External challenges for the acceptance of RWE

7th *European Medical Writers Association* symposium day

Dr. P Verpillat
Vienna – 9 May 2019

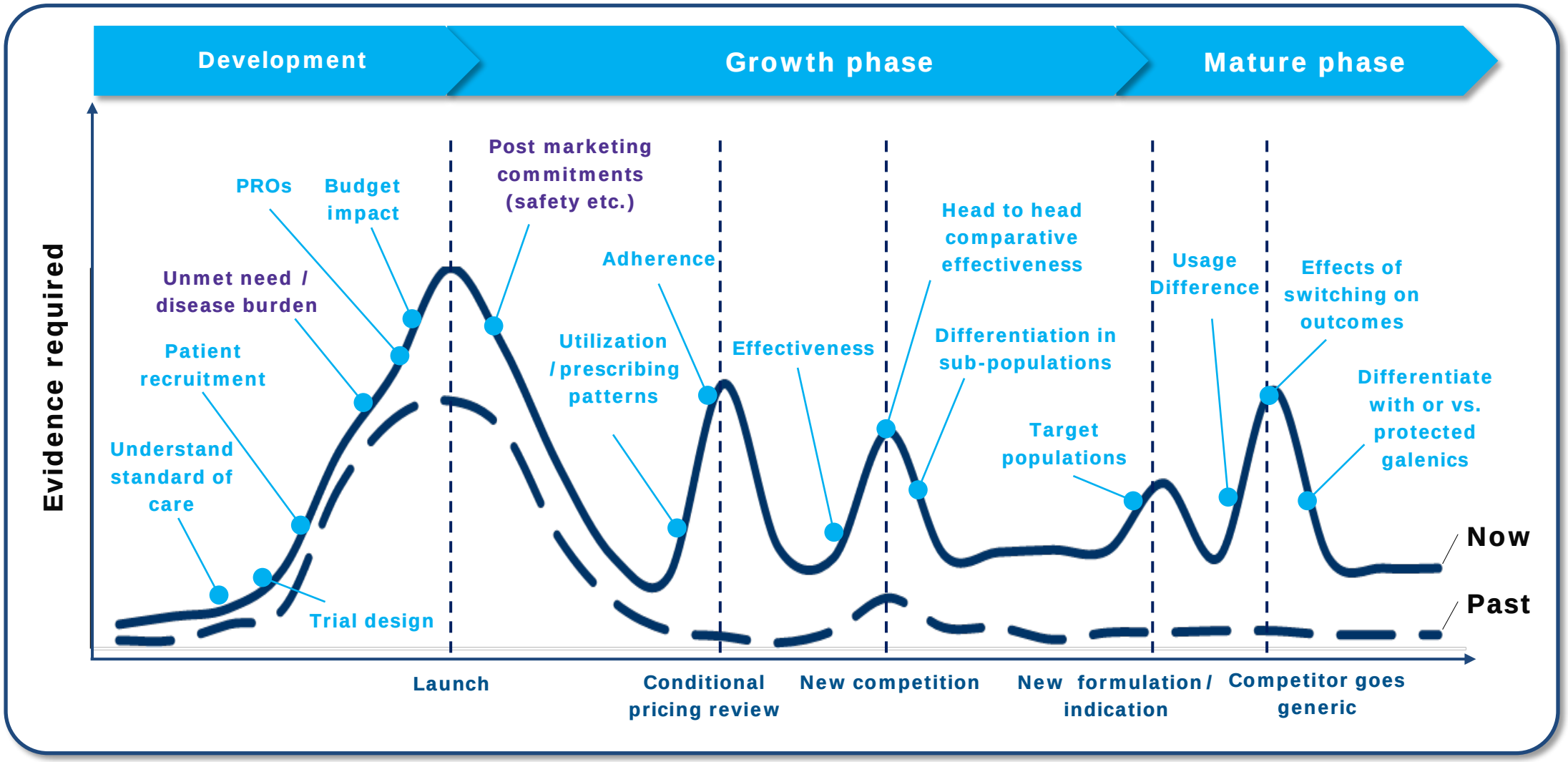
Conflicts of Interest

I am a permanent employee of
Merck KGaA

The views and opinions expressed in
the following PowerPoint slides are
my personal view and should not be
attributed to my company

RWE derived from RWD

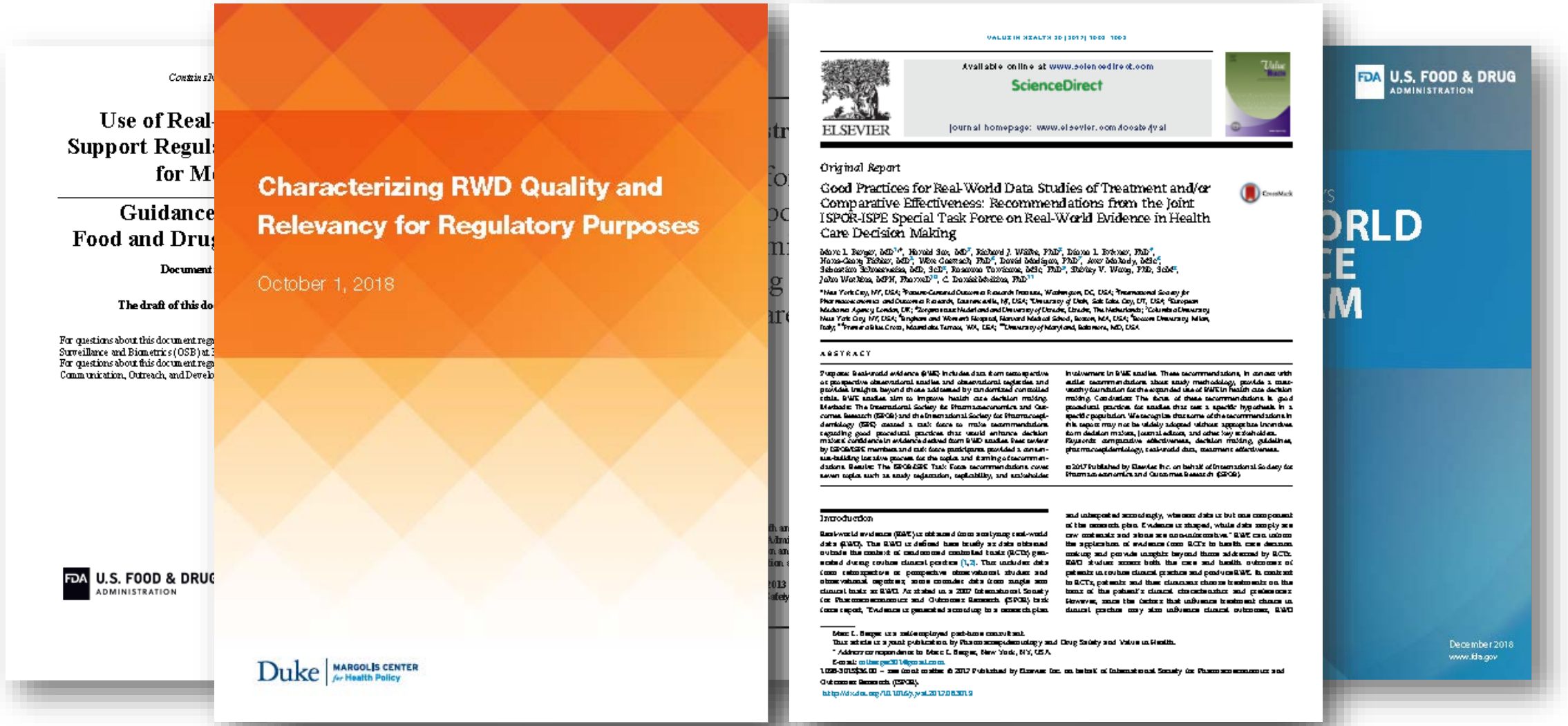
Not a new concept, but more and more used!



Adapted from IMI Get-Real

RWD & RWE

And more and more under the focus of decision-makers



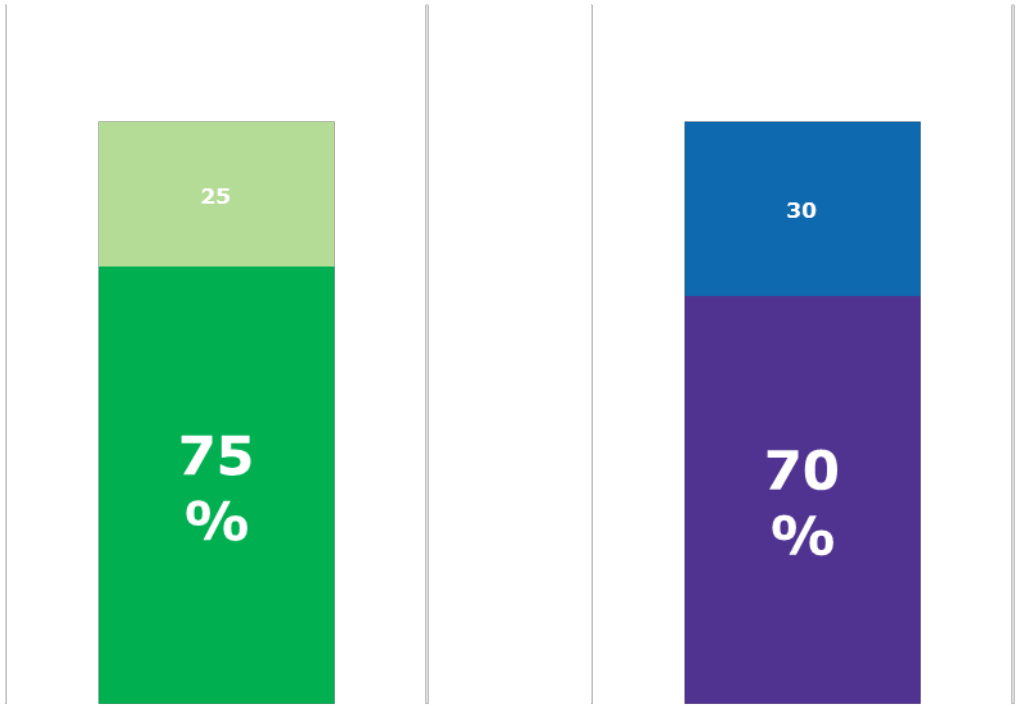
Definition

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



Lack of receptivity by payers and providers

Internal stakeholders' **lack of** understanding

Davis, B., Morgan, J., Shah, S. The future of real-world evidence. Biopharma companies focus on end-to-end, AI-driven, internally developed solutions, June 28, 2018. Available at: https://www2.deloitte.com/insights/us/en/industry/life-sciences/2018-real-world-evidencebenchmarking.html

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

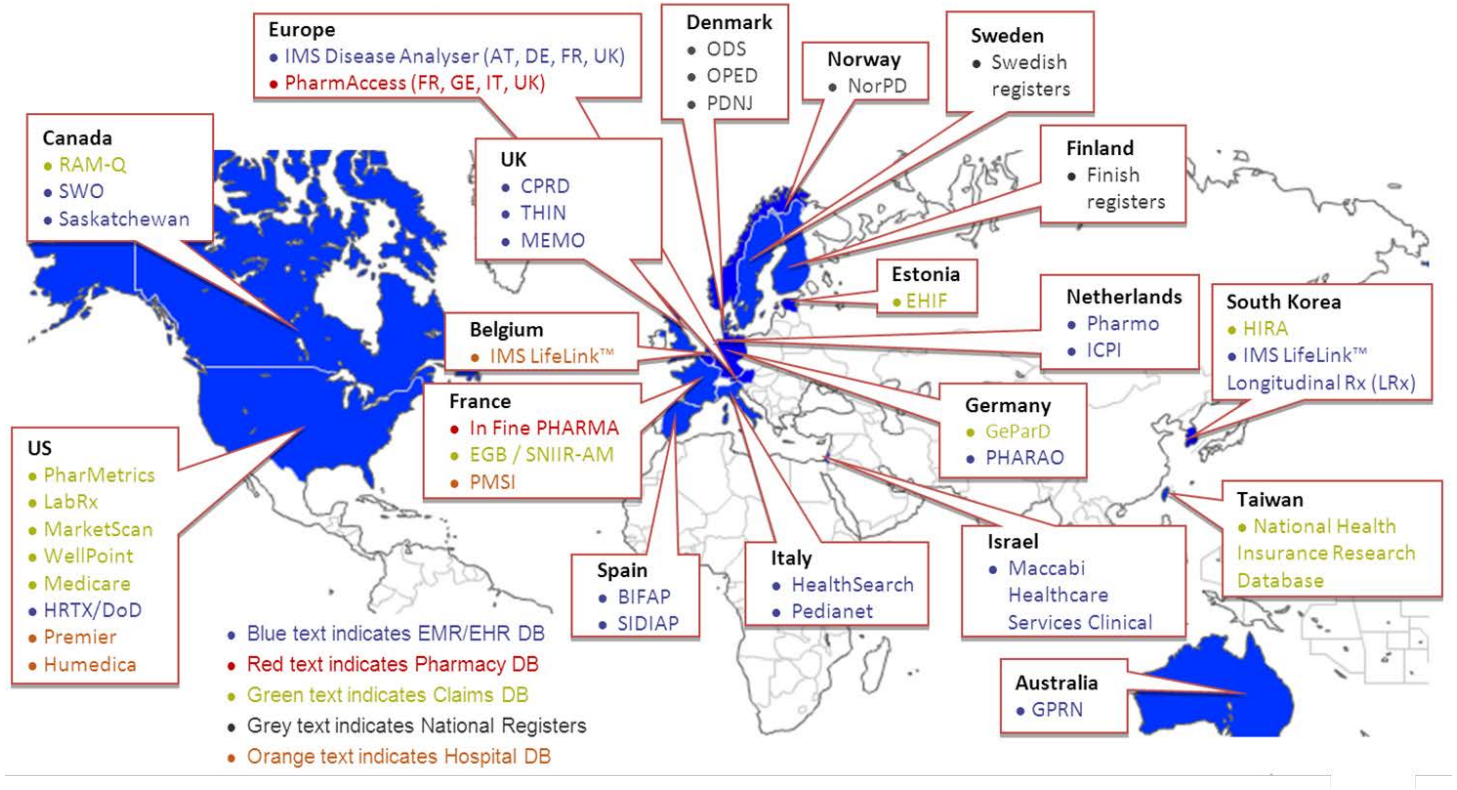
Transparency

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)

com pleteness

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

timeliness

Miksad RA, Abernethy AP. Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure Regulatory-Grade Data Quality. Clin Pharmacol Ther. 2018 Feb;103(2):202-205. doi: 10.1002/cpt.946. Epub 2017 Dec 6.

Challenge 2

Data quality

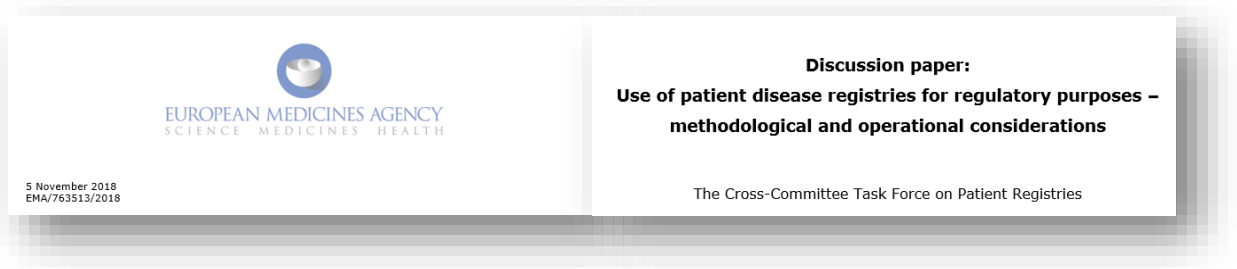
Data integrity refers to maintaining and assuring accuracy and consistency of collected data, especially after data processing and transformation

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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5 November 2018
EMA/763513/2018

Discussion paper:
Use of patient disease registries for regulatory purposes – methodological and operational considerations

The Cross-Committee Task Force on Patient Registries

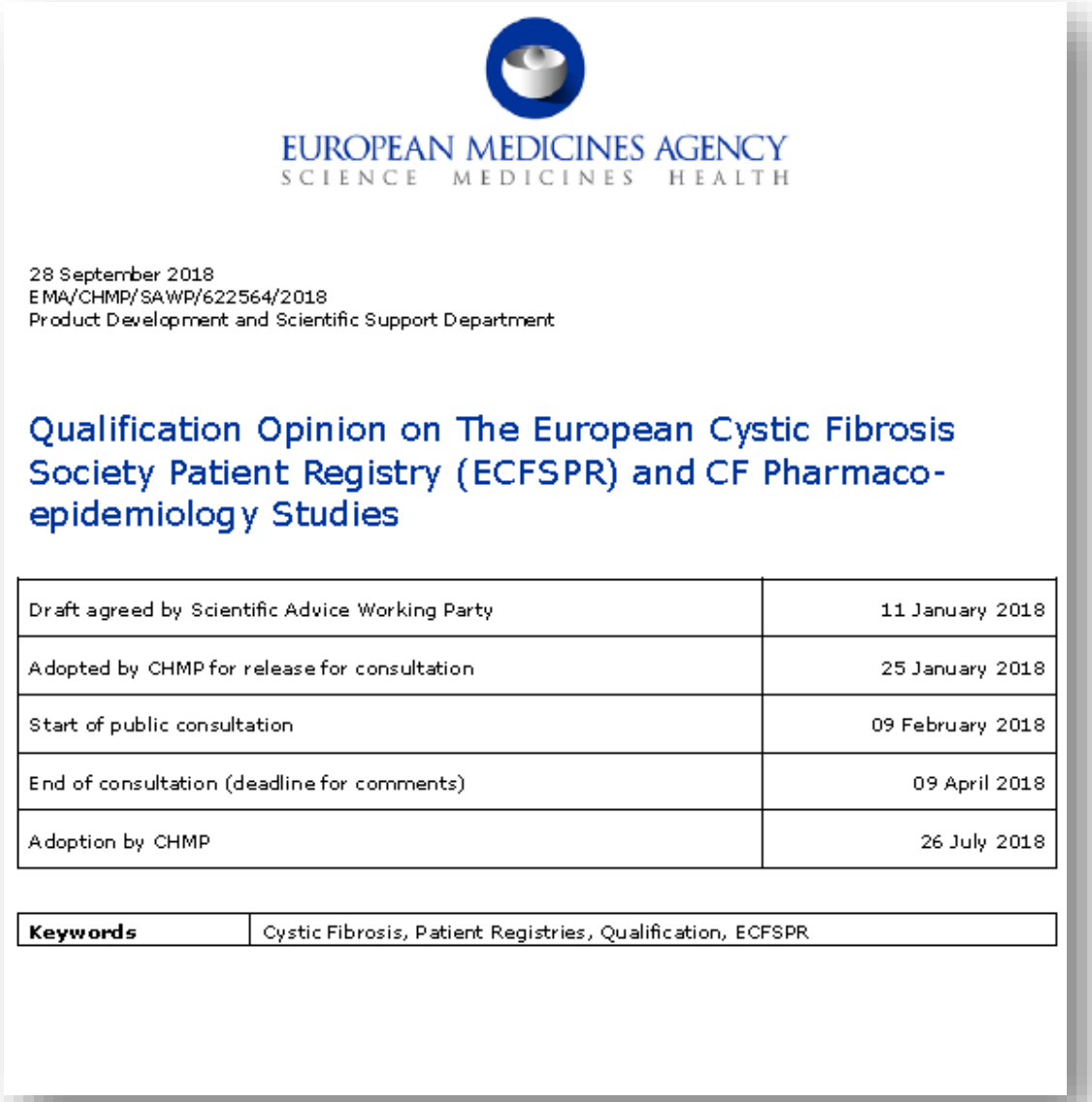
Data Quality Component	Definition	Proposed indicators of quality	Quality Solutions to facilitate data quality
Consistency	Uniformity of the data overtime (e.g. lab data routinely entered)	Number of fields changed over time	Manual checks at centres level, audits
		% of fields missing over time	Standard terminology, coding
		% of forms reported per scheduled follow-up	Standard operating procedures, user guides
			Campaigns, dashboards for clinicians
Accuracy	Accuracy of data entry: no errors, no contradictions or impossibilities in data, absence of duplicates	Change in value of data filed by x% creates alerts	Drop down menus, alerts, text prompts, flags
		Variability across fields	Validate against source data (e.g., 10%), cross form validation
			Staff training, software checks.
			Help screens/desks, training, newsletter
			Funding for data managers
Completeness	How much data is missing?	Agreed % of fields completed in audit procedures (e.g. >90%)	Audits
		Lost to follow up %	Mandatory fields
			Engagement with patients and/or health care providers (HCPs)
	Absence of core variables	Minimum agreed core common data elements reported	Agreed list of data elements and definitions
		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.



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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 Pharmaco-epidemiology Studies

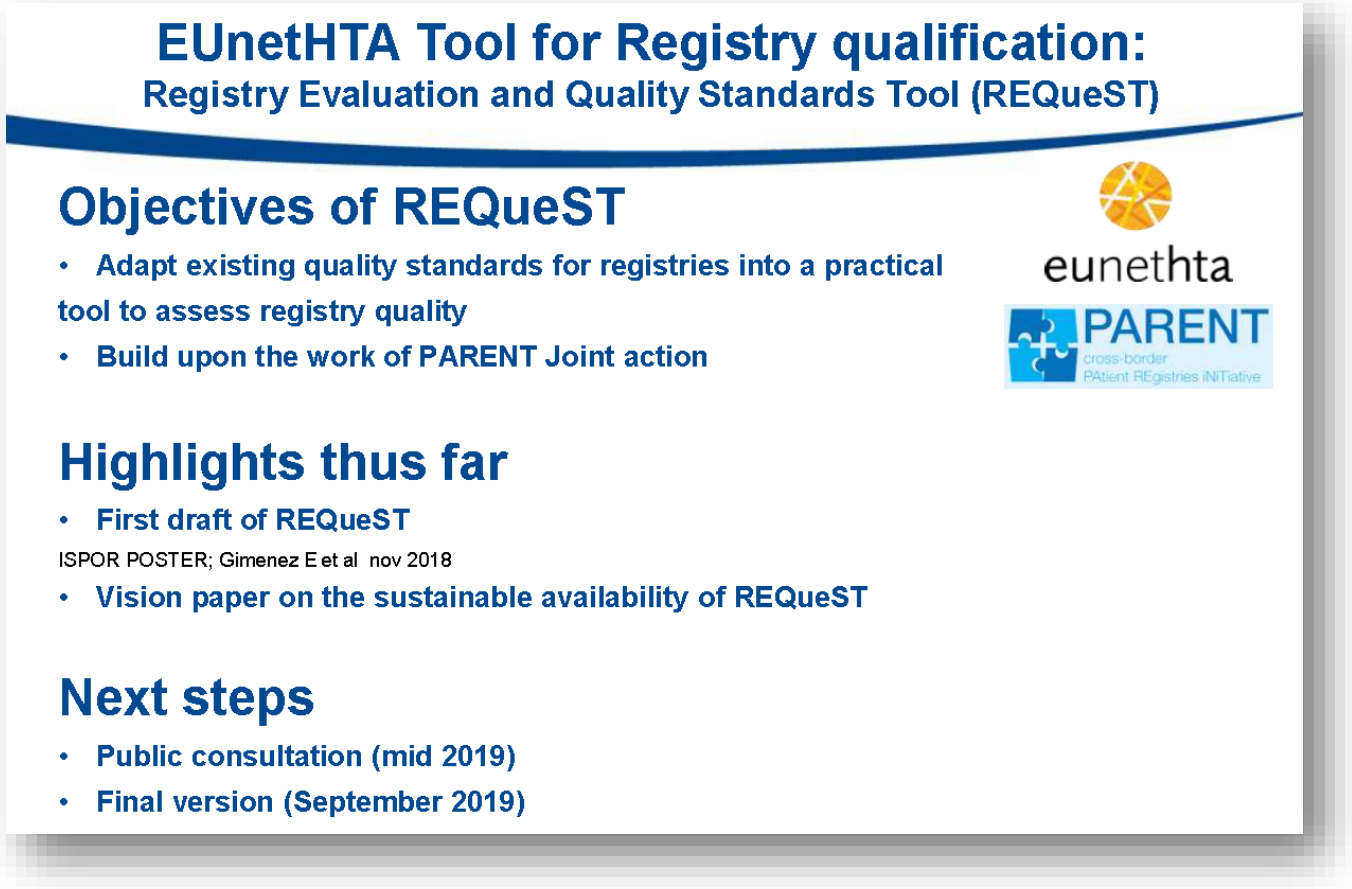
Draft agreed by Scientific Advice Working Party	11 January 2018
Adopted by CHMP for release for consultation	25 January 2018
Start of public consultation	09 February 2018
End of consultation (deadline for comments)	09 April 2018
Adoption by CHMP	26 July 2018

Keywords	Cystic Fibrosis, Patient Registries, Qualification, ECFSPR

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



Gimenez E, Valentic M, Espallargues M, Rodriguez J,m Varela L, Guzina I, Patrick H, Long J. The registry evaluation and quality standards tool (REQueST) for health technology assessment from am 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

2

Representativeness

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

1

Broad range of patients

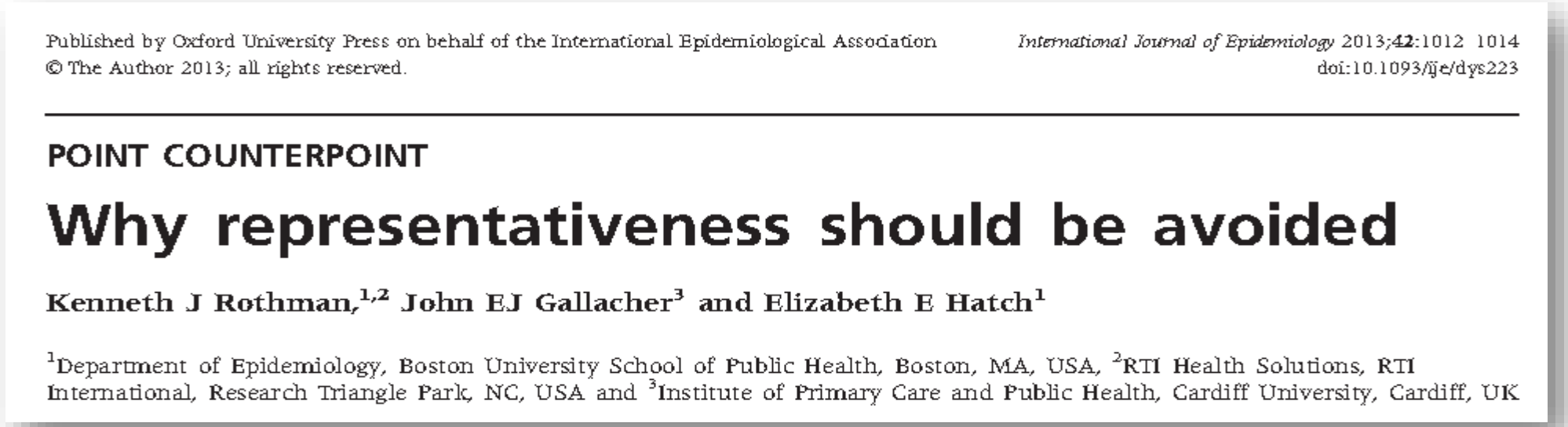
which can translate into better generalisability

3

Transferability

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

Challenge 3
Generalisability of the study results



Published by Oxford University Press on behalf of the International Epidemiological Association

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

POINT COUNTERPOINT

Why representativeness should be avoided

Kenneth J Rothman,[1,2] John EJ Gallacher[3] and Elizabeth E Hatch[1]

[1]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA, [2]RTI Health Solutions, RTI International, Research Triangle Park, NC, USA and [3]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

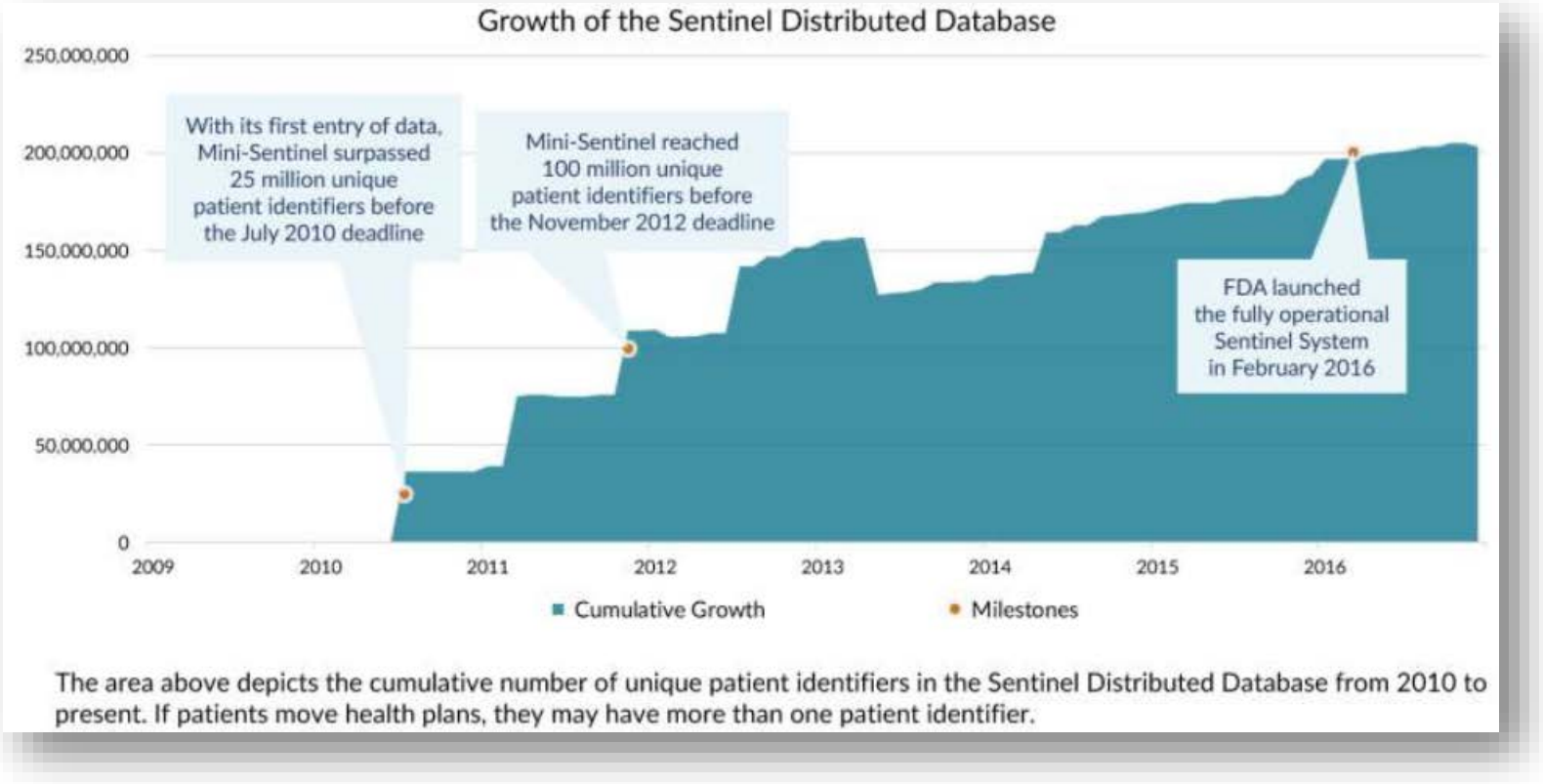
When Doll and Hill studied the mortality of male British physicians in relation to their smoking habits, their findings about smoking and health were considered broadly applicable despite the fact that their study population was unrepresentative of the general population of tobacco users with regard 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



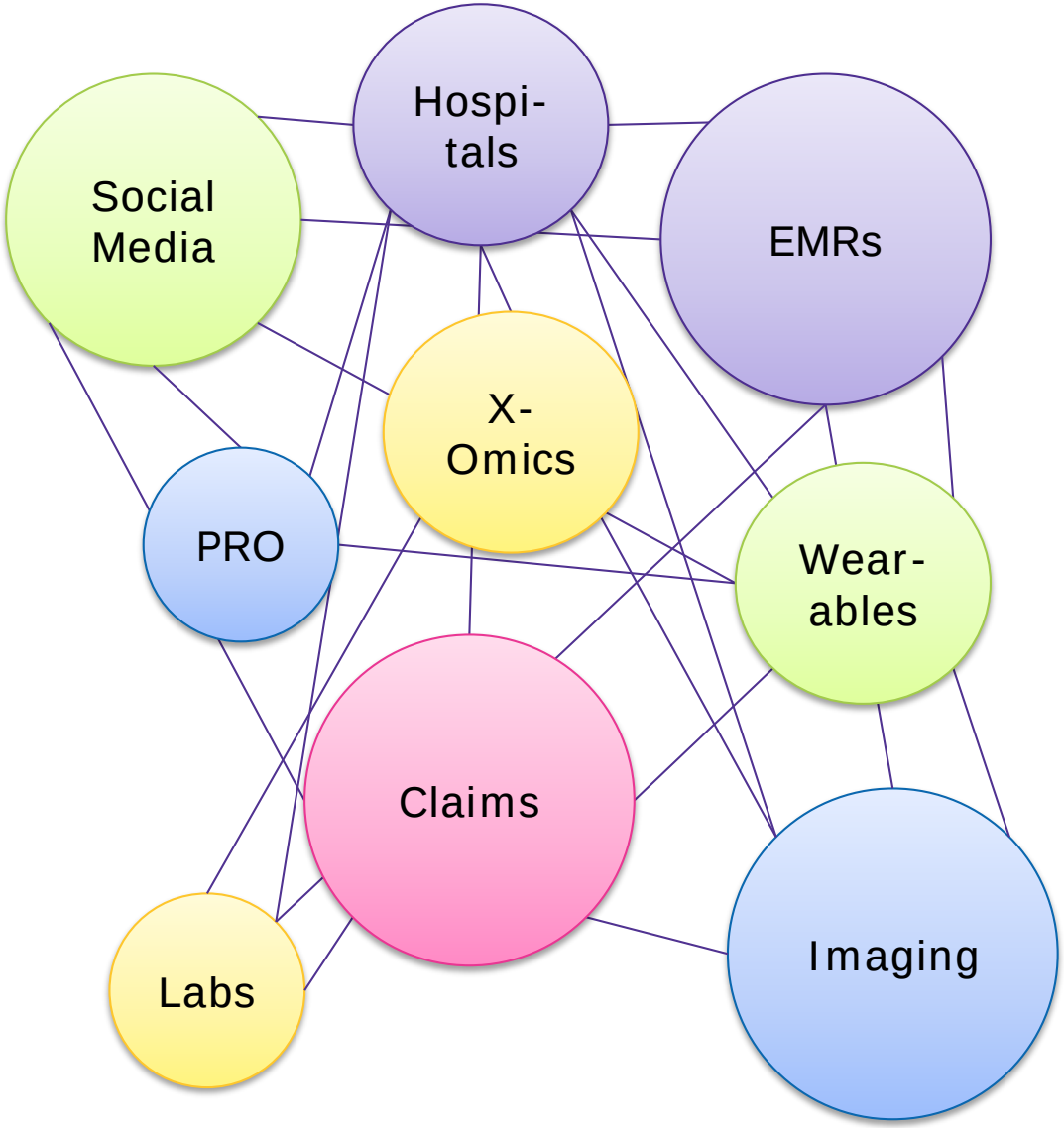
From “Framework for FDA’s Real-World Evidence Program - Jacqueline Corrigan-Curay, J.D., M.D. Director, Office of Medical Policy / CDER FDA

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/cer-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

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EU PAS Registry

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15 March 2018
EMA/929209/2011

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


Contents lists available at ScienceDirect
Vaccine
journal homepage: www.elsevier.com/locate/vaccine
Review
The ADVANCE Code of Conduct for collaborative vaccine studies
Xavier Kurz, Vincent Bauchau, Patrick Mahy, Steffen Glismann, Lieke Maria van der Aa,

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