Joint HMA/EMA Big Data Steering Group Workshop on RWE methods
Harnessing Real-World Data for Regulatory Use

14th June 2024

P. Verpillat

Head of Real-World Evidence – Data Analytics and Methods Task Force – EMA

Scene-setting

European Medicines Regulatory Network (EMRN) Strategy 2025

By 2025, the **use** of Real-World Evidence will have been **enabled** and the **value** will have been **established** across the spectrum of regulatory use cases

PERSPECTIVES

PERSPECTIVE

Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value

Peter Arlett[1]*, Jesper Kjaer[2], Karl Broich[3] and Emer Cooke[1]

We outline our vision that by 2025 the use of real-world evidence will have been enabled and the value will have been established across the spectrum of regulatory use cases. We are working to deliver this vision through collaboration where we leverage the best that different stakeholders can bring. This vision will support the development and use of better medicines for patients.

Real-world data (RWD) and real-world evidence (RWE) are already used in the regulation of the development, authorization, and supervision of medicines in the European Union. Their place in safety monitoring and disease epidemiology are well-established while their evidentiary value for additional use cases, notably for demonstrating efficacy, requires further evaluation.[1] During the coronavirus disease 2019 (COVID-19) pandemic, RWE rapidly provided impactful evidence on drug safety, vaccine safety, and effectiveness and we were reminded of the importance of robust study methods and transparency.[2] Our vision, anchored in the European Medicines Regulatory Network (EMRN) strategy to 2025, is that by 2025 the use of RWE will have been enabled and the value will have been established across the spectrum of regulatory use cases.[3] Delivering this vision will support the development and use of better medicines for patients.

In December 2018, the US Food and Drug Administration (FDA) published its framework for RWE underpinned by three pillars: whether RWD are fit for use, whether the study designs can provide adequate evidence, and whether the study conduct meets regulatory requirements.[4] In 2019 in the European Union, we published the OPTIMAL framework for RWE also consisting of three pillars: operational, technical, and methodological.[5] More recently, the EU approach places RWE in the wider context of big data and is guided by the priority recommendations of the Big Data Task Force. These recommendations are being implemented through the Big Data Steering Group and the second multi-annual work plan was published in August 2021.[6] Figure 1 represents the workplan with its 11 workstreams which will deliver our vision for RWE by 2025. The workplan places emphasis on collaboration across stakeholders and with international regulatory partners. This work also needs to be seen in the wider EU policy context, most notably the European Commission's plans for a European Health Data Space.[7]

Acknowledging different frameworks to conceptualize the challenges and opportunities of RWE, we believe the two main priorities for the European Union are to enable its use and establish its value for regulatory decision making. The EMRN is working to deliver on both priorities through a collaborative approach where we leverage the best that different stakeholders can bring, and where those stakeholders can complement the natural role of industry in generating evidence.

ENABLING USE

To enable use, we are working on multiple fronts with our stakeholders, including patients, healthcare professionals, industry, regulatory and public health agencies, health technology assessment bodies, payers, and academia. We are initiating work to establish a data quality framework, not just for RWD but for all data used in regulatory decision making. We are striving to improve the discoverability (findability) of RWD through agreement of metadata for RWD and through a public catalogue of RWD sources[8] that builds on the early work of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The ENCePP Guide on Methodological Standards in Pharmacoepidemiology,[9] extensively updated in 2021, is the core of our efforts to drive up the standards of study methods for RWE, and this is complemented by recently published guidance on conducting studies based on patient registries.[10]

The European Medicines Agency (EMA) and some national medicines agencies

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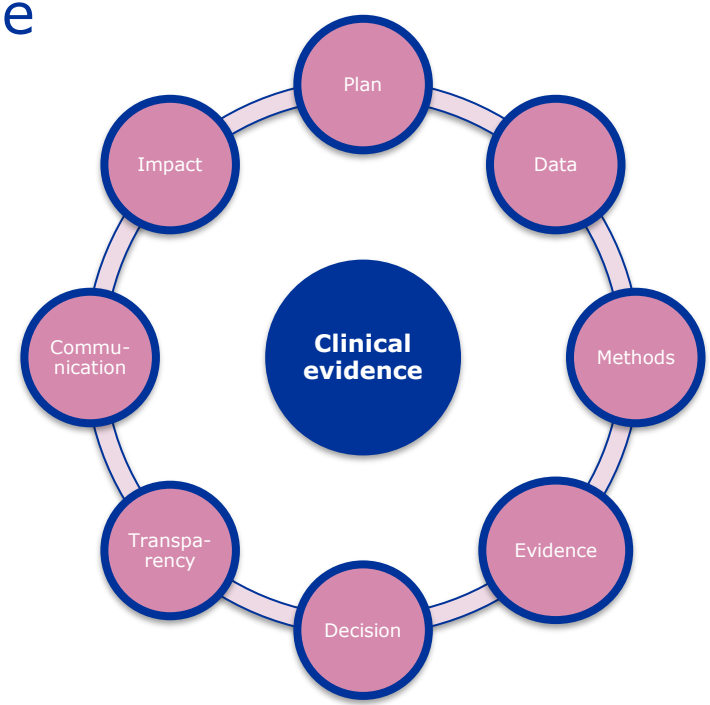
Arlett P. et al. Clin Pharmacol Ther. 2022 Jan;111(1):21-23. doi: 10.1002/cpt.2479

RWD and RWE play a crucial role in bridging the gap between clinical research and practice

- Evidence generation is planned and guided by data, knowledge and expertise
- Research question drives evidence choice and embraces spectrum of data and methods
- **Clinical trials remain core but are bigger, better and faster**
- **Real world evidence is enabled, and its value is established**
- The patient voice guides every step of the way
- Healthcare systems are supported in their choices
- High levels of transparency underpin societal trust



At the core of a successful MA dossier is excellent clinical evidence

Models and approaches for utilizing RWD

Non-Interventional Studies

Causal Inference Methods

Target Trial Emulation

Pragmatic Clinical Trials

Machine Learning and Artificial Intelligence

Natural Language Processing

…

Challenges and Opportunities

Data quality and completeness

Ethical considerations

Methodological rigor

Generalizability

Collaboration

…

Current landscape of EU guidance in this field

Oct. 2021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SCIENCE MEDICINES HEALTH

22 October 2021
EMA/426390/2021
Committee for Human Medicinal Products (CHMP)

Guideline on registry-based studies

Dec. 2021


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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 December 2021
EMA/447502/2021

European Medicines Regulatory Network Data Standardisation Strategy

May 2022


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EMA
EUROPEAN MEDICINES AGENCY

31 May 2022
EMA/563896/2022

List of metadata for Real World Data catalogues


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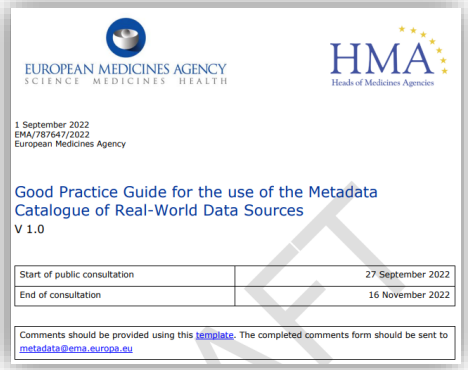
30 October 2023
Data Analytics and Methods Task Force
EMA/326985/2023

Data Quality Framework for EU medicines regulation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1 September 2022
EMA/787647/2022
European Medicines Agency

Good Practice Guide for the use of the Metadata Catalogue of Real-World Data Sources
V 1.0

Start of public consultation	27 September 2022
End of consultation	16 November 2022

Comments should be provided using this template. The completed comments form should be sent to metadata@ema.europa.eu

DRAFT


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9 October 2017
EMA/813938/2011 Rev 3*

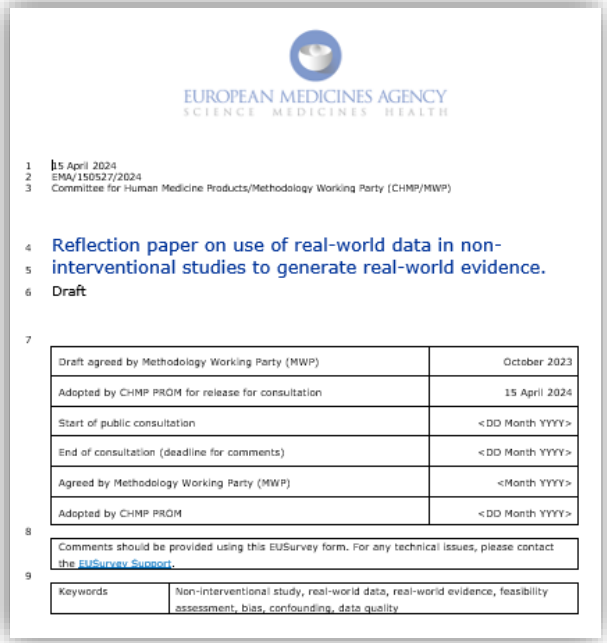
Guideline on good pharmacovigilance practices (GVP)
Module VIII – Post-authorisation safety studies (Rev 3)

Oct. 2023 + **RWD chapter**

Revision ongoing

Methodology Working Party (MWP)

- Established by **CHMP** to leverage expertise in key areas: **RWE**, biostats, modelling/simulation, PK, PGx
  - Product-related support to EMA Committees and SA Working Party
  - Engagement with stakeholders (regulators, trade associations, patient/HCP organisations)
  - Preparation, review, update of **guidelines/ concept papers**, training and workshops for assessors
- **EU experts** nominated by CHMP, 3-year **work plan**
  - **Roadmap** for the development of further RWE guidance



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 April 2024
EMA/150527/2024
Committee for Human Medicine Products/Methodology Working Party (CHMP/MWP)

Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence.

Draft

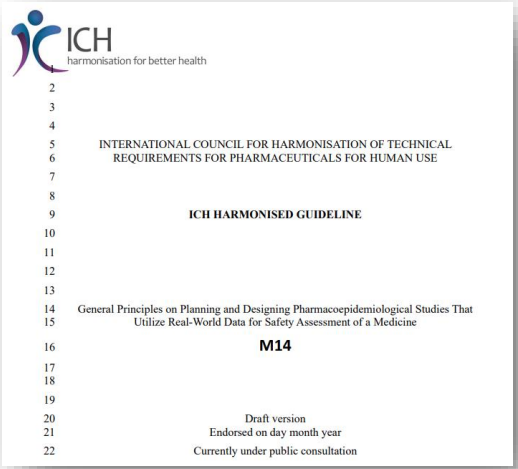
Draft agreed by Methodology Working Party (MWP)	October 2023
Adopted by CHMP PROM for release for consultation	15 April 2024
Start of public consultation	<DD Month YYYY>
End of consultation (deadline for comments)	<DD Month YYYY>
Agreed by Methodology Working Party (MWP)	<Month YYYY>
Adopted by CHMP PROM	<DD Month YYYY>

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	Non-interventional study, real-world data, real-world evidence, feasibility assessment, bias, confounding, data quality

International ‘guidance’ context

ICH M14 Guideline on non-interventional pharmaco-epidemiological studies for safety assessment of medicines → Public consultation on draft guideline on-going, establishment Jan 2025



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

General Principles on Planning and Designing Pharmacoepidemiological Studies That Utilize Real-World Data for Safety Assessment of a Medicine

M14

Draft version
Endorsed on day month year
Currently under public consultation

ICH Reflection Paper
Pursuing opportunities for harmonization in using RWD to generate RWE, with a focus on effectiveness of medicines

Two proposed guidelines: 1) RWD/RWE terminology, metadata, and assessment principles, 2) RWD/RWE protocol and report format, and study transparency

Initial step of an incremental approach towards harmonisation of regulatory RWE guidance

Following possible topics for subsequent ICH guidelines, based on interested parties’ feedback:

- Best practices for data quality including reliability and relevance, building on existing guidance documents
- Data standards for RWD
- Appropriate application of study designs and data analyses

Goals of the workshop

Objectives

- To hear the views of stakeholders and experts
  - on the draft RWE reflection paper open for public consultation
  - on priorities for further regulatory guidance development and collaboration beyond the reflection paper
- To engage with stakeholders on RWE methods in regulatory decision making

Agenda

- **Session 1.** Discuss and Present the Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence (*Open for public consultation up to August 31, 2024*)
- **Session 2.** RWE methods to support EU regulatory decision making
  1. Target Trial Emulation and Estimand framework for non-interventional studies (*Session 2a*)
  2. RWD-derived external controls in Clinical Trials (*Session 2b*)
- **Session 3.** The next three years: Roadmap for development of RWE guidance to support the Methodology Working Party workplan 2025-2028

Wishing you all a nice workshop and great discussions!