lessons learned from various regions

Heather M. Colvin

Director, Evidence & Outcomes Policy, Johnson & Johnson MedTech

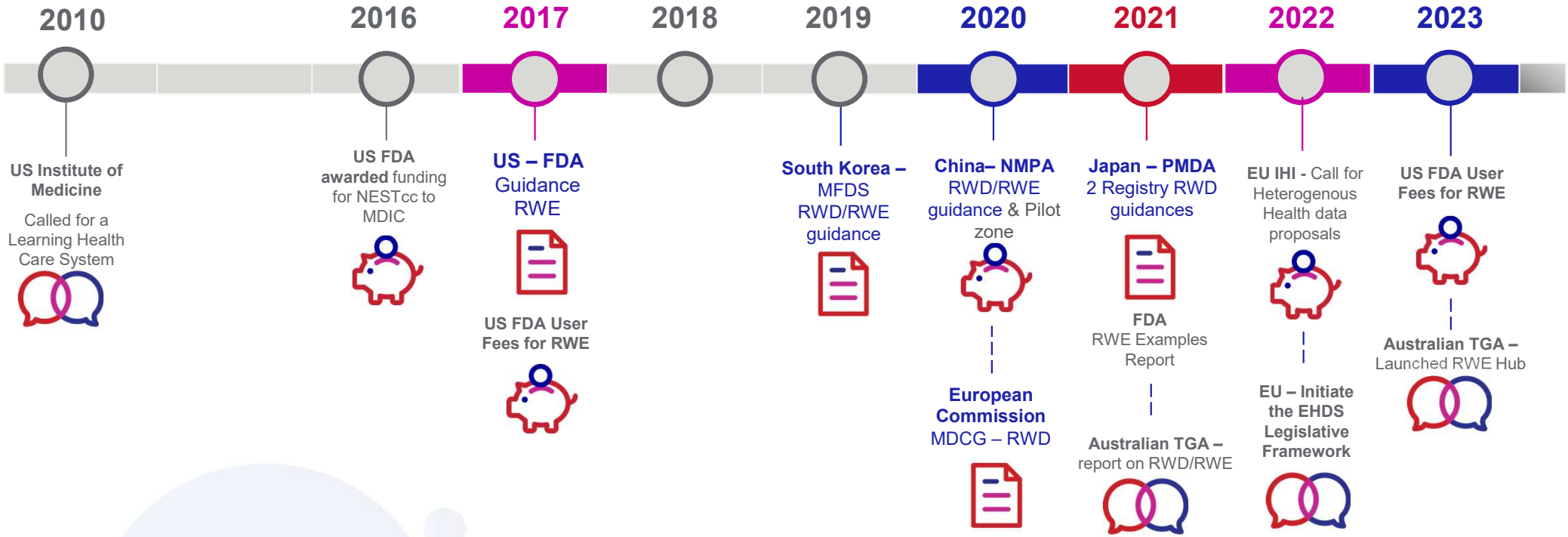
European Commission | European Union

Slide 108

AN(0 Begginign of slides start with timing allocation but it seems like this wasn’t followed? Could oyu kindly insert in each speaker's slide their timing alocation please? Same applies for Sessio n1

ALKHAYAT Nada (SANTE), 2023-03-20T10:26:02.743

Timeline of Medical Device RWE Activities & Guidances



Investment in Real-World Data and Evidence Capabilities

FDA

User Fee and Congressional Commitments

- Updated Guidance(s)
- Training for reviewers
- Reporting and Public Engagement
- Investment in infrastructure, processes and policies to improve the access to RWD and the generation of RWE

EU-MDR

RWD/RWE for EU MDR

- Guidance on sufficient clinical evidence for legacy devices (MDCG 2020-6)
- Post-market clinical follow-up (PMCF) Plan Template (MDCG 2020-7)

ihi innovative health initiative

- 2022 Call for Proposals for Access and integration of "heterogeneous health data" for improved healthcare (2023 launch)

CHINA NMPA

Real-World Evidence Activities

- 2019 Real-World Evidence Guidance(s) release
- Annual RWE conferences
- Creation of RWE Pilot Zones

BoAo Lecheng Pilot Zone

Great Bay Area (GBA)

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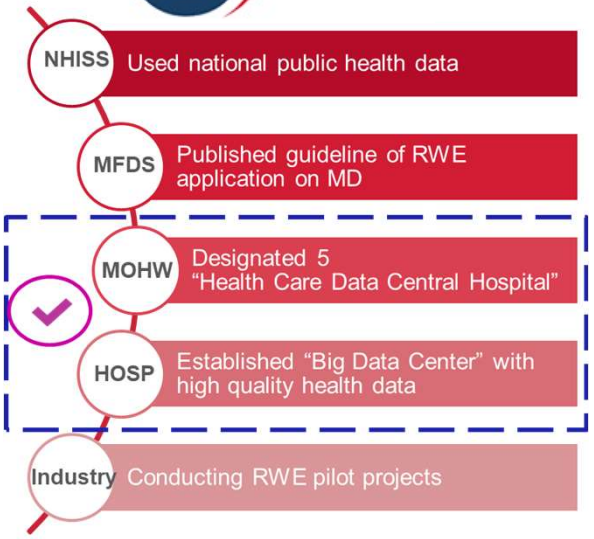
Investment in Real-World Data and Evidence Capabilities

KOREA MFDS



- Guidance for Utility of Health Care Data
- RWE guidance revision

JAPAN

Real-World Evidence Guidances

- Basic Principles on Registry Utilization for Applications
- Points to be Considered to Ensure Reliability in Utilization of Registry Data for Applications
- Data infrastructure and access (e.g., Mid-Net, National Database of Health Insurance Claims, and private companies' medical databases)
- Engagement with external stakeholders

TGA Health Safety Regulation

2021 Report Findings

- Ambiguity (internally and externally) limits adoption
- Need for improved communication

2022 Action Plan Created

2023 RWE Hub

- Adopted definition
- Launched online RWE Hub

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Lessons Learned

Relevance of Study Question	Data Characterization Fit for Purpose Assessment	Rigor of the Study Design and Analytical Methods	Totality of Evidence and Strength of the Findings
			
• Various Uses of RWE • Access to relevant RWD • Determining the feasibility • Limitation of different data sources	• Pooling & linking data • Differences in health care systems • Understanding the RWD and the Standard of Care	• Protocol development • Benefit of different methodological approaches	• Different roles RWE can play in submission • Complementary to traditional clinical evidence approaches

Establish ongoing transparency/communication through the study (pre-, during, post)

Challenges and Opportunities

Technical

Data "Quality"

- Terminology
- Standard of care and existing codes
- Common data models
- Characterization of data sources and outcomes

Methodology

- Alignment on appropriate analytic methods
- Data extraction and curation
- Data linkage capability

Policy & Process

Data Access & Sharing

- Data access/sharing policies
- Multi-stakeholder data sharing agreements
- Oversight/auditing for decision-making

Transparency

- Patient protections and informed consent
- Ethical concerns among professionals and public
- Transparency and reporting requirements

Adapted from The Network For Excellence in Health Innovation. Real World Evidence: A New Era for Health Care Innovation. (2015) Issue Brief.

Growing Need for Evidence

Evolution of Medical Products

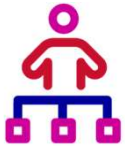
Expanding Sources of Clinical Data & Evidence

Emerging Needs of Decision Makers

Possible Next Steps

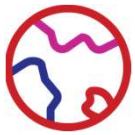
Build on the foundation laid by the early Guidance documents and experiences

Enable appropriate access to health data for quality research



Advance multi-stakeholder partnerships to develop consensus

- RWD Characterization and Fit-for-Purpose Assessment requirements
- Analytical methods
- Appropriate transparency expectations



Focus on International Harmonization

THANK YOU

Heather Colvin

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12:00 – 12:10

How to incorporate real-world data sources into regulatory decision-making processes?

Tom Melvin

Associate Professor of Medical Device Regulatory Affairs, Trinity College Dublin

European Commission | European Union

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

How to incorporate real-world data sources into regulatory decision-making processes?

23rd International Medical Device Regulators Forum

Tom Melvin
Associate Professor of Medical Device Regulatory Affairs
Director, MSc Medical Device Regulatory Affairs

Typical uses of RWD

Changes to claims / indications / intended purpose

Post-approval monitoring

Device traceability

Distribution of safety communications

Other uses of RWD

Orphan / pediatric / breakthrough / humanitarian uses

For devices with multiple indications – can track outcomes

To set more predictable clinical evidence requirements based on available knowledge

To understand human factors, usability, the learning curve and device interactions

REGION	AUTHORITY	AVAILABLE DOCUMENTATION
USA	FDA	Guidance: Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products
		Framework for FDA's Real-World Evidence Program
		Guidance: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products
		Guidance: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
		Guidance: Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products
		Guidance: Data Standards for Drug and Biological Product Submissions Containing Real-World Data
		Guidance: Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics
		Guidance: Use of Electronic Health Records in Clinical Investigations
		Guidance: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
		Publication 2020: Randomized, observational, interventional, and real-world- What's in a name?
		Publication 2022: Real-World Evidence- Where Are We Now?
Europe	EMA	Operational, Technical, and Methodological (OPTIMAL) framework for regulatory use of RWE in regulatory decision making
		Regulatory Science to 2025 strategic document
UK	MHRA	MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions
		MHRA guideline on randomised controlled trials using real-world data to support regulatory decisions
	NICE	NICE real-world evidence framework
Australia	TGA	Real world evidence and patient reported outcomes
		Clinical evidence guidelines for medical devices
		An Action Plan for Medical Devices
Canada	Sante Canada-Health Canada	Optimizing the Use of Real-World Evidence to Inform Regulatory Decision-Making
		Elements of Real-World Data/Evidence Quality throughout the Prescription Drug Product Life Cycle
	CADTH	Real-World Evidence for Decision-Making
Greater China	NMPA	Guideline on using real-world evidence to support drug research & development and review
		Technical guidelines (trial) for real-world research and support for drug research and development and review of children
		Guideline on using real-world evidence to support medical device evaluation (Trial)
		Guideline on using real-world data to generate real-world evidence (trial)
	TFDA	Basic considerations for real-world evidence supporting drug development
Japan	RWD Working Group of PMDA	Guidelines for the Conduct of Pharmacoepidemiological Studies in Drug Safety Assessment with Medical Information Databases
		Points to Consider for Ensuring the Reliability of Post-marketing Database Study for Drugs
		Points to Consider for Ensuring the Reliability of Post-marketing Database Study for Medical Devices
		Procedures for Developing Post-marketing Study Plan (originally published as "Procedures for Developing Post-marketing Study Plan
		Questions and Answers (Q&A) on Points to Consider for Ensuring the Reliability of Post-marketing Database Study for Drugs
		Points to Consider for Ensuring the Reliability of Post-marketing Database Study for Regenerative Medical Products
		Basic Principles on Utilization of Registry for Applications
		Points to consider for Ensuring the Reliability in Utilization of Registry Data for Applications

INTERNATIONAL INITIATIVES	SCOPE
REAL World Data In Asia for Health Technology Assessment in Reimbursement (REALISE) working group	A framework for the use of RWD and RWE in decision-making in Asia, which is designed to be adapted to users' local needs, reflecting an awareness of the differing practical barriers occurring in different countries
Duke-Margolis Center for Health Policy. Developing real-world data and evidence to support regulatory decision-making.	Cluster of stakeholders, which has released a number of whitepapers, including a suggested regulatory framework for the use of RWD and RWE in decision-making in the USA
HTx Next Generation Health Technology Assessment	A European Union (Horizon 2020) funded program monitoring the RWE use for the decision-making process throughout Europe, aiming to construct the future Framework for the "Next Generation Health Technology Assessment (HTA) and to enable the decision-making process to rely on patient-centred evidence, real-time, and socially oriented reimbursement policies in Europe
INNOVATIVE MEDICINES INITIATIVE'S COLLABORATIVE RESEARCH PROJECTS (105)	
Clinical Trials Transformation Initiative	Initiative aiming to modernize clinical trials, which has released a position paper on accelerating the use of RWD in clinical trials
Europe's Innovative Medicines Initiative's GetReal project	Initiative aiming to incorporate data from real-life clinical settings into drug development
RCT DUPLICATE (Randomized Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology) initiative	Led by Brigham and Women's Hospital in collaboration with the FDA and other academic and industry stakeholders, it is engaged in replicating large-scale RCTs using RWD sources to evaluate the latter's ability to replicate findings from RCTs and validate findings for RWE acceptance
ADAPT-SMART (Accelerated Development of Appropriate Patient Therapies: A Sustainable, Multi-Stakeholder Approach From Research to Treatment Outcomes)	Project to the EMA's Adaptive Pathways Pilot and the Medicines Adaptive Pathway to Patients concept. ADAPT-SMART generates evidence throughout the product life cycle and develops methods for adjusting for biases
Big Data for Better Outcomes initiative	European research programme aiming to develop enablers to support health care system transformation through the use of big data. The initiative has developed platforms for integrating and analysing diverse real-world data sets
HARMONIZATION INITIATIVES	
International Council for Harmonisation (ICH)	ICH has published a reflection paper on Good Clinical Practice and put forth plans to update the existing E8 (General Considerations for Clinical Trials) and the E6 (Guideline for Good Clinical Practice) guidelines to leverage data from more flexible study designs and a diversity of data sources. In particular, the ICH proposed to include discussion on pragmatic study designs and guidance on how RWD collection could be used to supplement or even replace traditional data collection within the E6
European Health Data & Evidence Network	European consortium aiming to harmonize health records to the Observational Medical Outcomes Partnership data model and create an EU-wide architecture for federated analysis of RWD
Council for International Organizations of Medical Sciences (CIOMS) - Working Group XIII - Real-World Data and Real-World Evidence in Regulatory Decision Making	The primary goal of the proposed CIOMS WG is to develop, for global use, a consensus report and recommendations on principles to be applied regarding triggers, objectives, research questions, design features, and timing of RWD and RWE as part of the regulatory process for products in the peri-approval stage of development or for authorized products
International Society for Pharmacoeconomics and Outcomes Research (ISPOR); Real World Evidence Strategic Initiative	Working to improve standards and practice for the collection and analysis of RWD. 4 Joint International Society for Pharmacoepidemiology (ISPE) -ISPOR Good Practices Reports have been published 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 Healthcare Decision Making Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0 Making Real-World Evidence More Useful for Decision Making (editorial) All Good Practices Reports for Real-World Data
International Coalition of Medicines Regulatory Authorities (ICMRA)	During a 2020 ICMRA working group meeting on building international cohorts, for example, the EMA, FDA, Agencia Espanola de Medicamentos y Productos Sanitaros, and Health Canada worked together to develop criteria to help prioritize key regulatory and public health research questions for international collaboration (e.g., large sample size, regional comparisons, and development of infrastructure)
International Network of Agencies for Health Technology Assessment (INAHTA)	INAHTA is a network of 50 HTA agencies that support health system decision-making, focusing on the sharing of information about producing and disseminating HTA reports for evidence-based decision making
International Society for Pharmaceutical Engineering (ISPE)	The International Society for Pharmaceutical Engineering is a non-profit association serving its members by leading scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle and has issued a position paper on the use of RWE

Ref, Valla V, et al. Use of Real-World Evidence for International Regulatory Decision Making in Medical Devices. International Journal of Digital Health. 2023; 3(1): 1, 1–27. DOI: https://doi.org/10.29337/ijdh.50

Europe

Move from Directive to Regulation system

Changed clinical evidence requirements

New clinical evidence processes

European Health Data Space - EHDS

Brexit and Swixit

The big picture

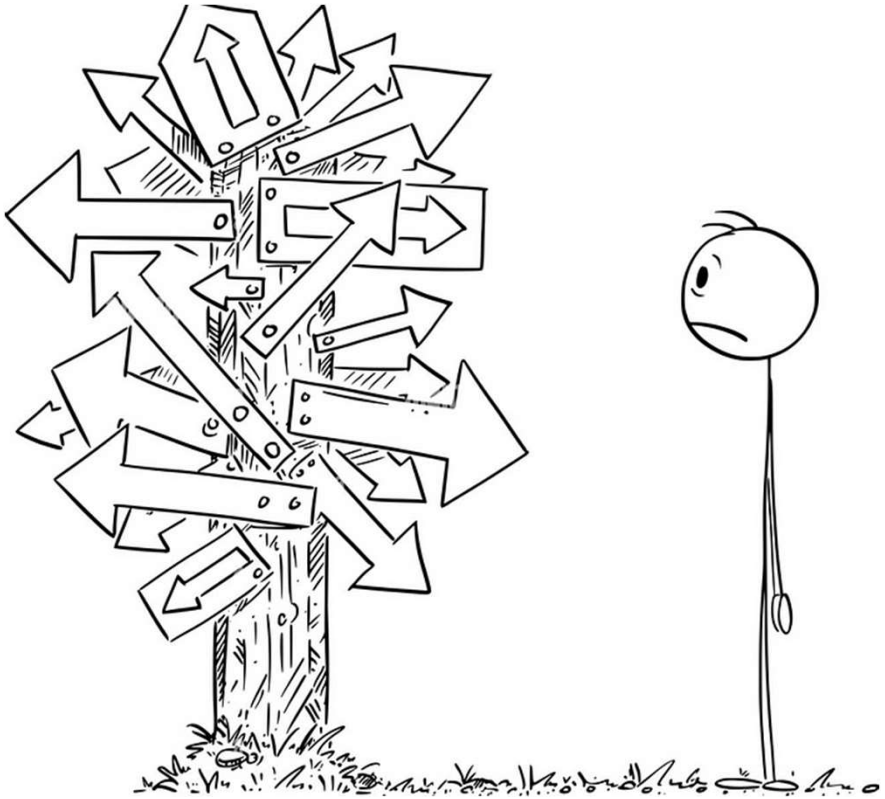
The big picture

Is there a willingness to work towards common clinical methodology in areas where RWD is available and regulatory requirements are similar?

If there is…

We need to map the areas where clinical evidence requirements are the same / different

This is needed to understand the starting point that we can build on



Example – snapshot of clinical data requirements in EU vs. US

Similarities

510k and **safety & performance** pathway in US

Article **61(10)** and **61(6)(b)** in EU

Differences

Safety and effectiveness in US

Safety and performance as intended by manufacturer in EU

RWD can help to improve clinical evidence requirements

Predictable	Proportionate	Reproducible
Setting **objective performance criteria** where possible **Common performance criteria** for lower risk devices Setting requirements for **equivalence** and **iterative** change	**Breakthrough** / **Orphan** / **Pediatric** devices **Lower risk** devices where **non-clinical & post-market** is sufficient	**Poolability** of registry data Methodologic **transparency** Assessing why outcomes are **similar** / **different**

The fine detail

The fine detail

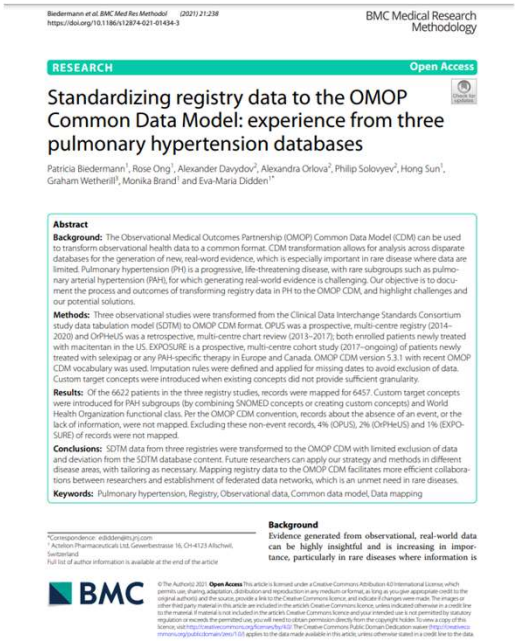
Initiatives to pool data

Policy for data privacy and management

Support registries and standardise interactions with industry and regulators

Develop quality assessments for registries

Example - Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM)



Biedermann et al. BMC Med Res Methodol (2021) 21:238
https://doi.org/10.1186/s12874-021-01434-3

BMC Medical Research Methodology

RESEARCH — Open Access

Standardizing registry data to the OMOP Common Data Model: experience from three pulmonary hypertension databases

Patricia Biedermann[1], Rose Ong[1], Alexander Davydov[2], Alexandra Orlova[2], Philip Solovyev[2], Hong Sun[1], Graham Wetherill[3], Monika Brand[1] and Eva-Maria Didden[1*]

Abstract

Background: The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) can be used to transform observational health data to a common format. CDM transformation allows for analysis across disparate databases for the generation of new, real-word evidence, which is especially important in rare disease where data are limited. Pulmonary hypertension (PH) is a progressive, life-threatening disease, with rare subgroups such as pulmonary arterial hypertension (PAH), for which generating real-world evidence is challenging. Our objective is to document the process and outcomes of transforming registry data in PH to the OMOP CDM, and highlight challenges and our potential solutions.

Methods: Three observational studies were transformed from the Clinical Data Interchange Standards Consortium study data tabulation model (SDTM) to OMOP CDM format. OPUS was a prospective, multi-centre registry (2014–2020) and OrPHeUS was a retrospective, multi-centre chart review (2013–2017); both enrolled patients newly treated with macitentan in the US. EXPOSURE is a prospective, multi-centre cohort study (2017–ongoing) of patients newly treated with selexipag or any PAH-specific therapy in Europe and Canada. OMOP CDM version 5.3.1 with recent OMOP CDM vocabulary was used. Imputation rules were defined and applied for missing dates to avoid exclusion of data. Custom target concepts were introduced when existing concepts did not provide sufficient granularity.

Results: Of the 6622 patients in the three registry studies, records were mapped for 6457. Custom target concepts were introduced for PAH subgroups (by combining SNOMED concepts or creating custom concepts) and World Health Organization functional class. Per the OMOP CDM convention, records about the absence of an event, or the lack of information, were not mapped. Excluding these non-event records, 4% (OPUS), 2% (OrPHeUS) and 1% (EXPOSURE) of records were not mapped.

Conclusions: SDTM data from three registries were transformed to the OMOP CDM with limited exclusion of data and deviation from the SDTM database content. Future researchers can apply our strategy and methods in different disease areas, with tailoring as necessary. Mapping registry data to the OMOP CDM facilitates more efficient collaborations between researchers and establishment of federated data networks, which is an unmet need in rare diseases.

Keywords: Pulmonary hypertension, Registry, Observational data, Common data model, Data mapping

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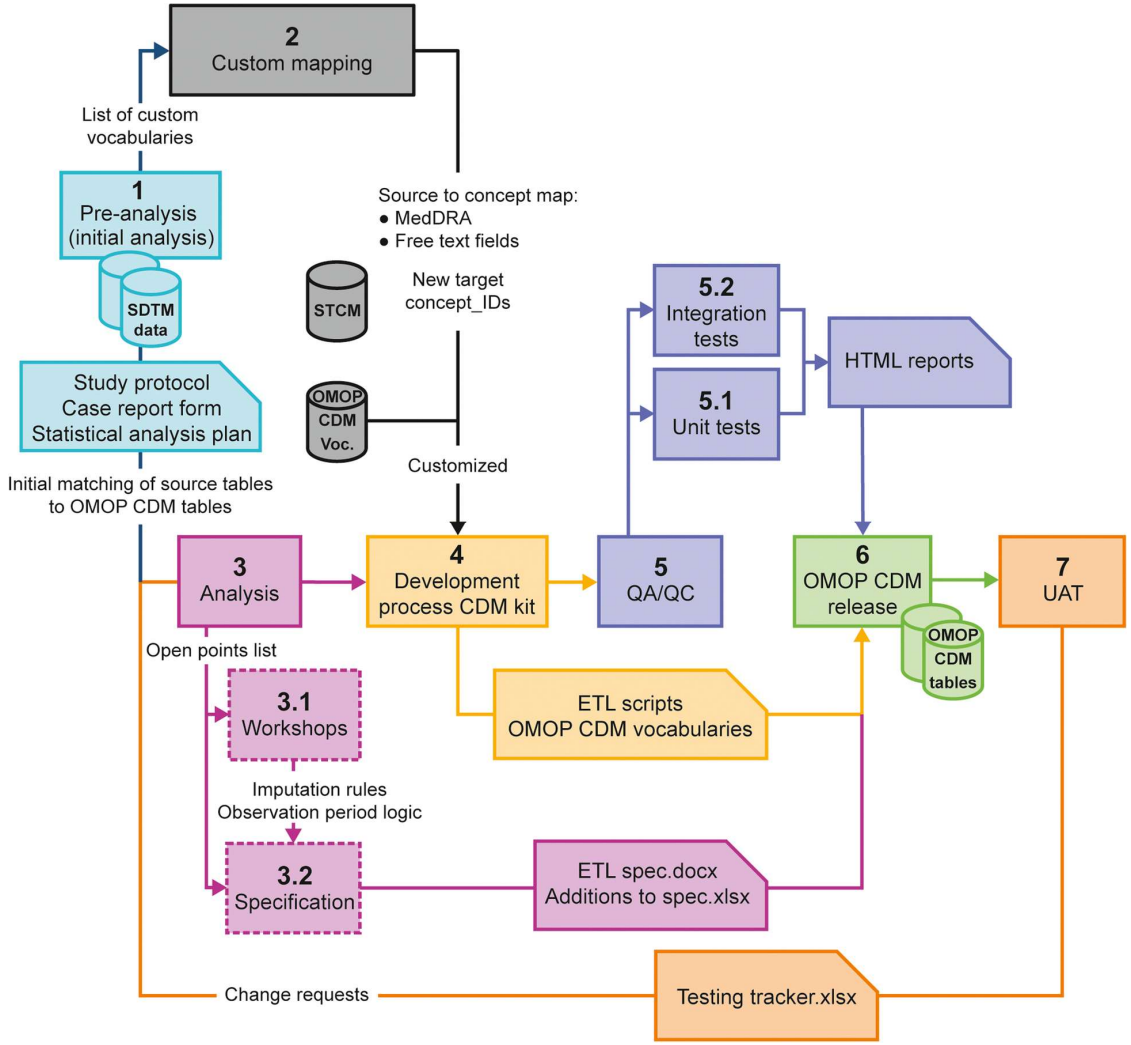
Full list of author information is available at the end of the article

Background

Evidence generated from observational, real-world data can be highly insightful and is increasing in importance, particularly in rare diseases where information is

BMC



Some suggestions

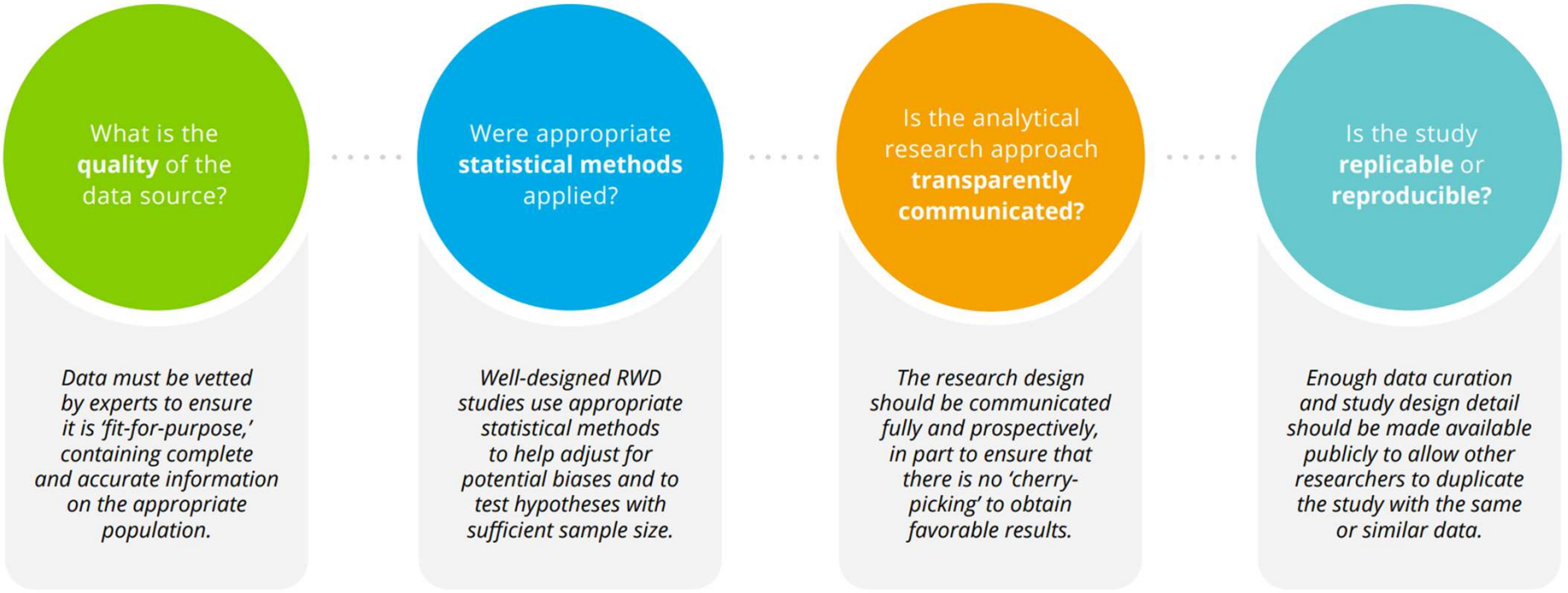
Suggestions

Take example with **high-quality registry**, **stable technology** and **new products** – eg. orthopedics or cardiovascular implants

Consider a '**harmonisation by doing'** approach for the regulatory assessment

Dedicate **resources** and **share** experience on key questions

Focus on key questions



Ref. https://www.ispor.org/docs/default-source/strategic-initiatives/pfizer-bms-ispor-infographic_final.pdf?sfvrsn=a7413b04_0

The real-world context in which devices are used can be very different

The data requirements (real world or not) should not be

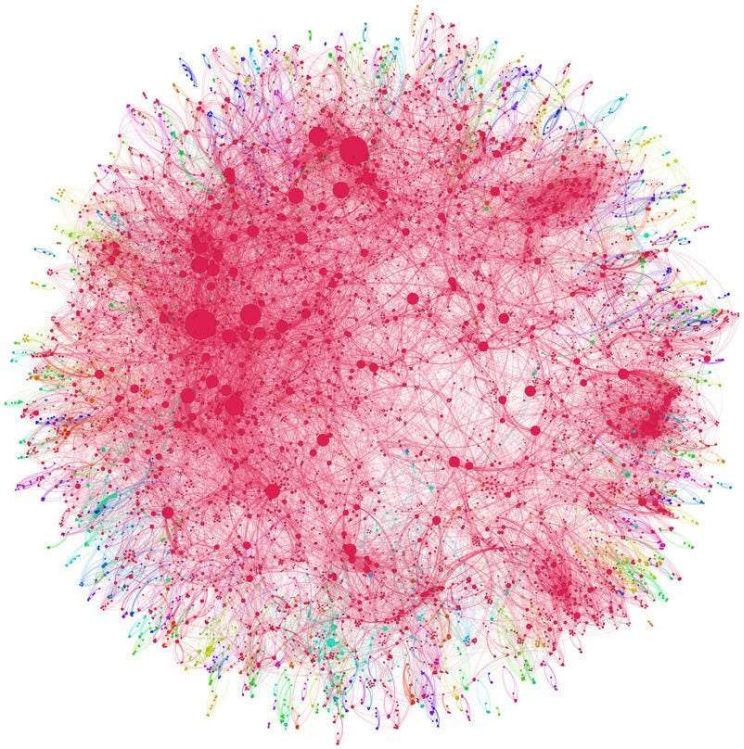
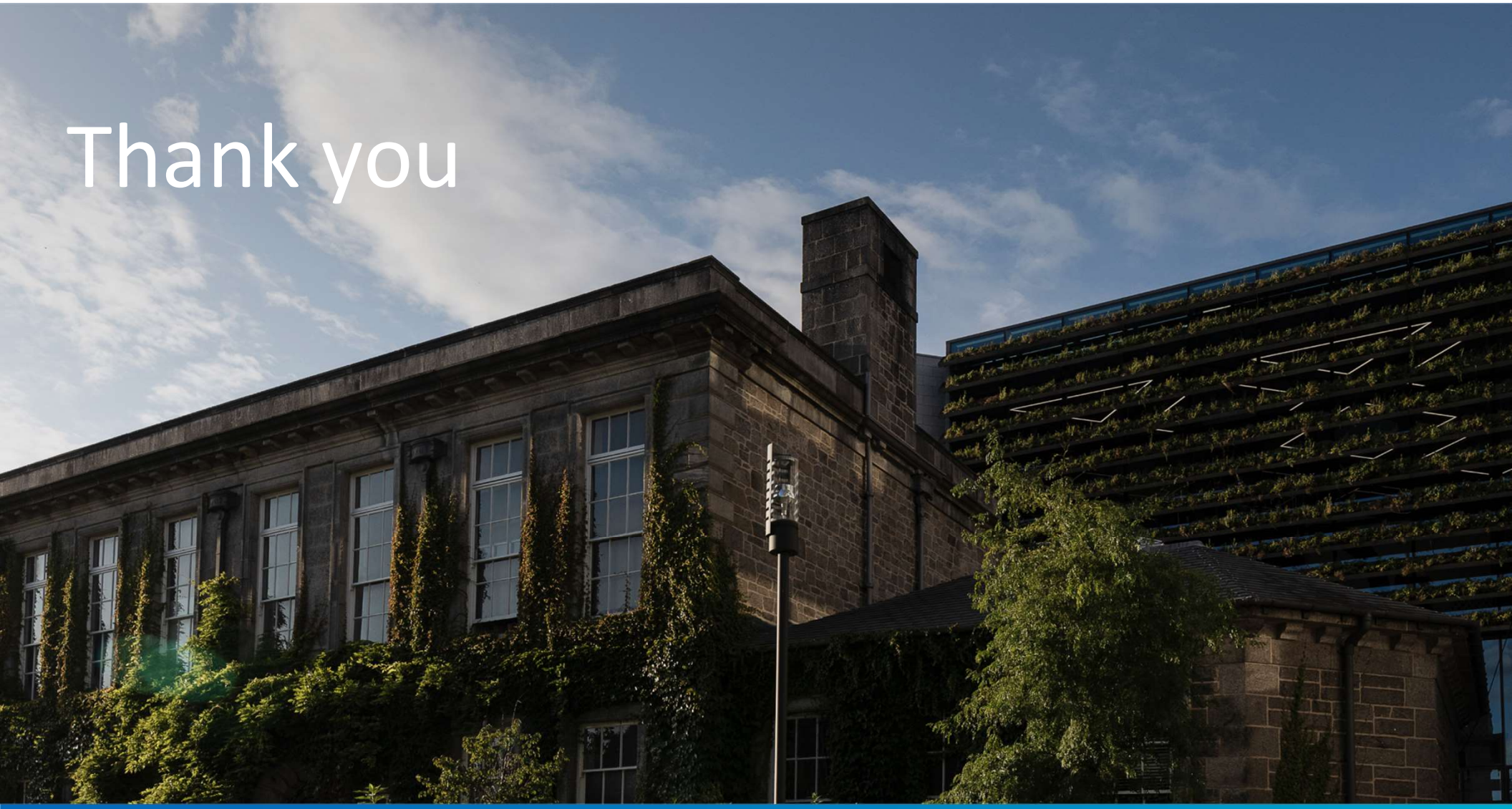


Image Ref. An Introduction to Complexity Theory

https://medium.com/@junp01/an-introduction-to-complexity-theory-3c20695725f8

Thank you



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12:10 – 12:40

Uses of real-world evidence

Erin Cutts

Senior International Policy Analyst, U.S. Food and Drug Administration

Sabina Hoekstra

Global Director Regulatory Strategy, TÜV SÜD Medical Health Services

Lyu Yunfeng

Head of clinical and biostatistics division II, Center for Medical Device Evaluation of NMPA

European Commission | European Union

Uses of Real World Evidence

Erin Cutts
Center for Devices and Radiological Health (CDRH)
US Food and Drug Administration (US FDA)

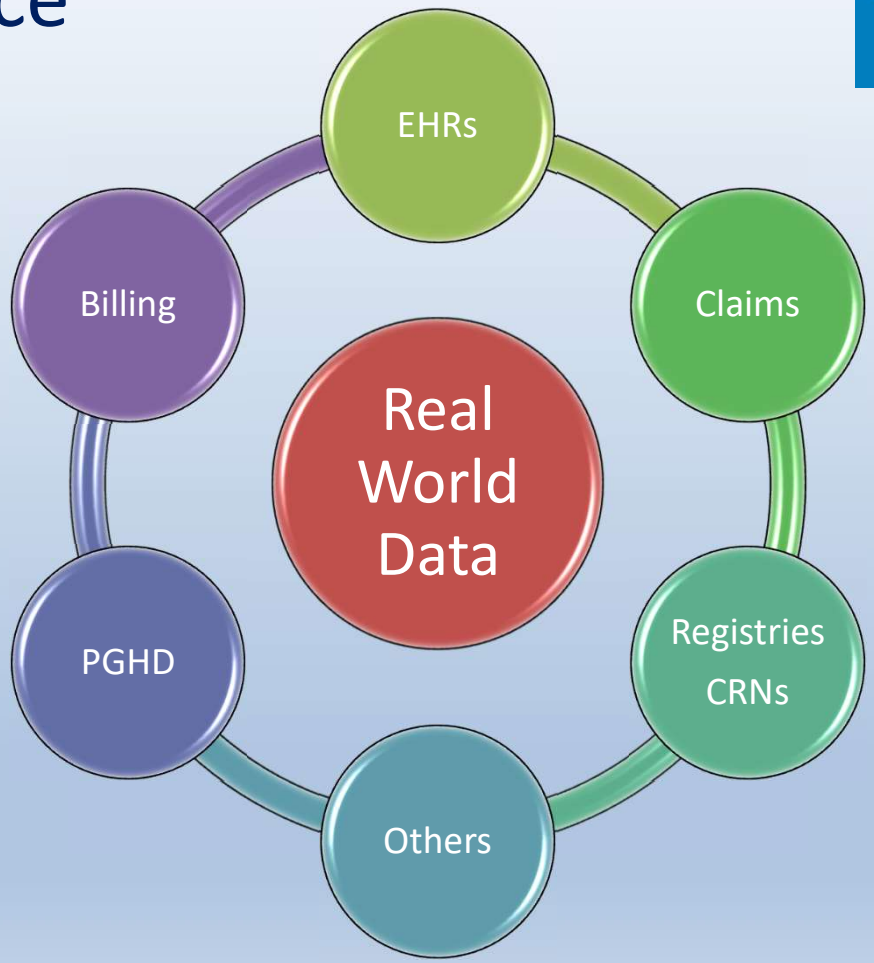
CDRH Vision

Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world

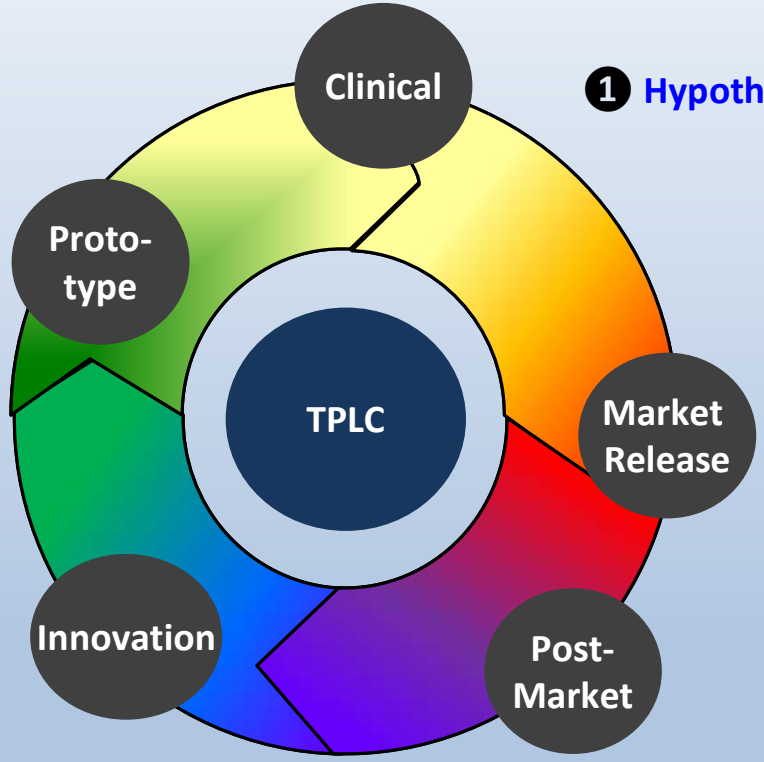
Real-World Data & Evidence

Real World Data *are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.*

Real World Evidence *is the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD.*



Potential Usages of RWE for Total-Product Life-Cycle Device Evaluation



1. **Hypothesis Generation** (e.g. treatment effect estimation for comparative studies)
2. **Inform prospective trial design**
3. **RWE as a control arm for a clinical trial**
4. **Real-world data source as a platform to support a clinical trial** (data collection / randomization)

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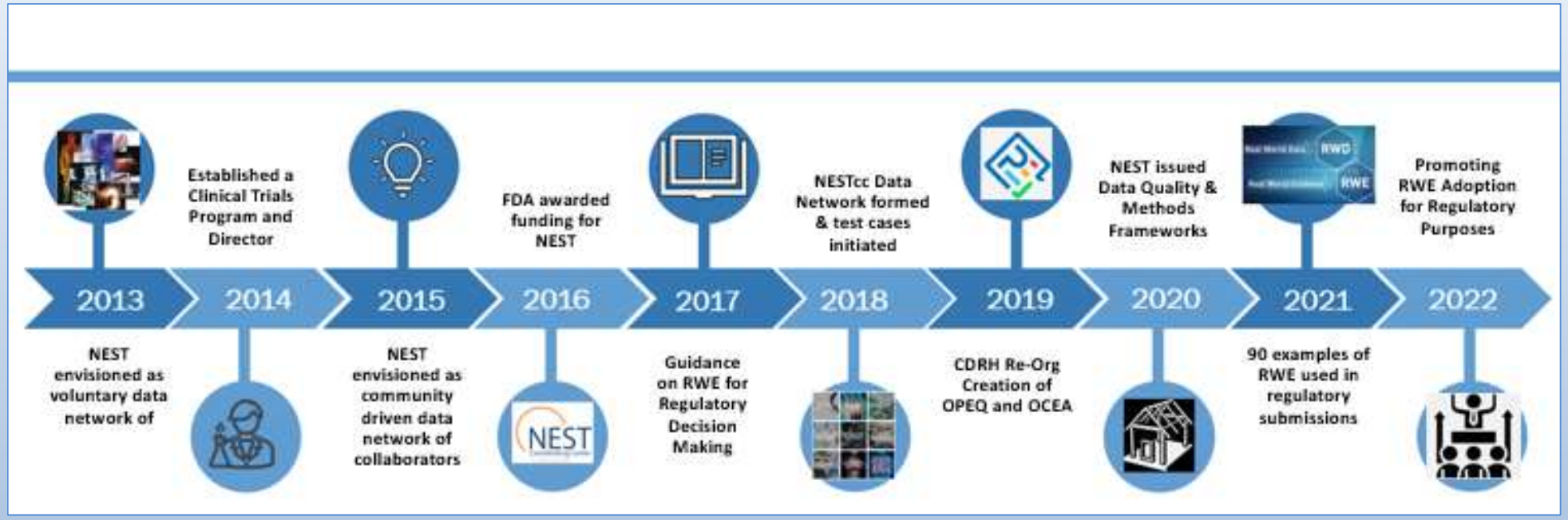
5. **Data collection framework for postmarket evidence generation (e.g. post-approval studies)**
6. **Public health surveillance**
7. **Generate evidence to support indication expansions and future innovation**

Benefits of Real-World Data Sources

- Understand device performance in real-world environment to inform benefit-risk
- Collect outcomes not always feasible in traditional trials
- Opportunities to partner w/patients in new ways
- Reduced time/cost to answer important questions
- Inform future device modifications and new technology development
- Better align evidence generation with innovation cycles

Real-World Evidence Program in CDRH



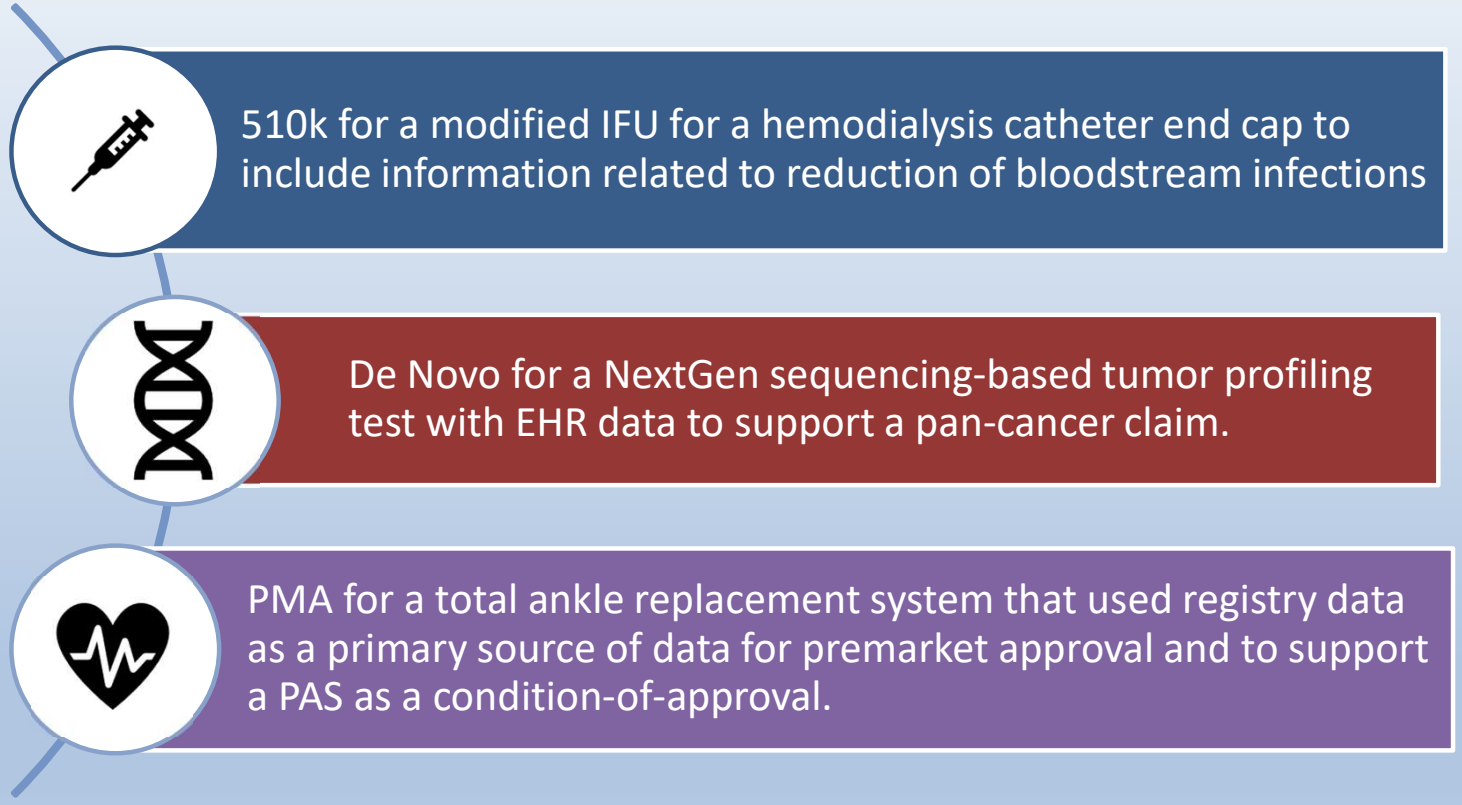
Leading the evolution of the clinical evidence landscape through:

- Optimizing Infrastructure to Develop Real-World Evidence (RWE)
- Promoting RWE Adoption and Use for Regulatory Purpose

Promoting RWE Adoption and Use for Regulatory Purposes: *Achievements*

- RWE Guidance for Medical Devices
  - Potential uses of RWD
  - Characteristics of RWD
    - Relevance
    - Reliability
  - Examples
- Compiled and published 90 publicly available, illustrative examples of RWE used in regulatory submissions FY ’12-’19
  - Variety of submission types, data sources, purposes, & TPLC stage
- Continuous staff training on RWE

A Few RWE Case Examples



CDRH Commitment to RWD/RWE

MDUFA PERFORMANCE GOALS AND PROCEDURES, FISCAL YEARS 2023 THROUGH 2027

F. Real World Evidence (RWE)

The Agency will use user fee revenue for the continued development of Real-World Data (RWD) and RWE methods and policies to advance regulatory acceptance for premarket submissions, including expanded indications for use and new clearance/approval of new devices, and clarify related reporting requirements.

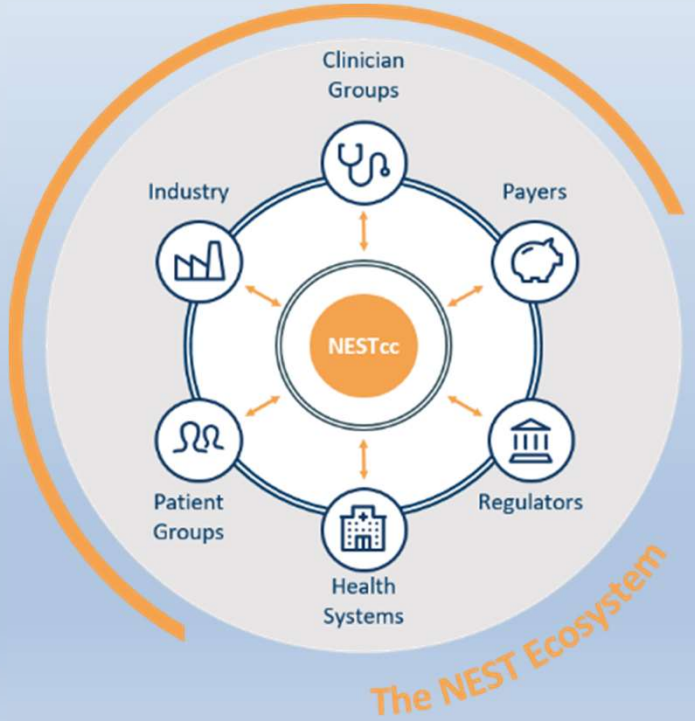
1. FDA will update the 2017 guidance document Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices to provide more clarity on:
    a. Least burdensome general expectations on what is needed to demonstrate the "Fit-for-Purpose of RWD" for premarket regulatory purposes, including expanded indications for use and new clearance/approval of new devices;
    b. More information, including generalized examples, on previously used and accepted methodologies; and
    c. Best practices for RWE review.
2. FDA will continue to advance CDRH's RWD/RWE Training program for FDA review teams including the medical review staff. Topics will include best practices for RWE review and when to engage with CDRH RWE subject matter experts.
3. FDA will provide transparent program development updates and financial accounting of User Fee revenue specifically intended for the activities in this section.
    a. FDA will update stakeholders on the RWE program activities at two or more open public meetings during the course of MDUFA V.
    b. FDA hiring of internal experts to support the review of RWD/RWE-related submissions will be tracked.
    c. If any portion of the user fee funding is distributed to the National Evaluation System for health Technology (NEST), the funding should be used to transparently:
        i. Support the development of RWD resources to facilitate appropriate access for research studies;

National Evaluation System for health Technology (NEST)

A voluntary data network of collaborators able to efficiently consolidate Real-World Evidence (RWE) from clinical registries, electronic health records, medical billing claims, patient-mediated data, and other sources to inform medical device development and evaluation, and to support regulatory decision-making throughout the total product lifecycle (TPLC).

- 21 Test Cases Conducted
  - Explored feasibility
  - Identified areas where NESTcc could reduce costs
  - Independent assessment of Test Cases revealed lessons learned

- Premarket Implementation Cases Ongoing
  - Multistakeholder involvement to develop RWE through the NEST ecosystem to support a premarket submission



Medical Device Active Surveillance System

- Request for Information (RFI)
  - Published in Feb. 2023
  - Inform the next evolution of the medical device active surveillance system
  - Understand the safety of medical devices as used within clinical practice, by achieving:
    - *Better* data capture
    - *Detection* of potential safety signals
    - Timely *assessment* leading to actionable findings

CDRH Fosters the Development and Use of High-Quality Real-World Evidence

- Collaborating with MDIC and NEST on framework documents
  - Active Surveillance Roadmap
  - Active Surveillance Methods
  - Data Quality Framework
- CDRH engages with 12 National CRNs and 4 International Registry Consortia
  - Include over 100 national or regional registries from 45 countries

Support Total Product Life Cycle Reviews

- Experts within CDRH provide support and training in Good Clinical Practice, Data Quality, Study Design, Analytic Methodology, and knowledge of specific RWD sources
- Leverage high-quality RWD sources to replace traditional post-approval studies and efficiently address postmarket questions
- Advance active surveillance to improve device safety

Thank you!

IMDRF International Medical Device Regulators Forum

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European Commission

European Union

RWE: EU notified body's perspective

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Global Director Regulatory Strategy

TÜV SÜD Medical Health Services

Brussels, 27 March 2023

OVERVIEW

- Notified bodies
- Current regulatory situation in EU
- Future

EU Notified Bodies

- EU medical device regulatory system is a ‘third party system’
- EU ‘third parties’ are called notified bodies
- Notified bodies are
  - Organisations
    - different format (e.g., semi-public, private)
  - Designated and monitored by EU authorities to perform regulator’s tasks
    - i.e. decisions on market access for medical devices in mid- and high risk classes
  - *De facto* ‘extended arm’ of the regulators

EU COM website factsheet

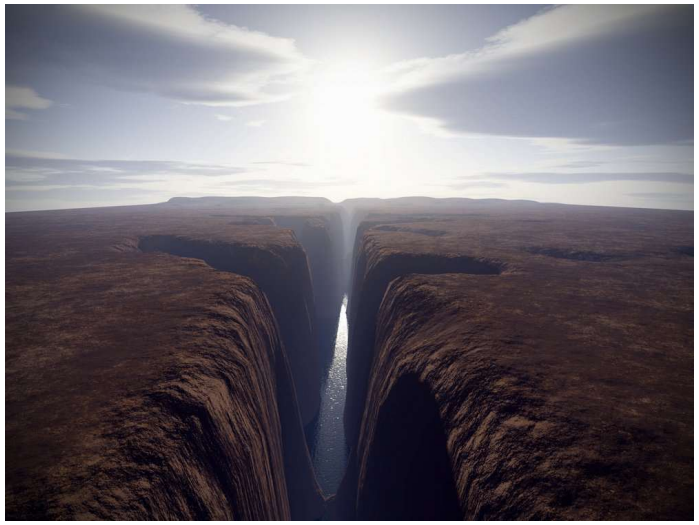
Building on Tom Melvin´s presentation:

Expectations can differ

Regulators

Overall compliance

- *with the current legal requirements*
- *for a specific device/IVD*



Clinicians

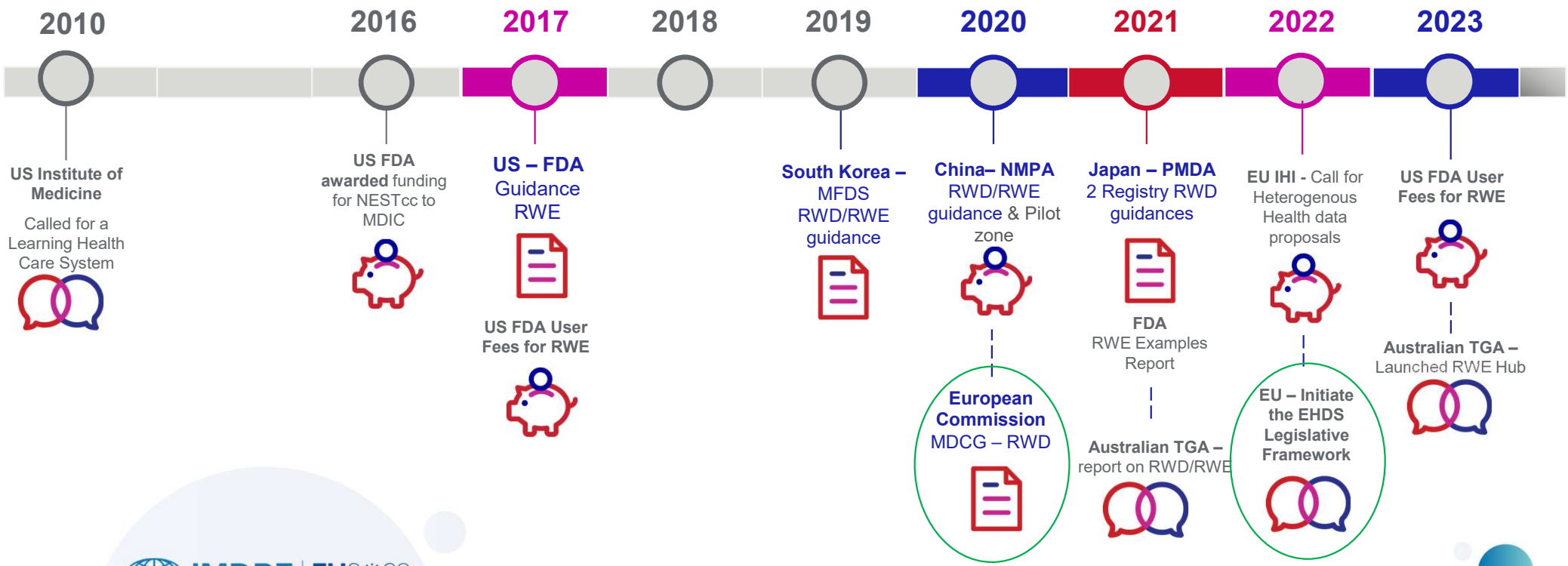
Evidence based practice

Clinical evaluation as key concept

- 'clinical evaluation' means a systematic and planned process to ***continuously*** generate, collect, analyse and assess the clinical data ***pertaining to a device*** in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer (*EU MDR art 2.44*)
- ***pertaining to a device***
- ***continuously***

Building on Heather Colvins´s presentation:

Timeline of Medical Device RWE Activities & Guidances



European Commission
MDCG – RWD

MDCG 2020-6 (April 2020)

Clinical evidence needed for legacy devices

- `legacy devices´ = medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC
- Table with ´hierarchy of clinical evidence for legacy devices' (in Appendix III)
  13 categories of clinical evidence sorted from 'strong' to 'weaker'
- Top 4:
  1. Results of high quality clinical investigations
  2. Results of high quality clinical investigations with some gaps
  3. Outcomes from high quality clinical data collection systems such as registries
  4. Outcomes from studies with potential methodological flaws but where data can still be quantified and acceptability justified
- Class III legacy devices and implantable legacy devices which are not well-established technologies should have sufficient clinical data as a minimum at level 4.

- Conclusion: Specific types of RWE (registries) accepted to substantiate market access of legacy devices

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European Commission
MDCG – RWD

MDCG 2020-7 (April 2020)

Post-market clinical follow-up (PMCF) Plan Template
A guide for manufacturers and notified bodies

- In Section C. Activities related to PMCF: general and specific methods and procedures .
  some examples of different activities related to PMCF are listed, e.g.
  - A manufacturer device registry (specific for the type of device or the group of the medical devices the product belongs to) can be indicated together with a description and a summary of the plan. A pre-specification of what quality and quantity data – based on the risk of the device(s) and the associated accessories – to be collected and analysed shall be included. Any possible evaluation of suitable national public registries with clinical data on the manufacturer's own device and/or on similar devices could be specified in this section, identifying the expected quantity and quality of data to be gathered and the search protocols to be adopted
  - Planned Real-world evidence (RWE) analyses could be indicated in this section, together with a summary of the plan including the design, sample size, the endpoints, and analysis population. The real-world data (RWD) from which these analyses are based on should be of sufficientquality and come from reliable data sources.
  - Surveys planned to collect information about the use of the concerned medical device could be described.
- Conclusion: Collection of RWE/RWD is the context of PMCF is encouraged

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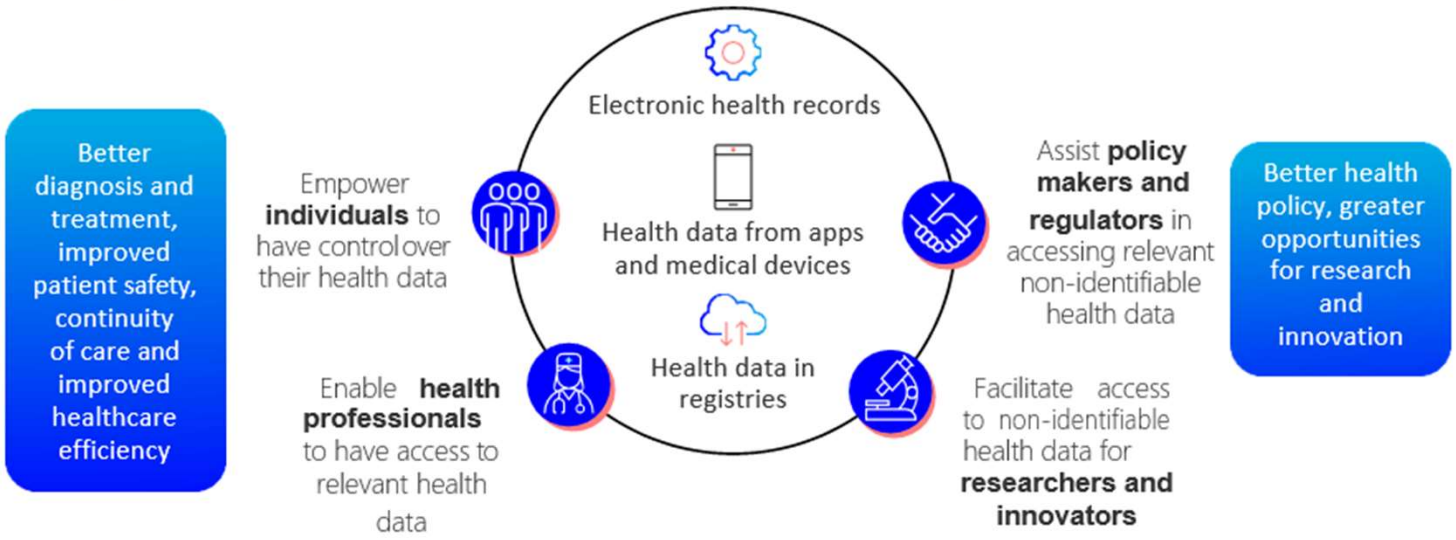
EU – Initiate the EHDS Legislative Framework

European Health Data Space



EU – Initiate the EHDS Legislative Framework

European Health Data Space

- advantages specific for regulators & policy makers:
  easier, more transparent and less costly access to non-identifiable health data for the benefit of public health and the overall functioning of healthcare systems and to ensure patient safety
- Advantages for all EU citizens
  - control of your own health data
  - security and privacy ensured
- High expectations for the future!

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THANK YOU

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Uses of real-world evidence in a regulatory context

Lyu Yunfeng CMDE NMPA CHINA

27-03-2023

OVERVIEW

1. The basic requirements of RWD;

Sources of RWD；

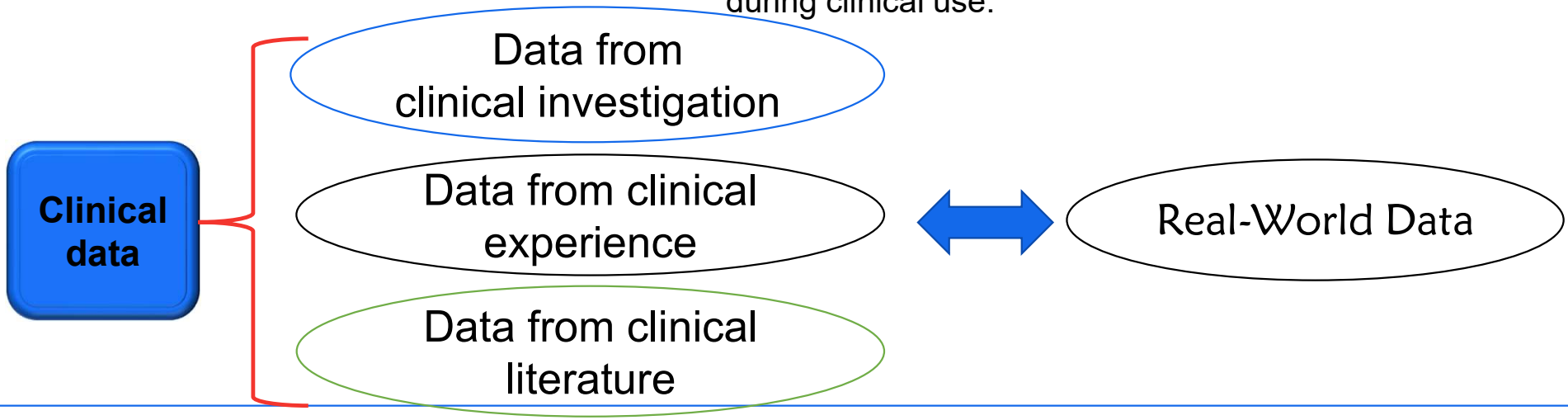
The differences between RWE and clinical investigation data;

Quality Control of RWD;

2.The application of real-world data in clinical evaluation of medical devices

Real-World Data (RWD)

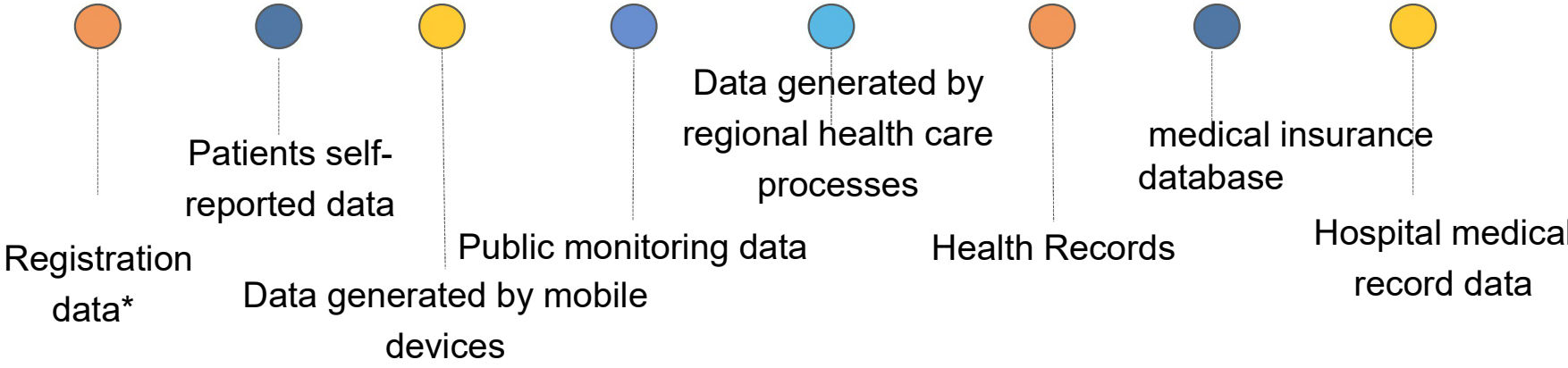
Clinical data: information on the safety, clinical performance, and/or effectiveness of a product generated during clinical use.



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（besides clinical investigation）.

Real-World Evidence (RWE) is the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD.

Sources of RWD



* Data Resources established in routine clinical practice, such as device registration data, etc.

- It comes from the process of providing and paying for health care services, such as hospital electronic medical record data, medical insurance data, health records, etc. .

The differences between RWE and clinical investigation data

	RWE	CLINICAL INVESTIGATION
Research populations	based on larger, more diverse, and more complex research populations	designed to control variability through detailed eligibility criteria and carefully designed clinical protocols performed by specialized research personnel
user	May be more inexperienced users	Researchers are selected on the basis of their expertise and competence, often with more training than other users.
Advantage	These data help to identify device-related rare SAE and provide long-term information on safety, clinical performance, and/or efficacy, clarify the user“Learning curve”.	Increased confidence in the relationship between the test MD and the outcome

Quality Control of RWD

Representativeness: the extent to which the population in the data source represents the target population;

completeness: the level to which key variables for analysis are collected on a continuous basis.

Accuracy: extent to which collected data accurately reflect health-care events (eg, right patient age, right device, and right type of surgery)

consistency: data sources follow the same data-collection processes and procedures (including uniform data definitions and stable case report forms or other version-controlled data-collection forms)

authenticity: extent to which medical devices can be uniquely identified in the data source (UDI has been consistently recorded) , so that all operations using the MD can be identified and analyzed.

Reliability: the degree to which key variables are repeatable

Quality Control of RWD

A prospective or retrospective study by systematically collecting real-world data and using rational design and analysis methods.

1.The purpose of the research should be clear.

Based on available real-world data and scientific and reliable research methods

2. Regulatory and ethical considerations

Data Protection, personal information protection, ethical review and informed consent processes, data verification

Quality Control of RWD

3. Protocol design

type of study;study population;Study variables;follow-up time; sample size and test efficacy; device identification and use information; statistical analysis.

4. Bias and confounding

Selection of appropriate study populations;

identification of clear inclusion and exclusion criteria; randomization;

use of uniform survey tools and measurement methods; training of researchers;

appropriate statistical methods.

2.The application of RWD in clinical evaluation of medical devices

- To support pre-market clinical evaluation of products, as a supplement to the existing evidence
- To use RWD as external control of clinical investigation;
- Consider using RWD to construct target values for single-group investigation
- Expanded Indications for Use or Contraindications；
- To modify product IFU based on RWD ；
- Long-term safety and/or effectiveness evaluation of medical devices such as high-risk implants
- whole-life-cycle clinical evaluation of medical devices used to treat rare diseases
- Post market Surveillance Studies ；
- Post-Approval Device Surveillance as Condition of Approval

2.The application of RWD in clinical evaluation of medical devices

□To support pre-market clinical evaluation of products, as a supplement to the existing evidence

◆At present, the real-world evidence in the clinical evaluation of medical devices is more as a supplement to the existing clinical evidence, and can not replace the existing clinical investigation and clinical evaluation by comparison with comparable devices.

--- 《Technical guidelines for the use of real-world data for clinical evaluation of medical devices》

NMPA China

2.The application of RWD in clinical evaluation of medical devices

- To use RWD as external control of clinical investigation;
- Consider using RWD to construct target values for single-group investigations

--Applicability;
--limitations ;
--quality requirements on real-world data;
--research design and statistical methods.

2.The application of RWD in clinical evaluation of medical devices

- Expanded Indications for Use or Contraindications；
- To modify product IFU based on RWD ；

2.The application of RWD in clinical evaluation of medical devices

- Long-term safety and/or effectiveness evaluation of medical devices such as high-risk implants

- whole-life-cycle clinical evaluation of medical devices used to treat rare diseases

Postmarket Surveillance Studies

Post-Approval Device Surveillance as Condition of Approval

- MD for rare diseases
- MD used to treat a serious life-threatening disease for which no effective treatment is available
- MD urgently needed to respond to public health emergency

- New Technology/new application
- High risk products
- Expand the research population ……

- To evaluate long-term safety effectiveness;
- To evaluate safety effectiveness based on a larger population;
- To identify rare adverse events

It is suitable for different situations, to solve different problems and to meet different clinical evidence needs

RWD

Postmarket Surveillance Studies

Clinical evidence

Risk benefit analysis

Clinical evaluation of the whole life cycle

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THANK YOU

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