

# EU/international guidance to support reliable and relevant RWE: what's new?

ENCePP Plenary  
01 December 2025, Amsterdam

Catherine Cohet, RWE workstream  
Data Analytics and Methods Taskforce



# Outline



- Reflection paper on use of RWD in non-interventional studies to generate RWE for regulatory purposes
- RWD chapter of the Data Quality Framework for EU medicines regulation
- HMA-EMA Catalogues
- Methodology Working Party work plan
- 2026 and beyond (GVP VIII, registry-based studies)



- ICH M14
- ICH E6(R3) Annex 2
- ICH E23
- ICMRA



17 March 2025  
EMA/99865/2025  
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 for regulatory purposes

Draft agreed by Methodology Working Party (MWP)	October 2023
Adopted by CHMP PROM for release for consultation	15 April 2024
Start of public consultation	3 May 2024
End of consultation (deadline for comments)	31 August 2024
Agreed by Methodology Working Party (MWP)	March 2025
Adopted by CHMP PROM	17 March 2025

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

**Scope** - design, conduct and analysis of non-interventional studies (NIS) using RWD to generate RWE for regulatory purposes (*out of scope: use of RWD in the context of CTs*)

**RWD** - data that describe patient characteristics (including treatment utilisation and outcomes) in routine clinical practice

**RWE** - evidence derived from the analysis of RWD

**NIS** - as per Art. 2 of Regulation (EU) No 536/2014



# Main features of the RP

- **Feasibility** assessments to ensure data sources are **fit for purpose**, i.e. of 'good' quality assessed using a **DQF** (ideally EMA's)
- RWD can be collected through **primary data collection** and **secondary use of data**
- Distinction made between **descriptive** studies and studies with **causal** objectives, given different implications for study design
- Use of **target trial emulation** for studies with causal objectives, with consideration to the **estimands framework** to specify key elements of the target trial
- Considerations given to appropriate **pharmacoepidemiological** and **statistical methods** applied to transform and analyse the data

# Contents



1. Introduction
2. Scope
3. Legal obligations and and regulatory requirements
4. Study design
  1. General considerations
  2. Feasibility assessment
  3. Studies with descriptive objectives
  4. Studies with causal objectives
5. Bias, confounding and effect modification
  1. General considerations
  2. Selection bias
  3. Information bias
  4. Time-related bias
  5. Confounding
  6. Effect modification
6. Governance and Transparency
7. Data quality
  1. Reliability
  2. Relevance
  3. Multi-database studies
  4. Data linkage
  5. Data quality frameworks
8. Statistical analyses
  1. Model specification
  2. Estimation and precision
  3. Time-dependent analyses
  4. Stratified analyses
  5. Sensitivity and supplementary analyses
  6. Missing data
  7. Heterogeneity
9. References

# Data Quality Framework for EU medicines regulation



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

## Data Quality Framework for EU medicines regulation

<b>Draft agreed by BDSG for release for consultation</b>	10 October 2022
<b>End of consultation (deadline for comments)</b>	18 November 2022
<b>Agreed by BDSG and MWP</b>	30 June 2023
<b>Adopted by CHMP</b>	30 October 2023

<b>Keywords</b>	Data quality framework, medicines regulation, data quality dimensions, primary and secondary use of data
-----------------	----------------------------------------------------------------------------------------------------------

- Drafted under co-sponsorship of BDSG and MWP – adopted by CHMP
- Sets out **quality criteria** for data to ensure they are **fit-for-purpose** for regulatory decision-making
- Definitions of **data** (sub)**dimensions** as well as their characterisation and related **metrics**

# Data Quality Framework: Main dimensions



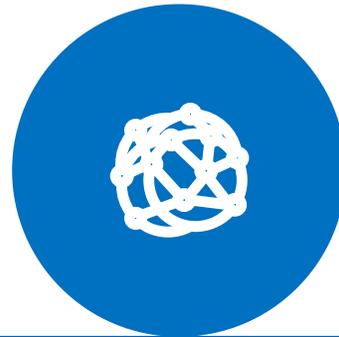
Is data correct?  
Is it representing what is meant to represent?

**RELIABILITY**



How much data is there?

**EXTENSIVENESS**



Can data be analysed as a whole?

**COHERENCE**



Is data available at the right time?

**TIMELINESS**



Is this the kind of data I need?

**RELEVANCE\***

\*Suitability to a research question

Data quality is assessed from the angle of *fitness for purpose* for users' needs

# DQF RWD chapter



**EUROPEAN MEDICINES AGENCY**  
SCIENCE MEDICINES HEALTH

4 November 2024  
EMA/503781/2024  
Committee for Medicinal Products for Human Use (CHMP)

**Data Quality Framework for EU medicines regulation:  
application to Real-World Data**  
Draft

<b>Draft agreed by Methodology Working Party (MWP)</b>	September 2024
<b>Adopted by CHMP for release for consultation</b>	4 November 2024
<b>Start of public consultation</b>	29 November 2024
<b>End of consultation (deadline for comments)</b>	31 January 2025

Draft under finalisation after public consultation

## Table of contents

<b>Executive summary</b> .....	<b>3</b>
<b>1. Background: Real-World Data and Data Quality</b> .....	<b>4</b>
1.1. Definition of Real-World Data .....	4
1.2. Distinctive traits of RWD .....	4
1.3. RWD use-based quality control.....	5
1.4. Impact of secondary use of RWD on data quality.....	5
1.4.1. Impact on Reliability .....	6
1.4.2. Impact on Extensiveness and Representativeness.....	6
1.4.3. Impact on Coherence .....	7
1.5. Responsibility for DQ in RWD .....	7
<b>2. Application of the EMRN DQF to RWD</b> .....	<b>7</b>
2.1. Purpose of this document .....	7
2.2. Scope of the RW-DQF .....	8
2.3. Structure of the RW-DQF.....	8
2.3.1. Understanding relevance .....	9
<b>3. Guidelines for the characterisation of systems and processes underpinning data</b> .....	<b>10</b>
3.1. Systems and process characterisation checklist and maturity model .....	10
3.2. General considerations on the characterisation of systems and processes.....	17
<b>4. Data quality metrics for RWD</b> .....	<b>18</b>
4.1. Framework for the categorisation and identification of metrics .....	18
4.2. Metrics for DQ assessments.....	20
4.3. Considerations for the implementation of RWD DQ metrics .....	23
4.3.1. Different roles of metrics .....	23
4.3.2. Additional considerations on level of application and maturity for metric assessments .....	24
<b>5. Guidelines to assess quality in relation to a specific research question</b> .....	<b>24</b>
5.1. General principles for assessment of data quality in relation to a research question .....	24
5.2. Framework for detailed fitness-for-use assessment.....	27
5.3. Illustrative example for detailed fitness-for-use assessment .....	28
5.4. Toward a generalisation of question-specific aspects.....	31
5.5. Providing supporting information for RWD in regulatory submissions .....	32
<b>6. Concluding remarks</b> .....	<b>32</b>
<b>7. References</b> .....	<b>32</b>
<b>Definitions</b> .....	<b>34</b>
<b>Glossary</b> .....	<b>34</b>

# Data Quality Framework: RWD chapter



## Metrics with examples

Proposed metrics supported by examples and guidance, where applicable on their recommended use



## Checklists and visuals

Checklists of elements to be taken into consideration to aid the assessment



## Leveraging HMA-EMA RWD sources Catalogue

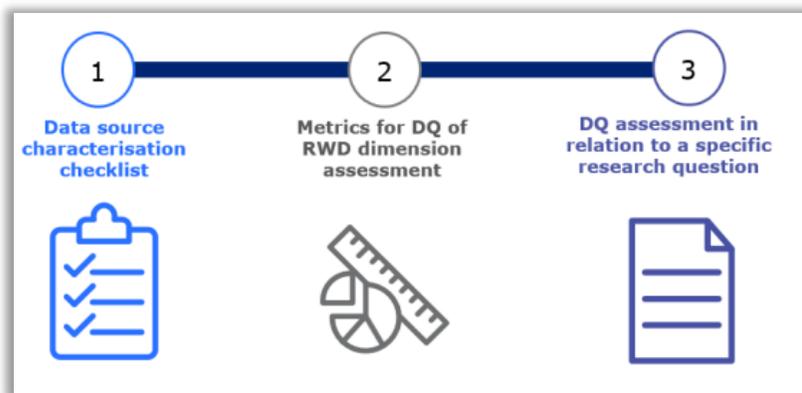
To support the provision of information on data quality of existing data sources

[HMA-EMA Catalogues of RWD sources and studies](#)



## Focus on research question

Data quality defined as 'fit for use'  
Focus on addressing data quality in this context



# HMA-EMA Catalogues of RWD sources and studies



Standardised metadata structure



Enhanced search functionalities



Linkage between data sources and study records



Open access



Study documents accessible



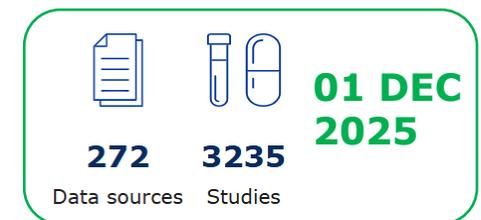
Steady increase of number of records

## New/updated resources in 2025

- [Good Practice Guide for the use of the Metadata Catalogue of RWD Sources](#) (April 2025)
- [User guide](#) (version 2, June 2025)
- [List of metadata for the HMA-EMA Catalogues of RWD sources and studies](#) (version 4, June 2025)

## Improvement pipeline

- Advanced search capabilities, dashboards and comparison functionality
- Record completeness score
- Active engagement and communication to further support growth and increase no. of end users
- Use cases



# Methodology Working Party work plan

- MWP established by CHMP to pool and use expertise in key domains: biostatistics, modelling & simulation, clinical pharmacology and pharmacokinetics, PGXs and diagnostics, AI and data science, and RWE



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

2 December 2024  
EMA/324489/2024  
Committee for Human Medicine Products / Methodology Working Party  
Human Medicines Division

Consolidated 3-year rolling work plan for the Methodology Working Party

<b>Chair:</b>	Kit Roes
<b>Vice Chair:</b>	Kristin Karlsson

Work plan period: January 2025 – December 2027 (with a first review point after one year)

## Real World Evidence

Following finalisation of the reflection paper on the use of Real-World Data (RWD) in non-interventional studies to generate Real-World Evidence (RWE), a **roadmap** shall be developed with the aim **to identify and prioritise further guidance development for the use of RWD in areas other than non-interventional studies**. It will also include a **summary of existing guidance on RWE across regulatory jurisdictions** as well as areas for potential future guidance. Based on gaps identified, several of these topics will be developed in a multi-disciplinary setting as they, e.g., may relate to clinical trials, modelling, biomarker development or safety monitoring.



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

19 February 2025  
EMA/100019/2025  
European Medicines Agency  
Human Medicines Division/Methodology Working Party

## Journey towards a roadmap for regulatory guidance on real-world evidence

- Provides contextual information on achievements so far
- Identifies RWD-related topics for potential guidance development
  - **Externally controlled trials**, where external controls may come from RWD sources or CTs
  - **Augmented-control trials**, where a small control arm is recruited in the current trial but supplemented with external controls from RWD sources or clinical trials
  - **Pragmatic trials**

- **Q&A document** aiming to clarify what is (is not) RWD in the context of current guidance, including the RP, the registry-based studies guideline, and the DQF and its application to RWD (under development)

# 2026 and beyond...

- Revision of **GVP Module VIII**
  - ✓ Adapted definitions based on 2022 EC Clinical Trial Regulation (e.g., clinical study, clinical trial, NIS) and review/integration of appendices/addendums
  - ✓ Alignment with ICH M14
  - ✓ Consideration of EMRN experience with PASS assessment
- Guidance targeted to groups establishing/contributing to patient registries, on how to make **registry** data relevant for regulatory use, including **PED** as suggested by the recent [PED Reflection Paper](#)
- Update of the EMA [Guideline on registry-based studies](#)





# International convergence and harmonisation

# RWE guidance from RAs across the world\*

## FDA, USA

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Use of Electronic Health Record Data in Clinical Investigations

Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products

Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Data Standards for Drug and Biological Product Submissions Containing Real-World Data

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products

Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

Considerations for the Use of RWD and RWE To Support Regulatory Decision-Making for Drug and Biological Products

RWE: Considerations regarding NIS for Drug and Biological Products

## ICH, M14

General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize RWD for safety assessment of medicines

## TFDA, Taiwan

RWD: Evaluating EHRs and Medical Benefit Data to Support Drug Regulatory Decision Guidelines

Guidelines for using electronic health care data to conduct drug epidemiological safety studies  
Things to note when using RWD and RWE as technical documents for drug review application

RWD - assessment considerations for relevance and reliability

Research design for real-world evidence – key considerations for pragmatic clinical trials

Guidelines for using electronic medical record data for clinical research

Real-world evidence supports fundamental considerations in drug development

Guideline on the use of Medical Information Database (Real World Data) in pharmacoepidemiologic study

Guidance on the use of RWD in clinical studies to support regulatory decisions

Guideline on randomized controlled trials using RWD to support regulatory decisions

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

DRAFT CADTH Real-World Evidence Reporting Guidance

## ANVISA, Brasil

Draft Real-World Evidence Guide

Swissmedic position paper on the use of RWE

RWD in Saudi Arabia: Current situation and challenges for regulatory decision-making

Guidelines for the conduct of pharmacoepidemiological studies in drug safety assessment with medical information databases

Basic Principles on the use of medical information databases in post-marketing pharmacovigilance

Points to consider for ensuring the reliability of post-marketing database study for regenerative medical products

Basic Principles on utilization of registry for applications

Guidance for Real-World Data Used to Generate Real-World Evidences (Interim)

Guidance on the Use of Real-World Evidence to Support Drug Development and Regulatory Decisions

Guidance on Communication with Regulatory Agency on Real- World Studies to Support Product Registration

Guidance on the Design and Protocol Development of Real-World Studies for Drugs

30 September 2025  
EMA/CHMP/ICH/155061/2024  
Committee for Medicinal Products for Human Use

## ICH M14 Guideline on general principles on planning, designing, analysing, and reporting of non-interventional studies that utilise Real-World Data for safety assessment of medicines

### Step 5

Transmission to CHMP	11 April 2024
Adoption by CHMP	25 April 2024
Release for public consultation	30 May 2024
Deadline for comments	30 August 2024
Final adoption by CHMP	18 September 2025
Date for coming into effect	18 March 2026

- First **harmonised** guidance for NIS generating **safety** evidence (key principles may also apply to **effectiveness**)

- **Iterative approach** to study development incl. feasibility assessments: data fitness-for-use, further refinement of design based on feasibility results

- Importance of **prespecifying** and **documenting** key decisions (exposure, outcome, and covariate definitions, analysis plans, data management, etc...)

- **Transparency** in study conduct, reporting, and dissemination of results

- Interaction with **regulators** for key decisions throughout study process

- Out of scope: detailed instructions for design and execution of NIS (includes supportive refs)

# Table of Contents

**Section 1: Introduction**

**Section 2: General Principles**

**Section 3: Conceptual Framework for Generating Adequate Evidence using Real-World Data**

**Section 4: Initial Design and Feasibility**

- o Development of research question and feasibility assessments

**Section 5: Protocol Development**

- o Study Design, Target/Study Population, Data Sources, Exposures/Outcomes/Covariates, Bias and Confounding, Validation

**Section 6: Data Management and Curation**

- o Data Management, Quality assurance and control, Roles of data holders and researchers

**Section 7: Analysis**

**Section 8: Reporting and Submission**

- o Adverse event reporting, regulatory submission of safety studies

**Section 9: Dissemination and Communication of Study Materials and Findings**

**Section 10: Study Documentation and Record Retention**

**Section 11: Considerations in Specific Populations**

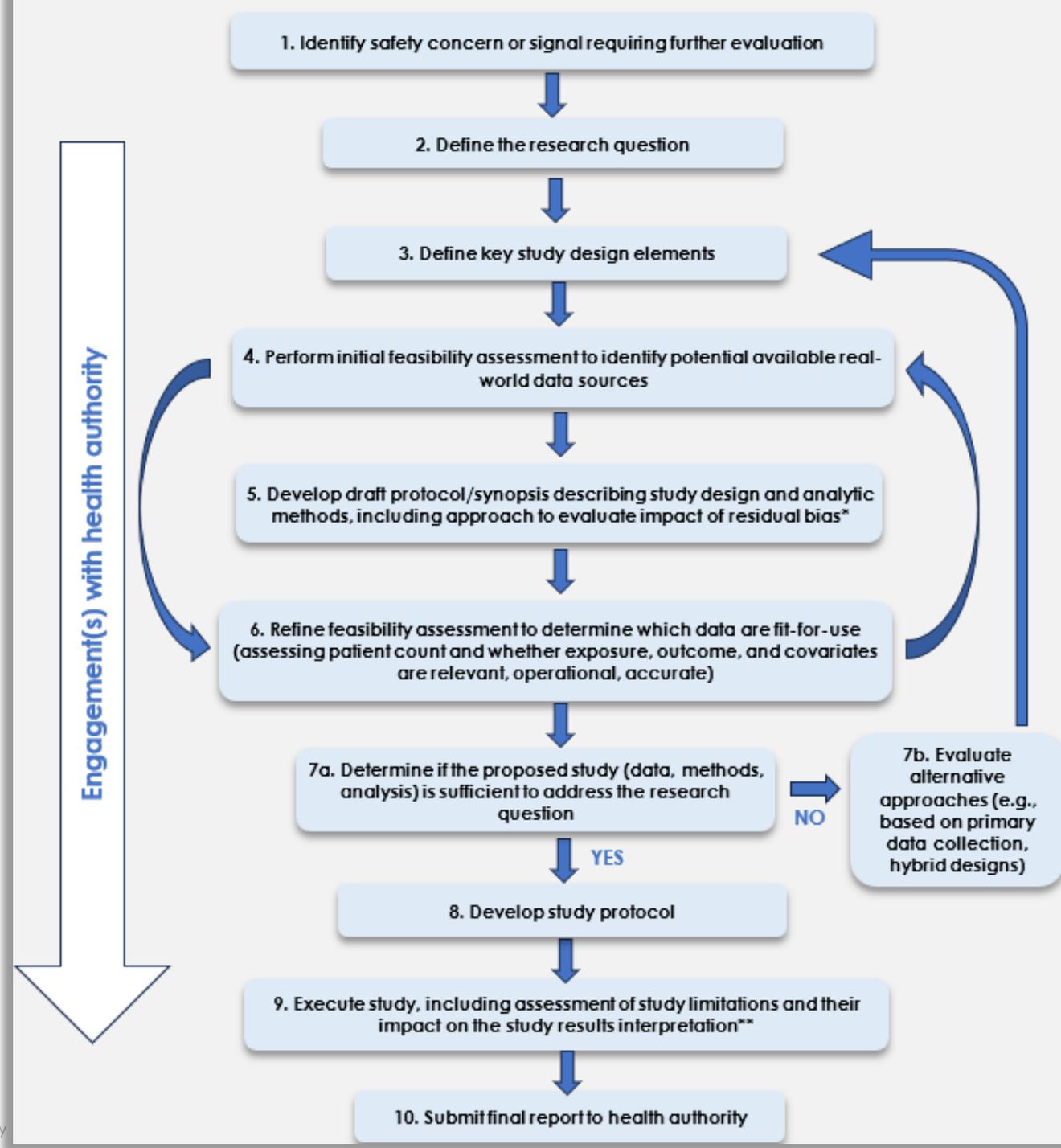
**Section 12: Glossary**

**Section 13: References**

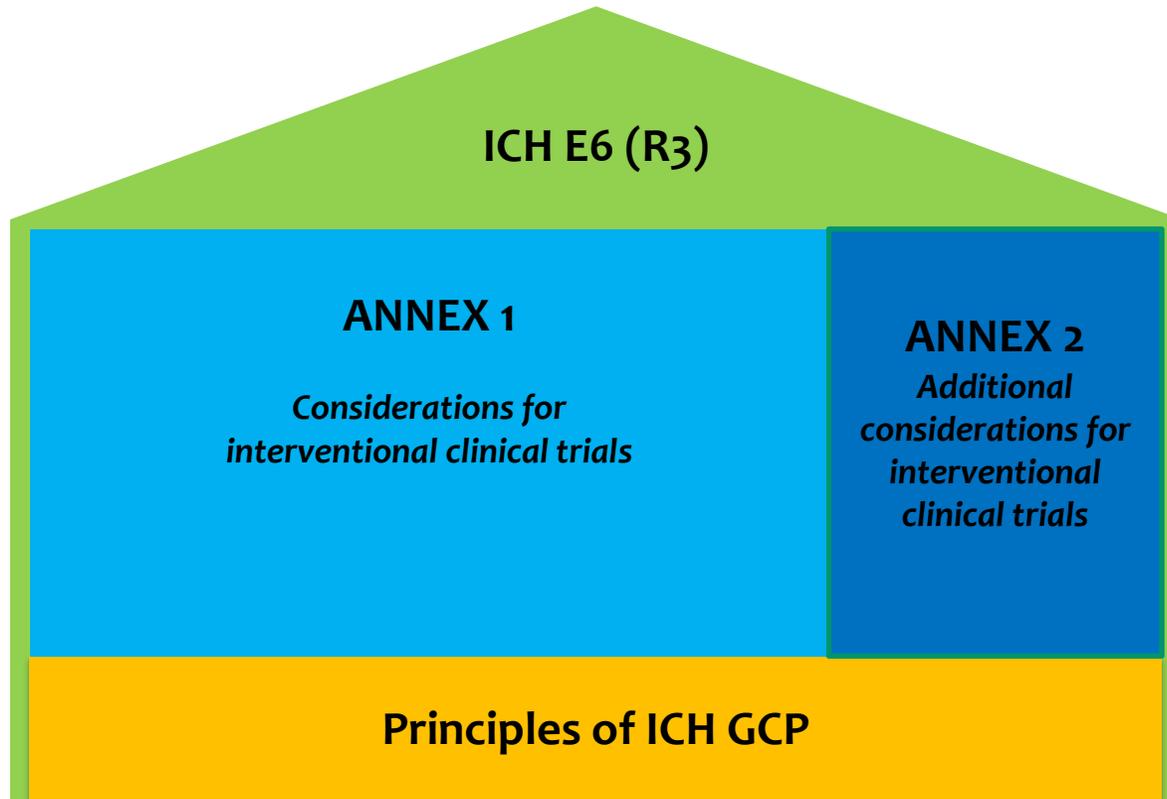
# A Conceptual Framework for Generating Adequate Evidence using RWD

**Fit-for-Use:** A determination of the relevance and reliability of a proposed data source for a given study

\***Quantitative bias analysis** can assist study design and **fit-for-use** data evaluation to understand impact of bias, and can be used in the analysis to evaluate impact on results interpretation of residual/unmeasured confounding or misclassification



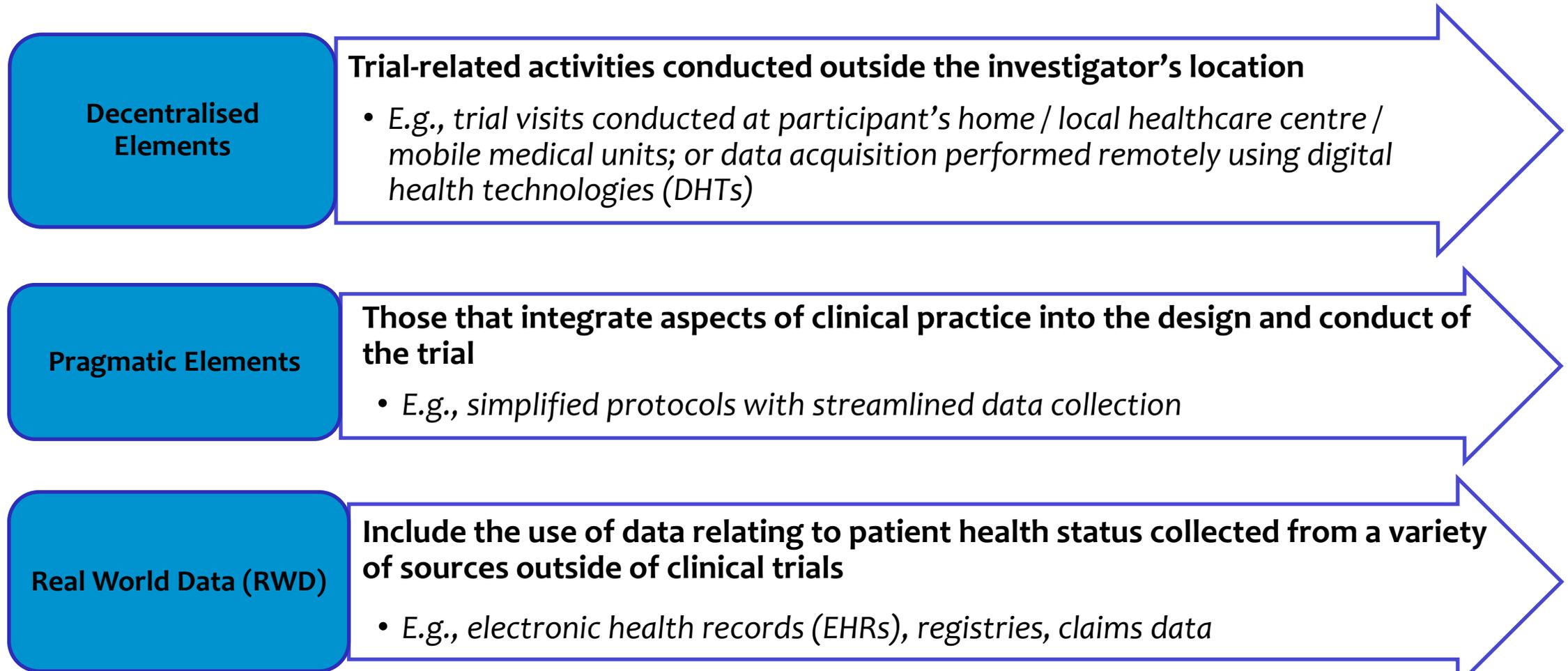
# ICH E6(R3)



- **Annex 2** aim: to provide GCP considerations in the context of CTs with various design elements and data sources to ensure they are fit for purpose
- Appropriate and proportionate application of GCP to support these approaches while safeguarding participant rights, safety and well-being, and helping ensure reliability of trial results

# ICH E6(R3) Annex 2

- Considerations that focus on examples of trials that incorporate:

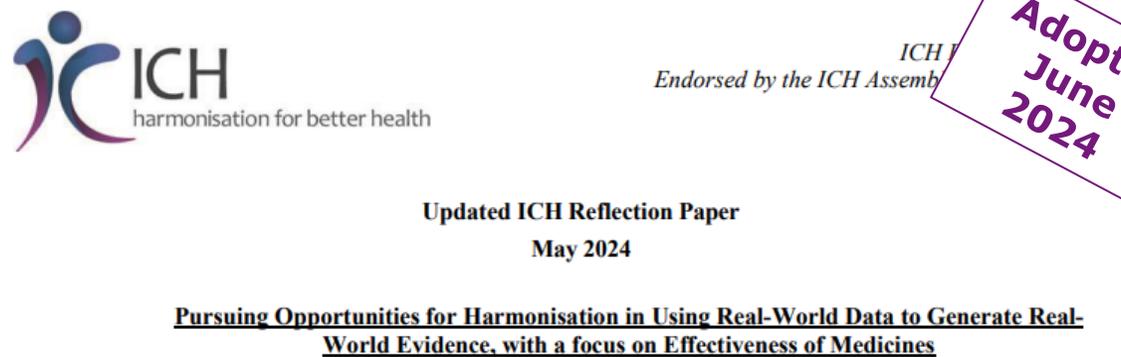


# Incremental approach towards harmonisation of regulatory RWE guidance



**July 2022**

ICMRA statement on international collaboration to enable real-world evidence (RWE) for regulatory decision-making

**Adopted June 2024**

Updated ICH Reflection Paper  
May 2024

Pursuing Opportunities for Harmonisation in Using Real-World Data to Generate Real-World Evidence, with a focus on Effectiveness of Medicines

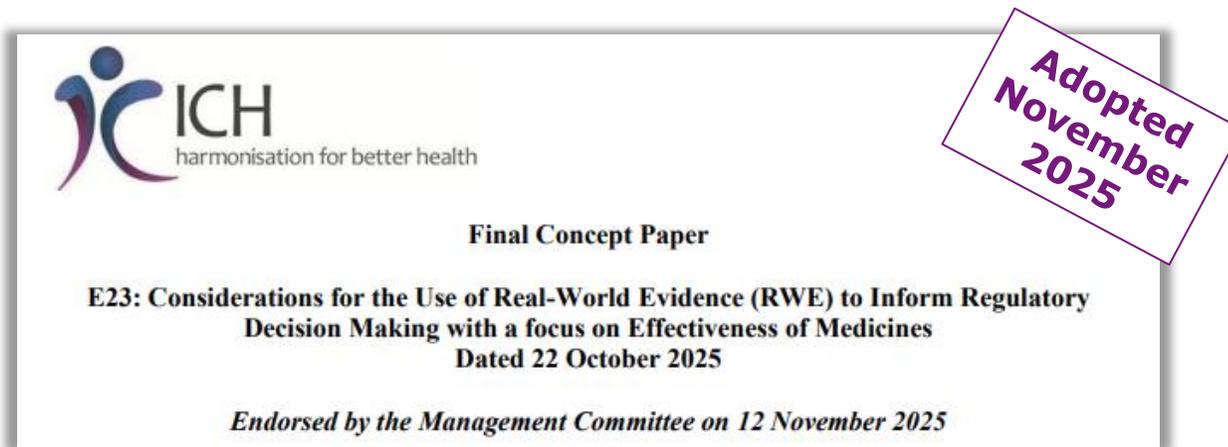
## 4 focus areas for regulatory cooperation

- Harmonisation of terminologies for RWD and RWE
- Regulatory convergence on RWD and RWE guidance and best practice
- Readiness to address public health challenges and emerging health threats

- Transparency

- Proposed by EC, Europe and Health Canada (HC), Canada / co-sponsored by EFPIA
- Convergence on:
  - 1) RWE terminology, metadata and assessment principles (GL1)
  - 2) format of study protocols and reports, study transparency (GL2)

## Considerations for the Use of Real-World Evidence (RWE) to Inform Regulatory Decision Making with a focus on Effectiveness of Medicines



[LINK](#)

### *Issues to be resolved*

- Inconsistent definitions of RWD and RWE across jurisdictions
- Need for better characterisation of RWD
- Lack of convergence of general principles for assessment of RWD and RWE when RWE is used to support effectiveness

## And more...

- ICH Efficacy Guideline on *Natural History Studies and Registry Data to Advance Rare Disease Drug Development*
  - Adopted at the ICH Assembly, May 2025
  - Aim to provide high-level, harmonised principles for designing and conducting natural history studies and registries in rare diseases



# Working Group on RWE for public health emergencies

- Co-chaired by EMA and Health Canada
- 16 agencies\* + WHO
- Objectives
  - Facilitate international collaboration to enhance efficiency of response through **collaborative studies**
  - Optimise **preparedness** by leveraging regional infrastructures and keep governance and processes 'ever-warm'
  - Promote **knowledge sharing** and **transparency**

Builds on experience from former COVID-19 WG:

## Clinical Pharmacology & Therapeutics

Review |  Open Access | 

### Collaborative Real-World Evidence Among Regulators: Lessons and Perspectives

Andrew E. Beck  Melissa Kampman, Cindy Huynh, Craig Simon, Kelly Plueschke, Catherine Cohet, Patrice Verpillat, Kelly Robinson, Peter Arlett

First published: 21 October 2024 | <https://doi.org/10.1002/cpt.3457>

Kelly Robinson and Peter Arlett contributed equally.

Two collaborative studies under development (feasibility stage)

\*Brazil, Canada, China, Denmark, EU (EMA), Germany, Japan, Netherlands, New Zealand, Saudi Arabia, Singapore, South Africa, Switzerland, Chinese Taipei, UK, USA



ICMRA provides a global architecture to support enhanced communication, information sharing, crisis response and address regulatory science issues.

[10th Anniversary](#) [COVID-19](#) [About Us +](#) [Meetings +](#) [Strategic Initiatives +](#) [Relationships](#) [News](#) [Links](#) [Contact Us](#) [Q](#)

[Home](#) > [Real-World Evidence for Public Health Emergencies](#)

## Real-World Evidence for Public Health Emergencies

The ICMRA Working Group on Real-World Evidence for Public Health Emergencies was established to provide a collaborative forum for international regulatory agencies to proactively enhance the efficiency and coordination of critical responses to emerging public health emergencies through joint studies and evidence generation.

The Working Group achieves this by establishing agile governance principles and streamlined processes designed to accelerate the generation of timely evidence to support prompt regulatory action.

The Working Group works to optimise preparedness by leveraging existing infrastructures across participating jurisdictions. This approach enables members to test, refine, and maintain 'ever-warm' governance and operational processes, ensuring readiness to rapidly launch collaborative studies when new public health threats arise.

### Recent Content

17 October 2025

New page - [Real-World Evidence for Public Health Emergencies](#)

1 October 2025

Update - [Identifiers to enable a pharmaceutical quality knowledge management capability](#)

29 August 2025

[ICMRA-industry virtual workshop: Strengthening](#)

[Real-World Evidence for Public Health Emergencies | International Coalition of Medicines Regulatory Authorities \(ICMRA\)](#)



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Thank you

[encepp\\_secretariat@ema.europa.eu](mailto:encepp_secretariat@ema.europa.eu)

Follow us

