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

23rd International Medical Device Regulators Forum

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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

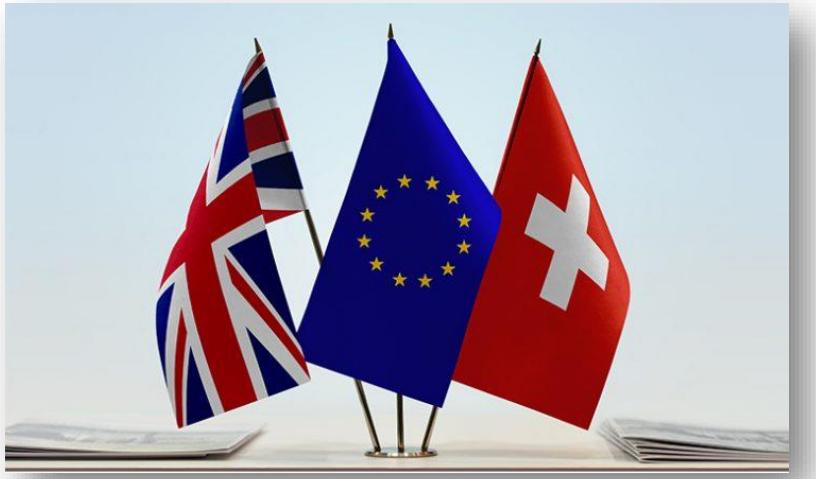
Move from Directive to Regulation system

Changed clinical evidence requirements

New clinical evidence processes

European Health Data Space - EHDS

Brexit and Swixit



The big picture

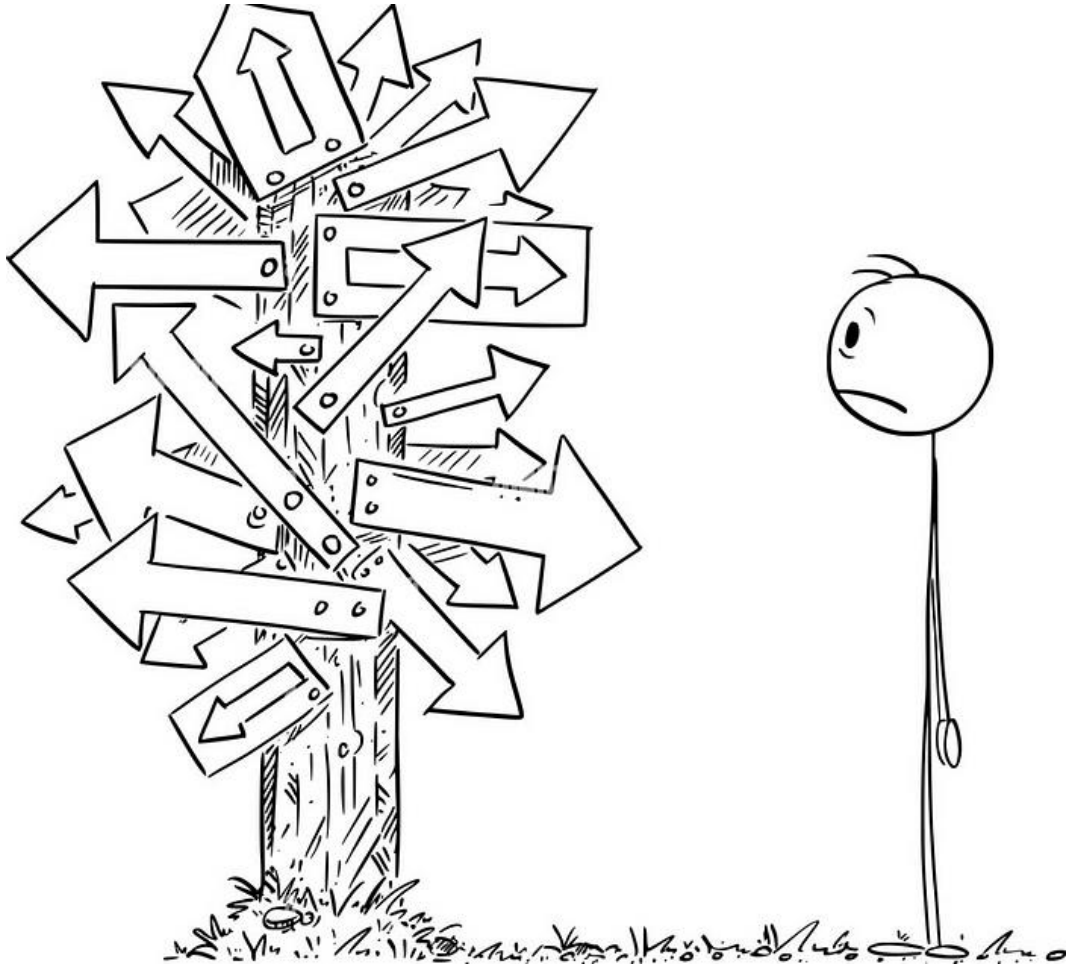
The big picture

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

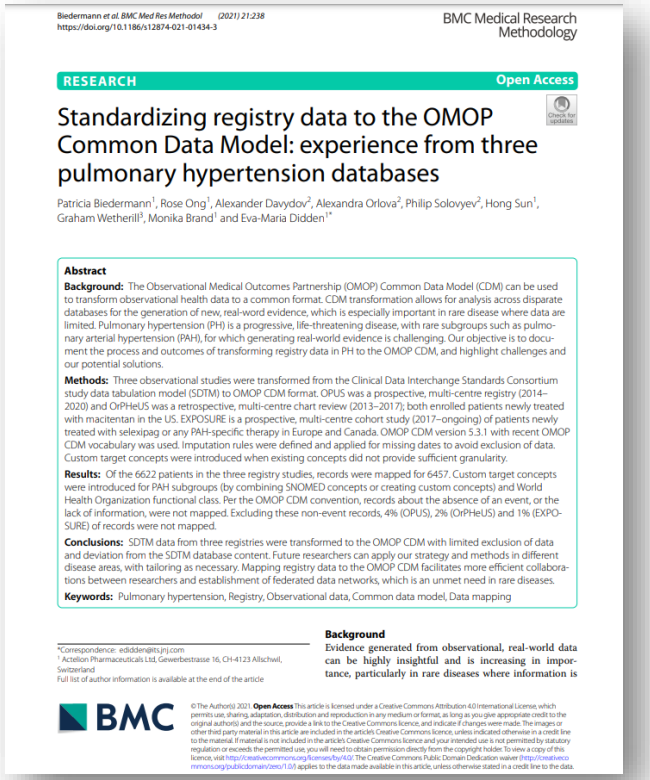
Initiatives to pool data

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

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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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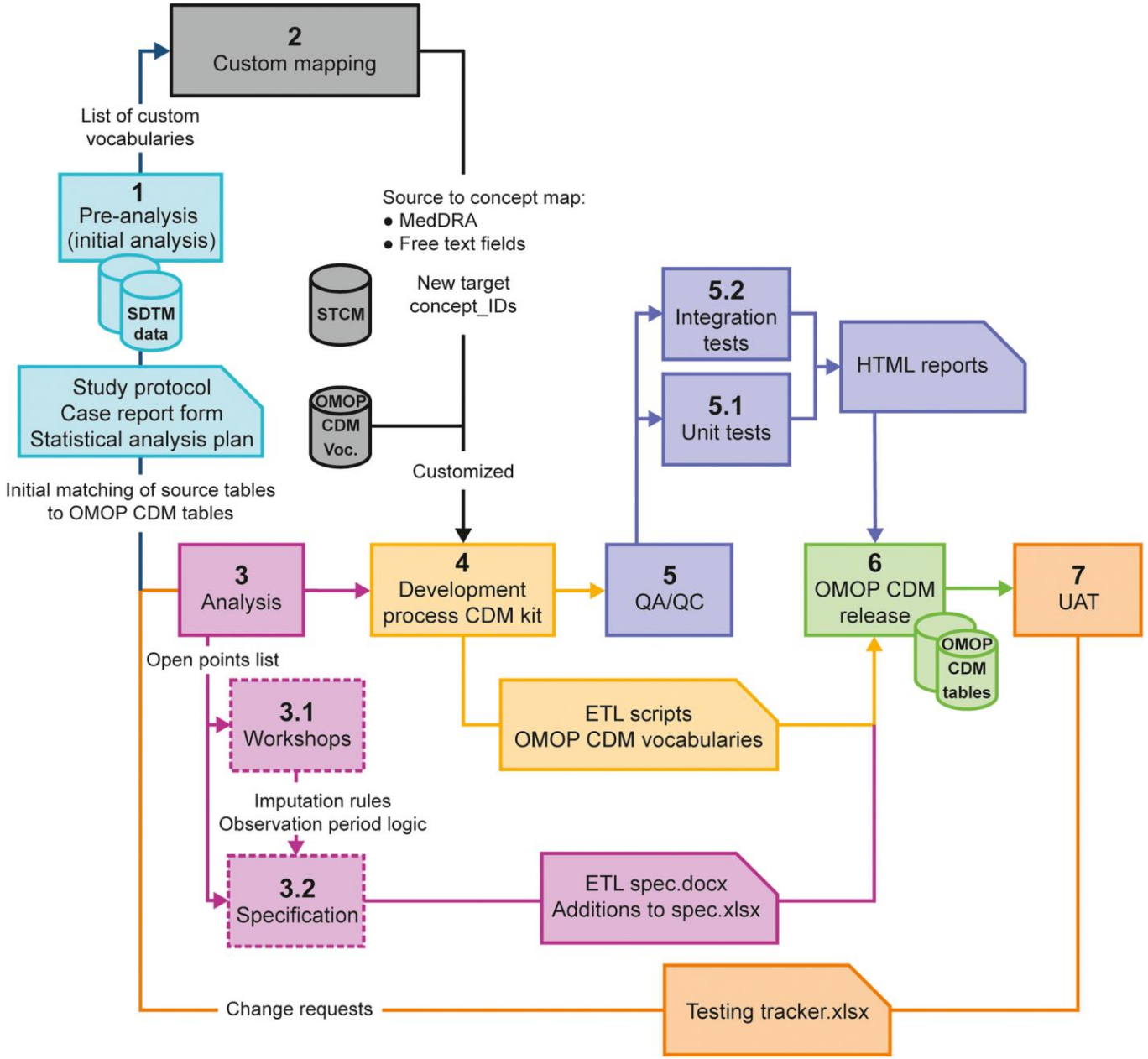
Background

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



Some suggestions

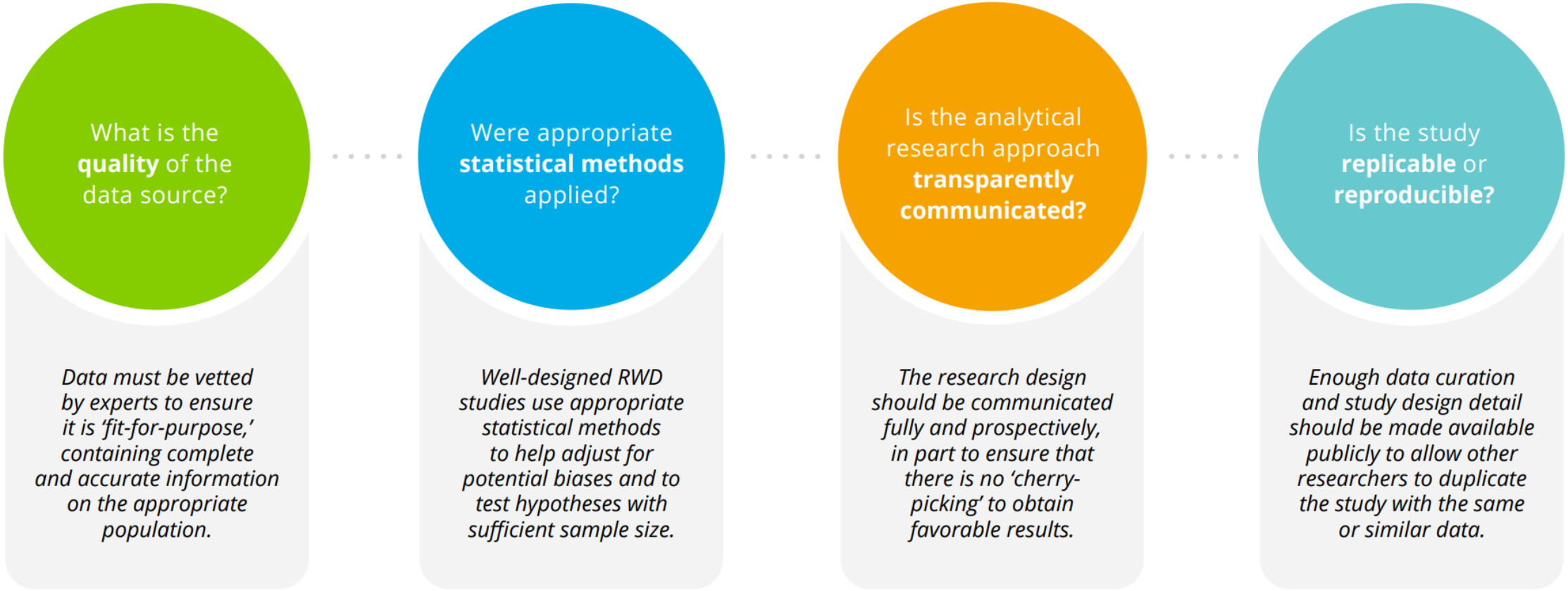
Suggestions

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

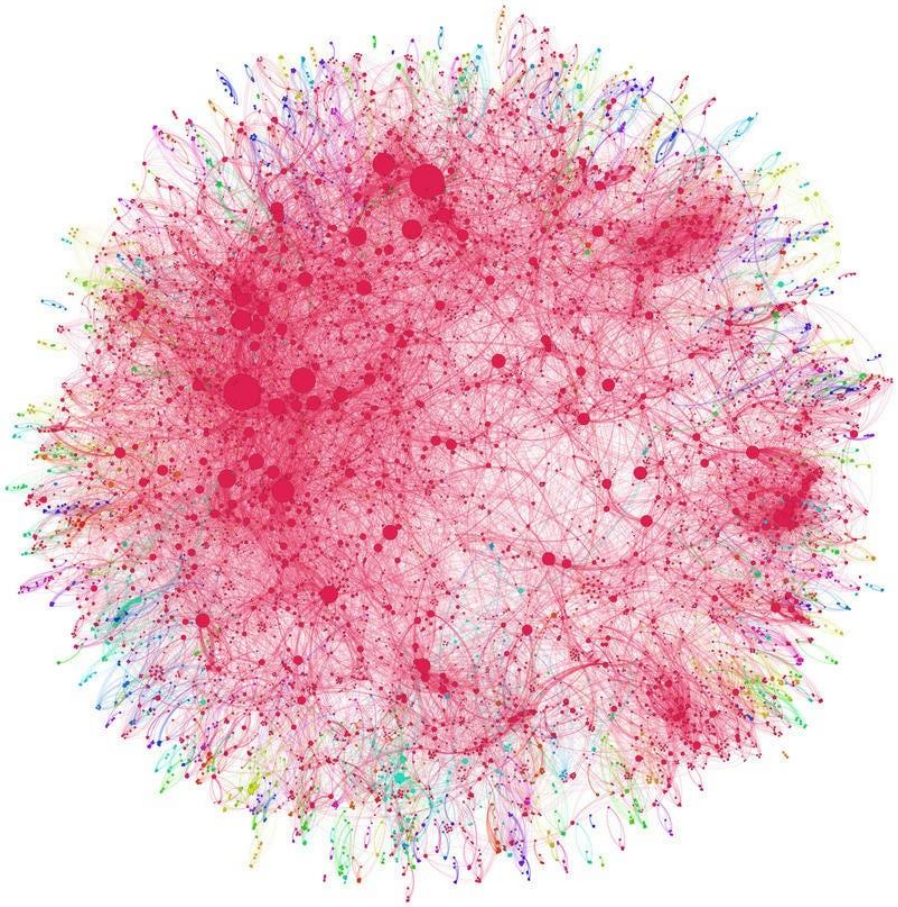


Image Ref. An Introduction to Complexity Theory

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

Thank you