



# External challenges for t h e a c c e p t a n c e o f R W E

*7<sup>th</sup> European Medical Writers Association symposium day*

Dr. P Verpillat  
Vienna – 9 May 2019



**MERCK**

## Conflicts of Interest

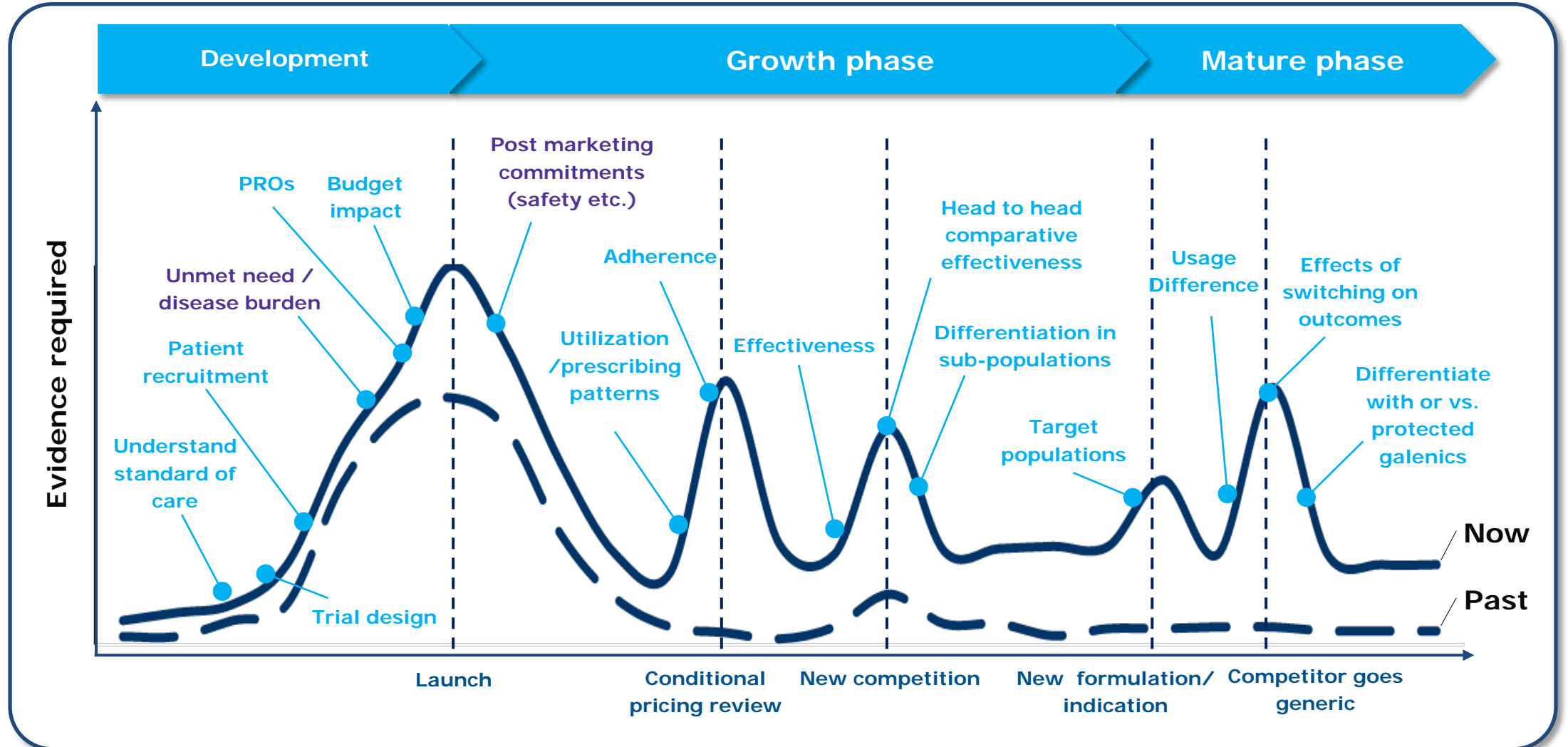
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the following PowerPoint slides are  
my personal view and should not be  
attributed to my company



RWE derived from RWD

**Not a new concept, but more and more used!**



# RWD & RWE

## And more and more under the focus of decision-makers

### Use of Real-World Data to Support Regulatory Decision Making for Medical Products

### Guidance for Industry: Food and Drug Administration

Document

The draft of this document is available for public comment.

For questions about this document, regulatory information, or other matters, please contact the Office of Regulatory Affairs, Division of Regulatory Operations, Office of Communications, Outreach, and Development, U.S. Food and Drug Administration, Washington, DC 20204.



## Characterizing RWD Quality and Relevancy for Regulatory Purposes

October 1, 2018

Duke MARGOLIS CENTER for Health Policy



### 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

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#### ABSTRACT

**Purpose:** Real-world evidence (RWE) includes data from comparative or prospective observational studies and observational registries 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 practical practices that would enhance decision maker confidence in evidence derived from RWE studies. Peer review by ISPOR/ISPE members and other focus participants provided a consensus-building iterative process for the topic and formulation of recommendations. **Results:** The ISPOR/ISPE Task Force recommendations cover seven topics such as study registration, eligibility, and enrollment

involvement in RWE studies. These recommendations, in concert with other recommendations about study methodology, provide a reasonably foundation for the expanded use of RWE in health care decision making. **Conclusion:** The focus of these recommendations is good practical practices for studies that use a specific hypothesis in a specific population. We recognize that some of the recommendations in this report may not be widely adopted unless appropriate incentives from decision makers, journal editors, and other key stakeholders. **Keywords:** comparative effectiveness, decision making, guidelines, pharmacoeconomics, observational data, treatment effectiveness.

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#### Introduction

Real-world evidence (RWE) is obtained from analyzing real-world data (RWD). The RWD is defined here broadly as data obtained outside the context of randomized controlled trials (RCTs) generated during various clinical practices [1,2]. This includes data from retrospective or prospective observational studies and those without registries, as well as data from single-arm clinical trials or RWE. As defined in a 2017 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force report, "Evidence is generated as a result of a research plan

and implemented accordingly, whereas data is but one component of the research plan. Evidence is shaped, while data merely is a raw material and value are non-derivative." 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 various clinical practice and provide RWE. It contrasts to RCTs, patients and their clinicians choose treatments on the basis of the patient's clinical characteristics and preferences. However, since the choices that influence treatment choices in clinical practice may also influence clinical outcomes, RWE

Marie L. Berger is an employed part-time consultant. This article is a joint publication by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoeconomics and Outcomes Research (ISPE). Address correspondence to Marie L. Berger, New York, NY, USA. E-mail: mberger@nyu.edu. 1098-3015/18/0000-0000 © 2017 Published by Elsevier Inc. on behalf of International Society for Pharmacoeconomics and Outcomes Research (ISPOR). <http://dx.doi.org/10.1016/j.jval.2017.08.019>



# WORLD EVIDENCE M

December 2018  
[www.fda.gov](http://www.fda.gov)



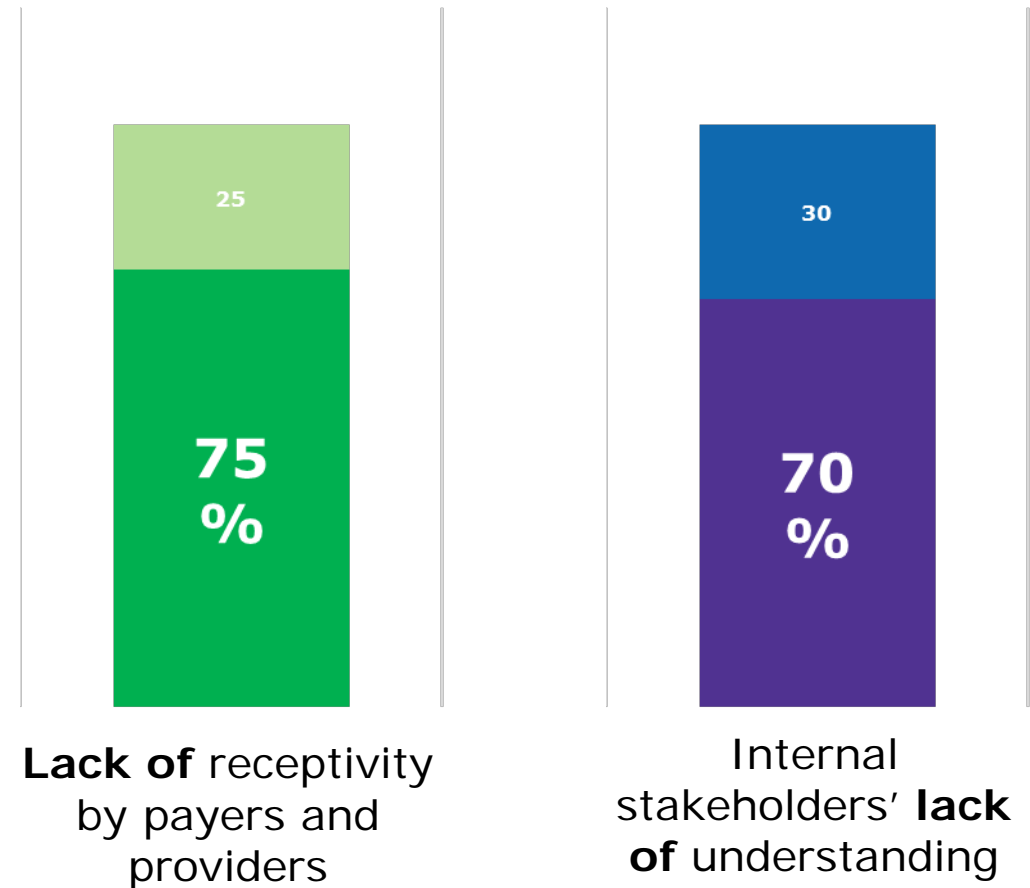
## Definition

# External challenges for acceptance of RWE

Survey among 20 leading bio-pharmaceutical companies on receptivity to RWE generated by Pharma Industry, both internally and by healthcare stakeholders

(Deloitte 2018)

- 60% lack access to necessary external data
- Lack of trust and collaboration between key stakeholders



Definition

## External challenges for acceptance of RWE

### Internal

Linked to study design  
(Observational  
studies)

### Acceptance...

by regulators, HTA  
bodies, payers, any  
decision-makers...

including physicians  
and patients

### External

Data access and/or availability

Data quality

Generalisability of the study results

Inconsistent results

Transparency

Openness to RWE

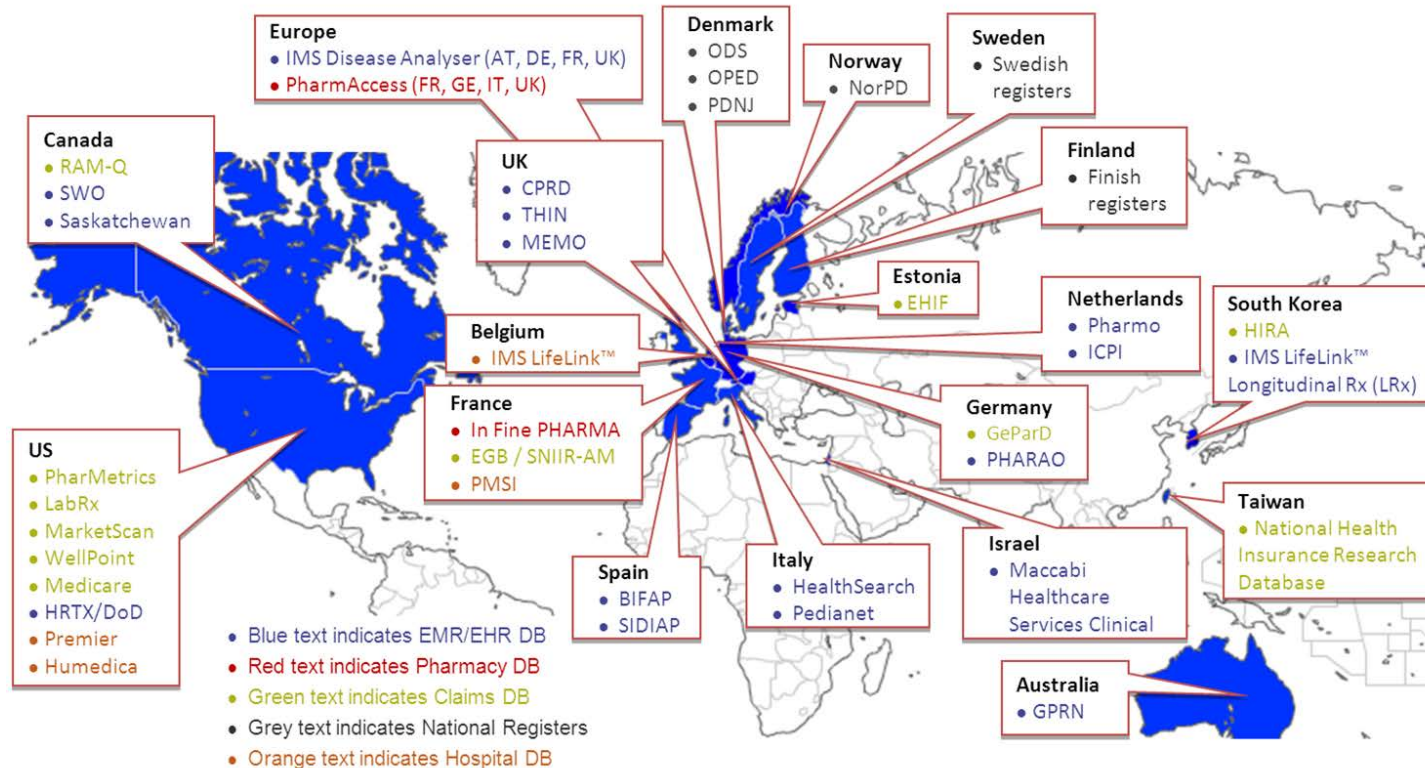
# Challenge 1

## Data access and/or availability ... to industry

# 1

### Access to RWD

And clear lack of governance



# 2

### Lack of sustainability

Especially critical for long-term outcome studies

## Challenge 1

### Data access and/or availability ... to industry

#### 3

##### Data infrastructure

- Significant challenges in sharing RWD across countries linked to differences in structure, setup and content of different data sources
- No or poor standards for collaboration, lack of incentives for data sharing

#### 4

##### Patient consent, privacy and data security

##### Balancing public and privacy interests

- Advancing society's understanding of medical treatments through evaluation and research thanks to rich patient-level data
- Protecting individuals' privacy, which is necessary to safeguard against improper use of personal information

##### Feasibility of re-consent

- for primary data, opportunities for re-contact with the patient, but difficult and likely high drop-out
- for secondary data, even more challenging as no open lines of communication with the patient

=> Streamlining consent for use of patients data for future potential research that has been approved via appropriate processes (e.g., ethics board), with an opt out option at any point

May severely hamper access to data and can result in high costs for data protection in order to comply with relevant regulation (e.g., adherence with privacy laws, such as the EU General Data Protection Regulation)



## Challenge 2

### Data quality

#### Data reliability (data accuracy and data consistency)

- Data must be collected and maintained in a way that provides an appropriate level of reliability (e.g., diagnostic precision, lab results within the limits of biological plausibility...)
- Data must be suitable to address specific regulatory question of interest (relevant outcomes captured across populations, robust data on covariates)
- Data must be consistent for each patient within related data fields and over time
- Provenance of each datapoint must be clear, traceable, and auditable

Data quality should be systematically measured – validated within predetermined frameworks and against benchmarks (e.g., SEER)

Reliability  
Accuracy  
consistency

## Challenge 2

### Data quality

**Completeness** requires predefined rules for abstraction of structured and unstructured data, data harmonisation, and quality monitoring... but are the data measured but not available or not captured during routine care?

& needs to be benchmarked to appropriate gold standards (e.g., National Death Index for date of death)

RWD reflects daily clinical decisions



Reliable RWE needs to be **recent and timely**

Details about the timepoint that the data analysis represents must be reported

completeness

timeliness

## Challenge 2

### Data quality

**Data integrity** refers to maintaining and assuring accuracy and consistency of collected data, especially after data processing and transformation

Includes data source and intention, fidelity (e.g. a female is coded as a female), completeness (i.e. absence of missing data), plausibility (i.e. the data is believable), and cohort construction and linkage

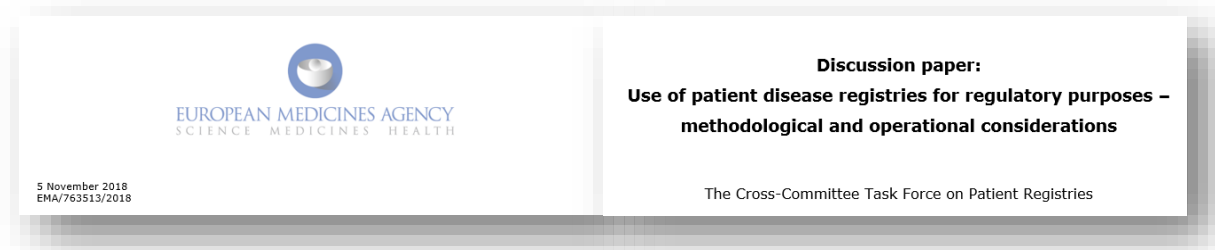
=> Ensuring data point validity by validating algorithms that identify the study population accurately, validating the approaches to derive data points if not directly recorded in the data...



Integrity

# Challenge 2

## Data quality




Data Quality Component	Definition	Proposed indicators of quality	Quality Solutions to facilitate data quality
<b>Consistency</b>	Uniformity of the data overtime (e.g. lab data routinely entered)	Number of fields changed over time	Manual checks at centres level, audits
		% of fields missing over time	Standard terminology, coding
<b>Accuracy</b>	Accuracy of data entry: no errors, no contradictions or impossibilities in data, absence of duplicates	% of forms reported per scheduled follow-up	Standard operating procedures, user guides
		Change in value of data filed by x% creates alerts	Campaigns, dashboards for clinicians
		Variability across fields	Drop down menus, alerts, text prompts, flags
			Validate against source data (e.g., 10%), cross form validation
<b>Completeness</b>	How much data is missing?	Staff training, software checks.	
		Help screens/desks, training, newsletter	
		Funding for data managers	
		Audits	
<b>Completeness</b>	Absence of core variables	Agreed % of fields completed in audit procedures (e.g. >90%)	Mandatory fields
		Lost to follow up %	Engagement with patients and/or health care providers (HCPs)
		Minimum agreed core common data elements reported	Agreed list of data elements and definitions
<b>Completeness</b>	Absence of core variables	All treated patients reported, not selected patients only	Cross check patient numbers with numbers of products used at treating centres during a defined period

## Challenge 2 Data quality

Possibility to “qualify” the data sources to further assure quality of RWD

Thanks to one global & independent accreditation body?

This report provides a final agreed Context of Use describing where ECFSPR is deemed by CHMP as an appropriate data source for post-authorisation studies to support regulatory decision making on medicines for the treatment of cystic fibrosis, together with CHMP’s response to the questions posed by the Consortium.



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

28 September 2018  
EMA/CHMP/SAWP/622564/2018  
Product Development and Scientific Support Department

### Qualification Opinion on The European Cystic Fibrosis Society Patient Registry (ECFSPR) and CF Pharmacology Epidemiology Studies

Draft agreed by Scientific Advice Working Party	11 January 2018
Adopted by CHMP for release for consultation	25 January 2018
Start of public consultation	09 February 2018
End of consultation (deadline for comments)	09 April 2018
Adoption by CHMP	26 July 2018

<b>Keywords</b>	Cystic Fibrosis, Patient Registries, Qualification, ECFSPR
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# Challenge 2

## Data quality

### Current draft version


- 8 „methodological“ items related to the suitability of the registry for a specific purpose
  - Type of registries, objectives and research question, geographical and organisation setting, duration, data providers, size, inclusion and exclusion criteria, follow-up
- 13 „essential“ standards relevant to any registry for regulatory and HTA purposes
  - Covering governance aspects, data and information, legal and ethical issues
- 3 additional requirements for specific purposes

### **EUnetHTA Tool for Registry qualification: Registry Evaluation and Quality Standards Tool (REQueST)**


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#### **Objectives of REQueST**

- Adapt existing quality standards for registries into a practical tool to assess registry quality
- Build upon the work of PARENT Joint action



eunetha



**PARENT**  
cross-border  
PATient REGistries INitiative

#### **Highlights thus far**

- First draft of REQueST

ISPOR POSTER; Gimenez E et al nov 2018

- Vision paper on the sustainable availability of REQueST

#### **Next steps**

- Public consultation (mid 2019)
- Final version (September 2019)

Gimenez E, Valentic M, Espallargues M, Rodriguez J, Varela L, Guzina I, Patrick H, Long J. The registry evaluation and quality standards tool (REQueST) for health technology assessment from an outcome assessment perspective. ISPOR Europe Annual Meeting 10-14 November Barcelona - Spain

## Challenge 2 Data quality

Is the data set **fit -**  
**for -purpose** on these  
dimensions of data  
**quality and relevancy**  
for a potential decision  
within the context  
of a specific disease  
or therapeutic area?



## Challenge 3

### Generalisability of the study results

1

#### Broad range of patients

which can translate into better generalisability

2

#### Representativeness

Is the used data source representative of the wider patient population?

3

#### Transferability

Can results of a study in one country be easily transferable to other countries?

Is this an ultimate goal?



## Challenge 3

# Generalisability of the study results

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*International Journal of Epidemiology* 2013;42:1012-1014  
doi:10.1093/ije/dys223

### POINT COUNTERPOINT

## Why representativeness should be avoided

Kenneth J Rothman,<sup>1,2</sup> John EJ Gallacher<sup>3</sup> and Elizabeth E Hatch<sup>1</sup>

<sup>1</sup>Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA, <sup>2</sup>RTI Health Solutions, RTI International, Research Triangle Park, NC, USA and <sup>3</sup>Institute of Primary Care and Public Health, Cardiff University, Cardiff, UK

Representativeness may be essential for opinion polls, but is not a reasonable aim for a scientific study

*When Doll and Hill studied the mortality of male British physicians in relation to their smoking habits, their findings about smoking and health were considered broadly applicable despite the fact that their study population was unrepresentative of the general population of tobacco users with regard to sex, race, ethnicity, social class, nationality and many other variables*

“It is not representativeness of the study subjects that enhances the generalization, it is knowledge of specific conditions and an understanding of mechanism that makes for a proper generalisation”

## Challenge 3

### Generalisability of the study results

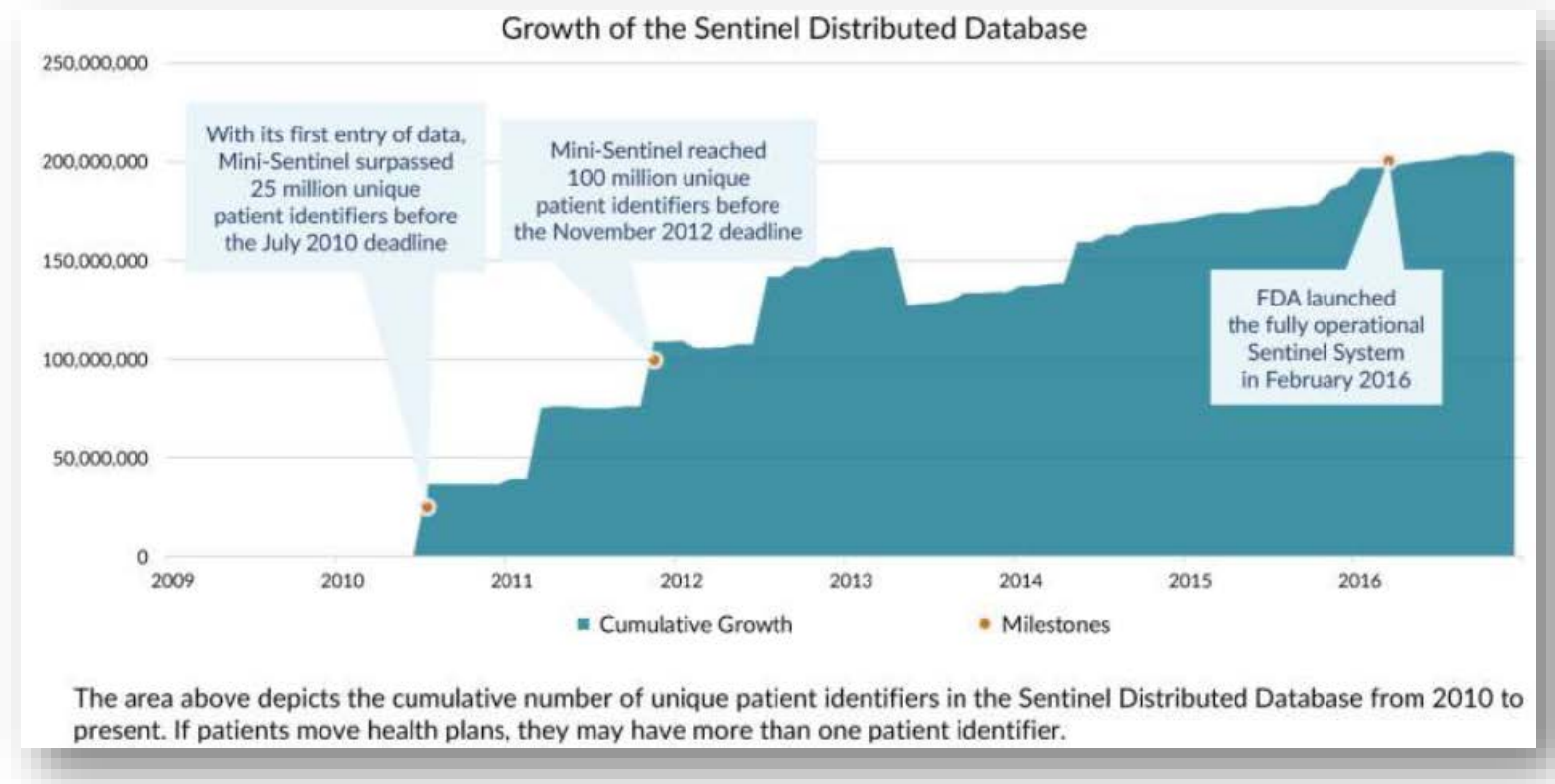
Differences in clinical practices between and within countries/regions, leading to wide heterogeneity in RWD and limitation in the interoperability between different datasets



Minimum requirements for data input and collection to ensure high-quality data and interoperability where possible using existing standards or guidance that are applied in clinical practice



Common Data Model



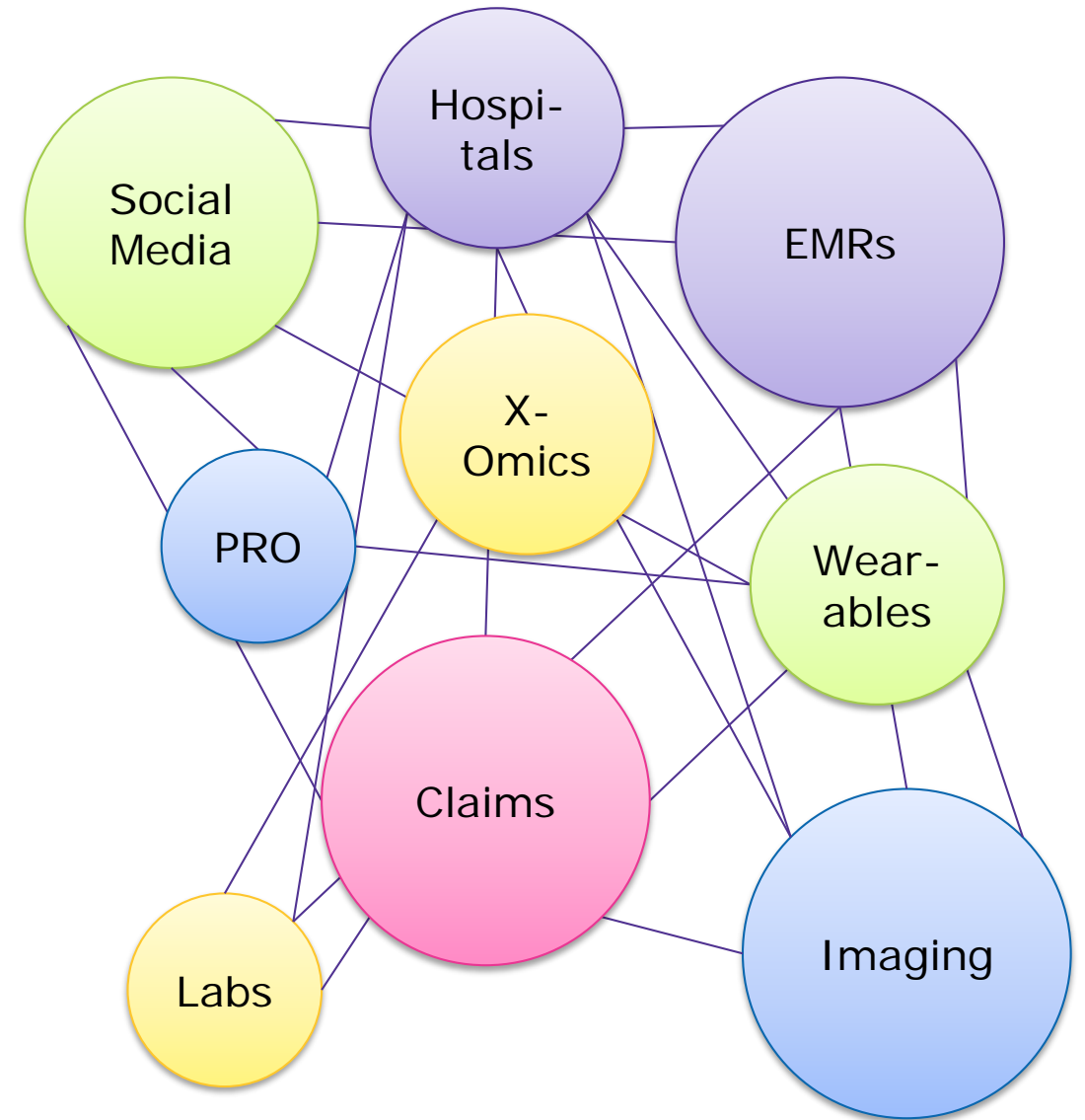
From "Framework for FDA's Real-World Evidence Program - Jacqueline Corrigan-Curay, J.D., M.D. Director, Office of Medical Policy / CDER FDA

## Challenge 4

### Inconsistent results

Given the plethora of data sources and analytical approaches, differences in RWE study results are inevitable!

- **Competing sources of RWD**
  - Verifying the analyses by using different methods in the same datasets (sensitivity analysis) or the same method in different datasets
- With **insufficient technical expertise** (or time or willingness?) to conduct a critical comparison of the methodological aspects of each study, no predictability of results interpretation for the Industry and the average decision maker is likely to ignore RWE\*



\*White R. Building trust in real-world evidence and comparative effectiveness research: the need for transparency. J Comp Eff Res. 2017 Jan;6(1):5-7. doi: 10.2217/ce-2016-0070. Epub 2016 Oct 19.

## Challenge 5 Transparency

About **1** study methodology **2** data source selection **3** analyses

### Pre-specification of protocol and SAP

Avoid deviations from pre-specified study design **BUT** allow some flexibility linked to unexpected findings that require additional exploration (unanticipated changes clearly documented in study reports or in protocol or SAP amendments)

**Code lists, algorithms, associated logs, and analytical data files shared** to facilitate study reproducibility

Internal policies on RWD studies with clear **mandate for posting** study protocol on an appropriate forum and **commitment for publication** of study results regardless of the outcome



EU PAS Registry



15 March 2018  
EMA/929209/2011

The ENCePP Code of Conduct

For Scientific Independence and Transparency in the Conduct of  
Pharmacoepidemiological and Pharmacovigilance Studies



## Challenge 6

### Openness to RWE

#### Still limited expertise

- Need core capabilities to critically assess the method, the analysis and do the interpretation

#### Lack of agreement between different parties

- Regarding what data are needed, for what purpose, at which point in time, and when enough is enough to be persuasive

#### Lack of trust and collaboration between key stakeholders

- For all the above-cited external challenges & lack of randomization leading to potential uncertainty & bias in RWD studies, and resulting impact on the study's findings

How can we change  
these challenges into  
opportunities?

Important to engage with all  
stakeholders (regulators, HTA  
bodies, payers, caregivers,  
clinicians, clinical administrators,  
patients, industry) when  
designing, conducting, and  
disseminating RWD studies

