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

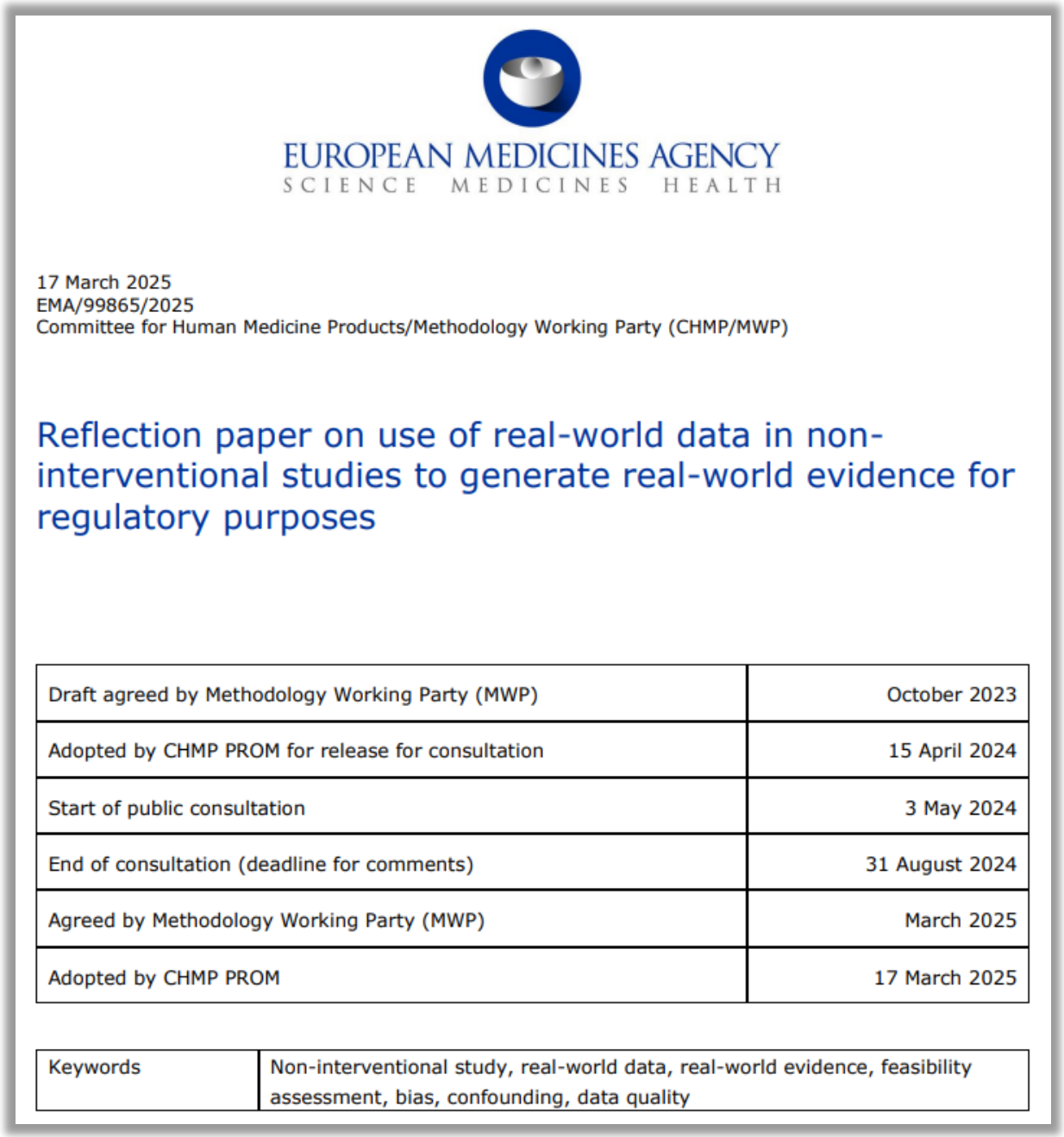
ENCePP Plenary
01 December 2025, Amsterdam

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



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SCIENCE MEDICINES HEALTH

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

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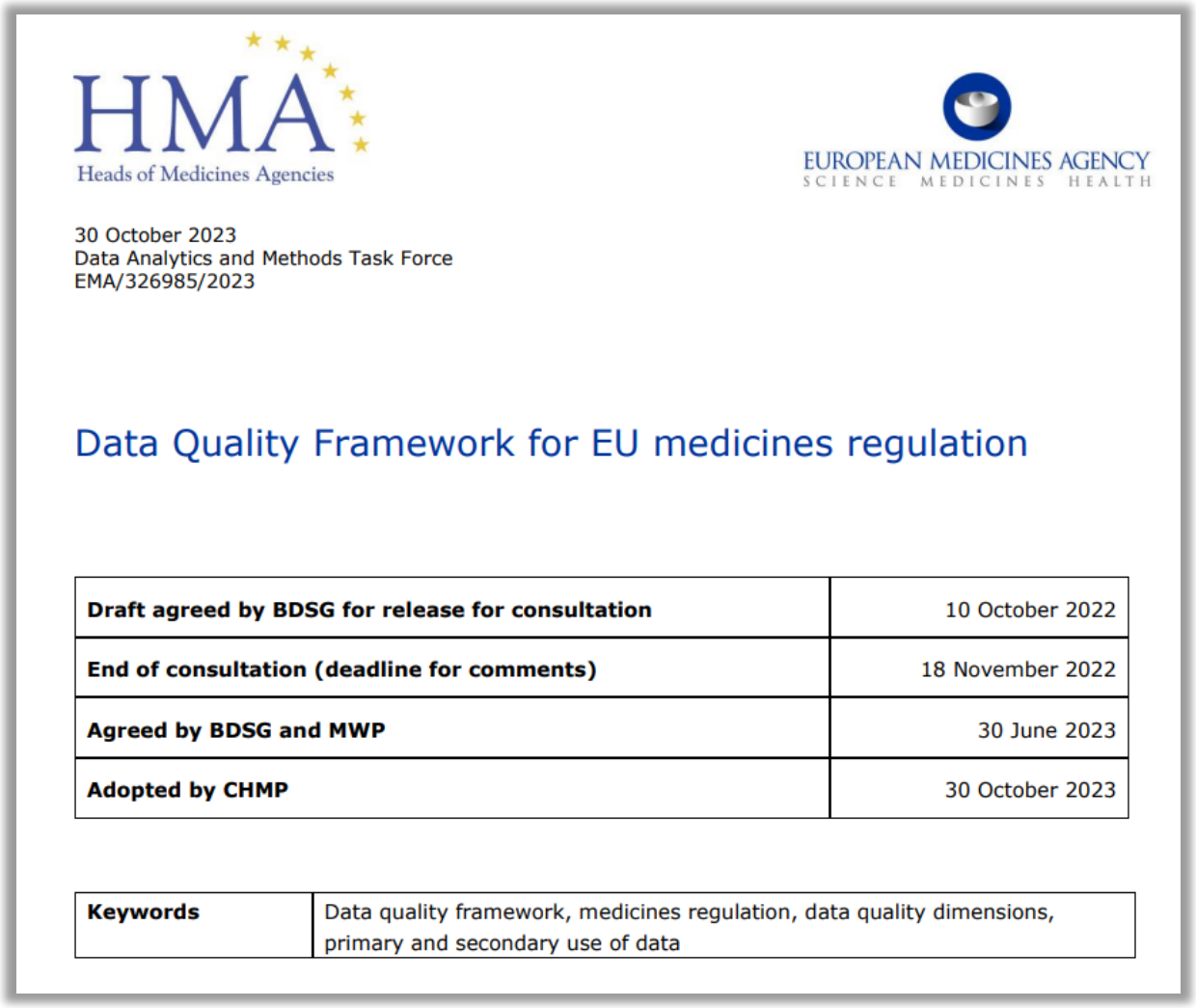
17 March 2025
EMA/99865/2025
Committee for Human Medicine Products/Methodology Working Party (CHMP/MWP)

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

Data Quality Framework for EU medicines regulation



HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Data Quality Framework for EU medicines regulation

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

Keywords	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**

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Data Quality Framework: Main dimensions

*Suitability to a research question

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

DQF RWD chapter

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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

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

Draft under finalisation after public consultation

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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

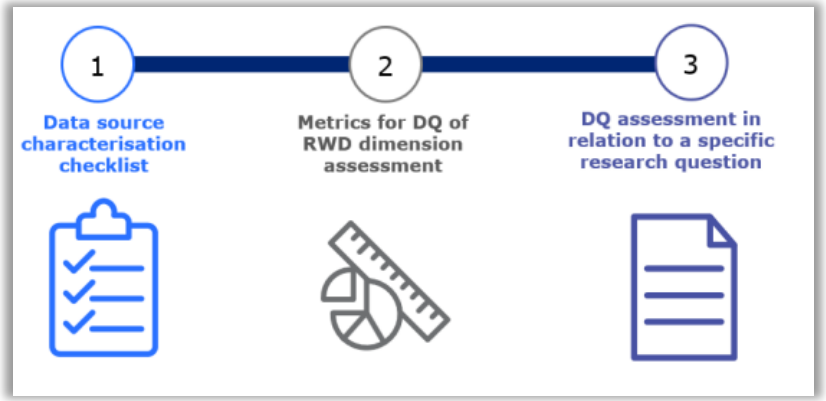
Leveraging HMA-EMA RWD sources Catalogue

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

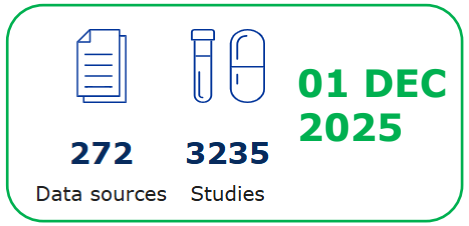
Steady increase of number of records

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

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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

Chair:	Kit Roes
Vice Chair:	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.

Methodology Working Party | European Medicines Agency (EMA)

- 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

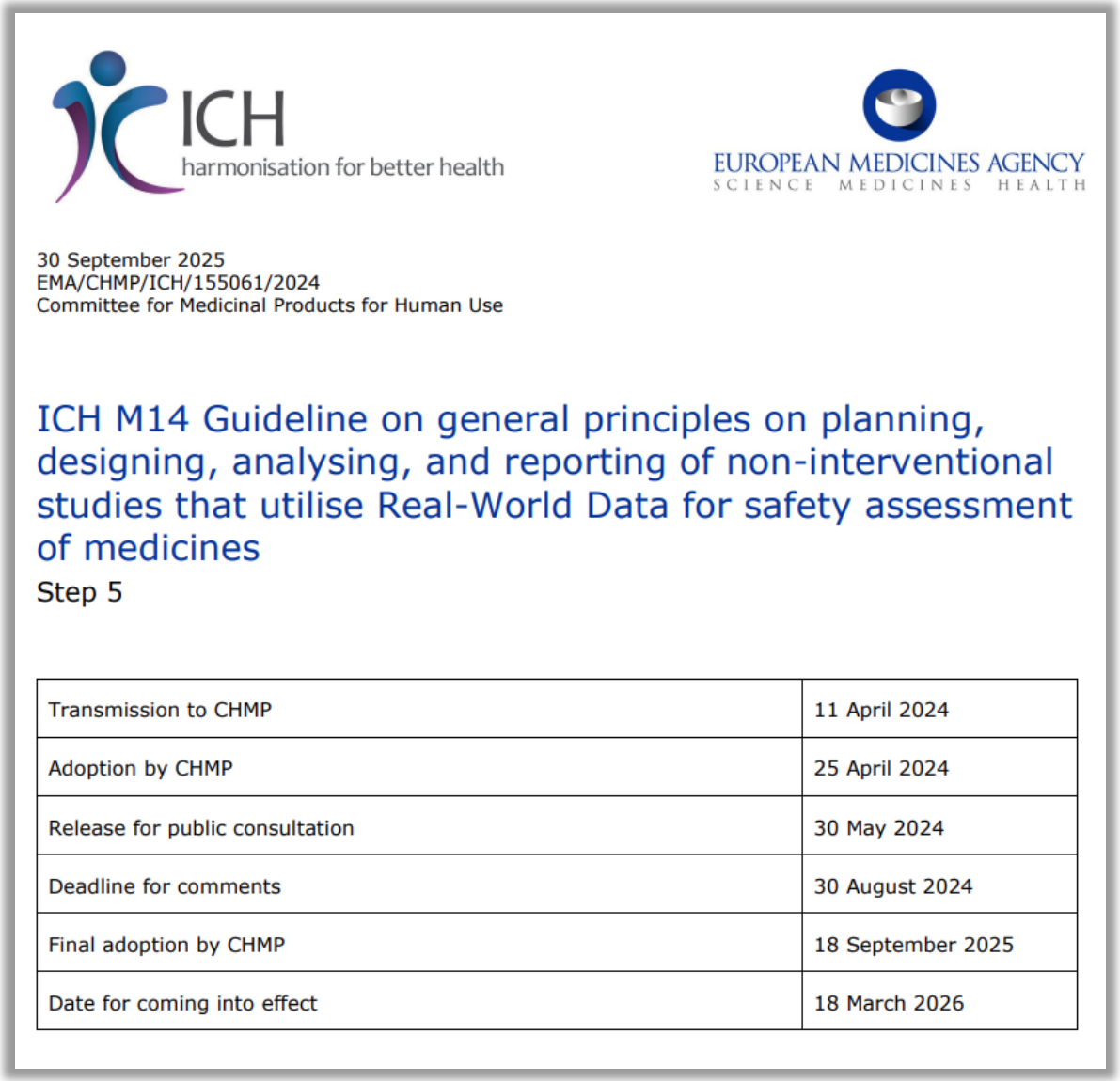
Guidance for Real-World Data Used to Generate Real-World Evidences (Interim)

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

*as of Q1 2025, list not exhaustive



ICH harmonisation for better health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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)

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ICH harmonisation for better health

ICH M14 Step 4

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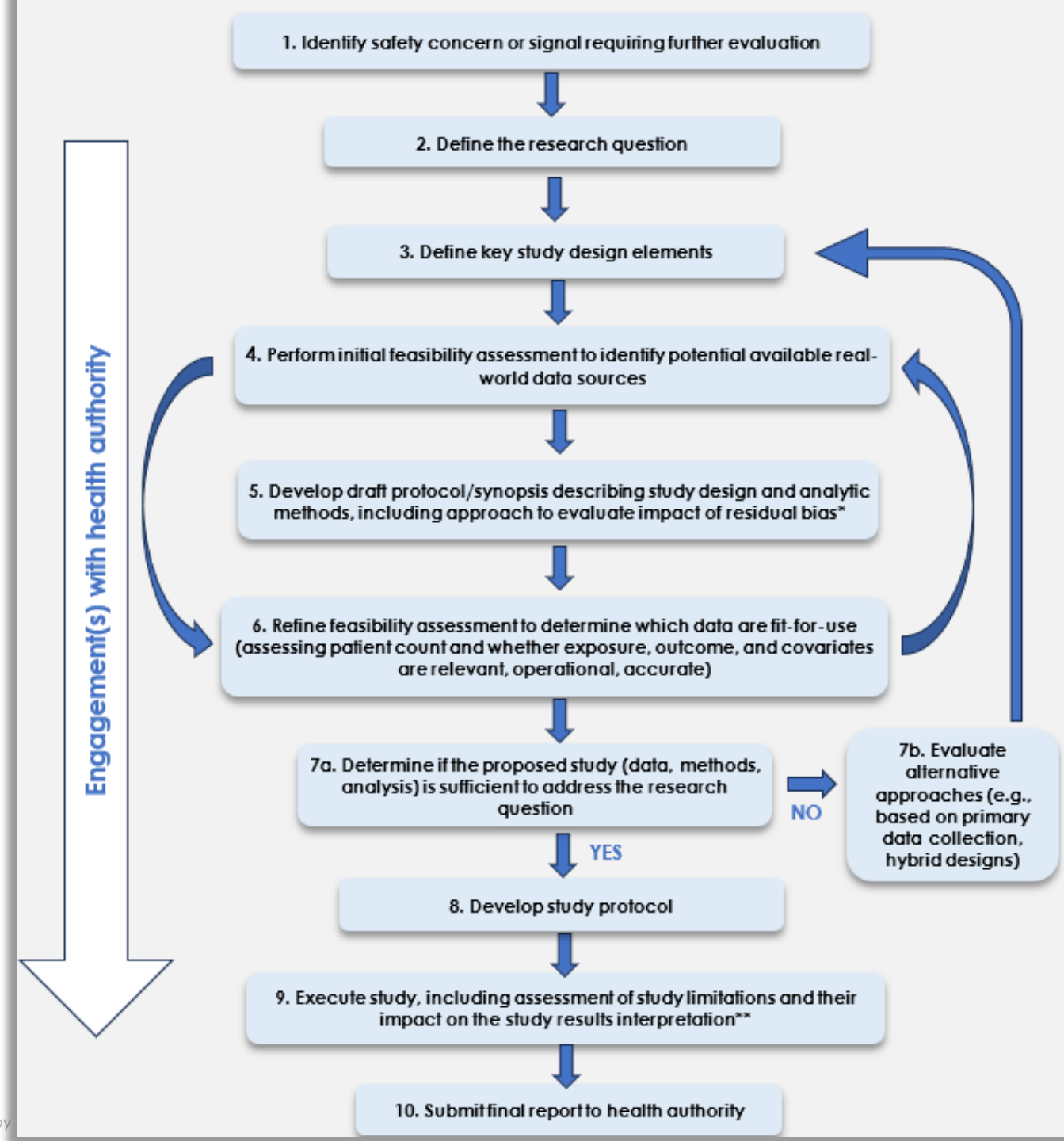
harmonisation for better health

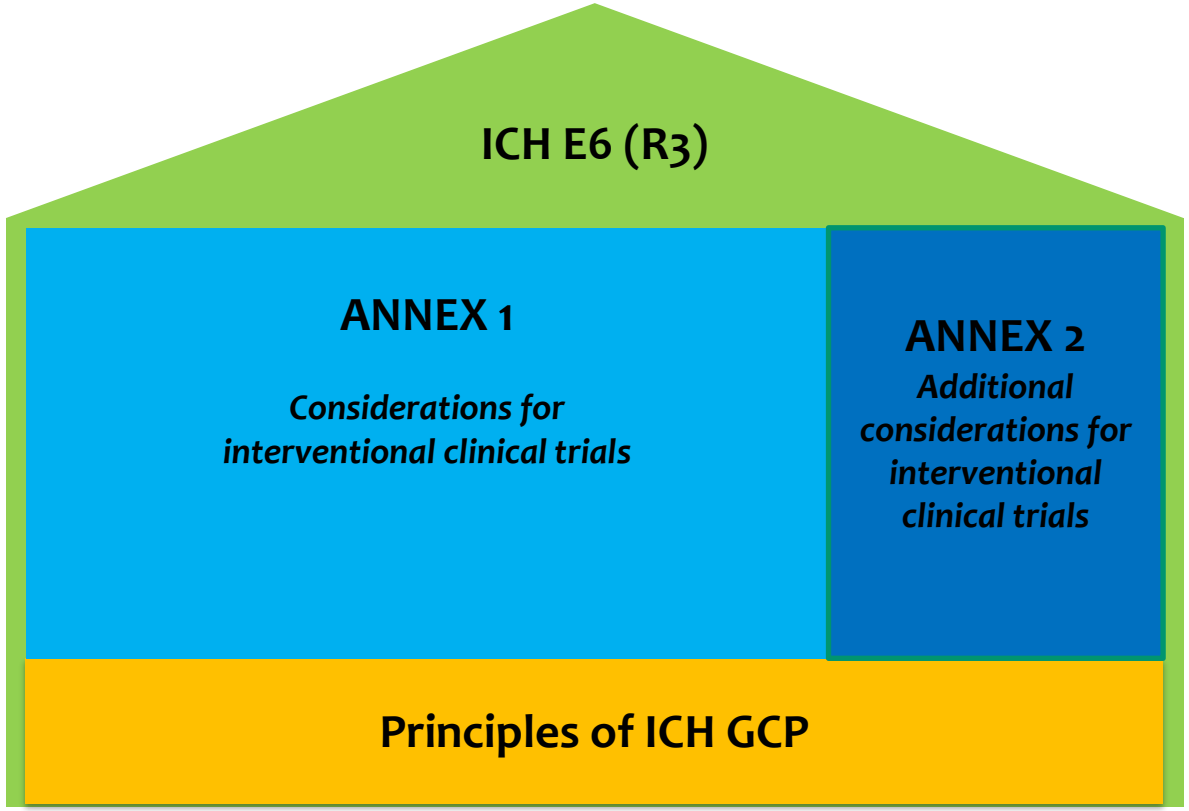
A Conceptual Framework for Generating Adequate Evidence using RWD

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:

Decentralised Elements

Trial-related activities conducted outside the investigator's location

- *E.g., trial visits conducted at participant's home / local healthcare centre / mobile medical units; or data acquisition performed remotely using digital health technologies (DHTs)*

Pragmatic Elements

Those that integrate aspects of clinical practice into the design and conduct of the trial

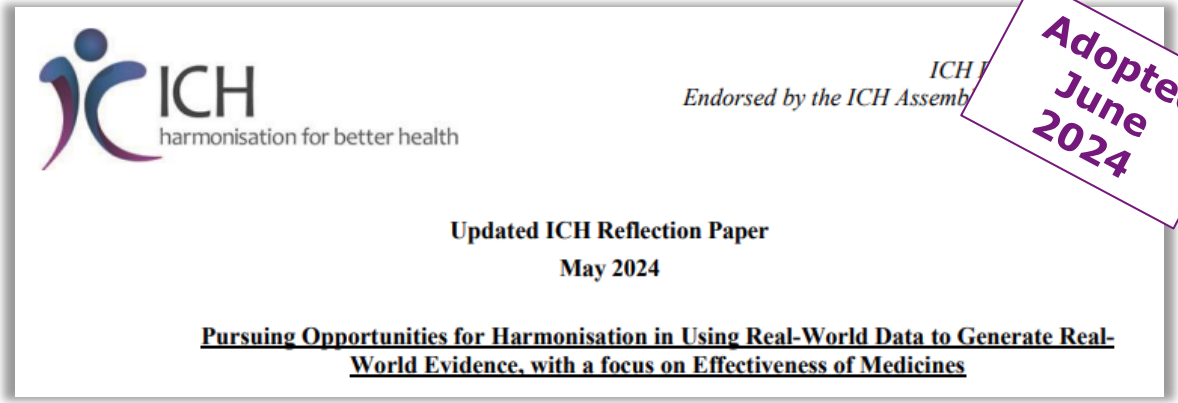
- *E.g., simplified protocols with streamlined data collection*

Real World Data (RWD)

Include the use of data relating to patient health status collected from a variety of sources outside of clinical trials

- *E.g., electronic health records (EHRs), registries, claims data*

Incremental approach towards harmonisation of regulatory RWE guidance



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

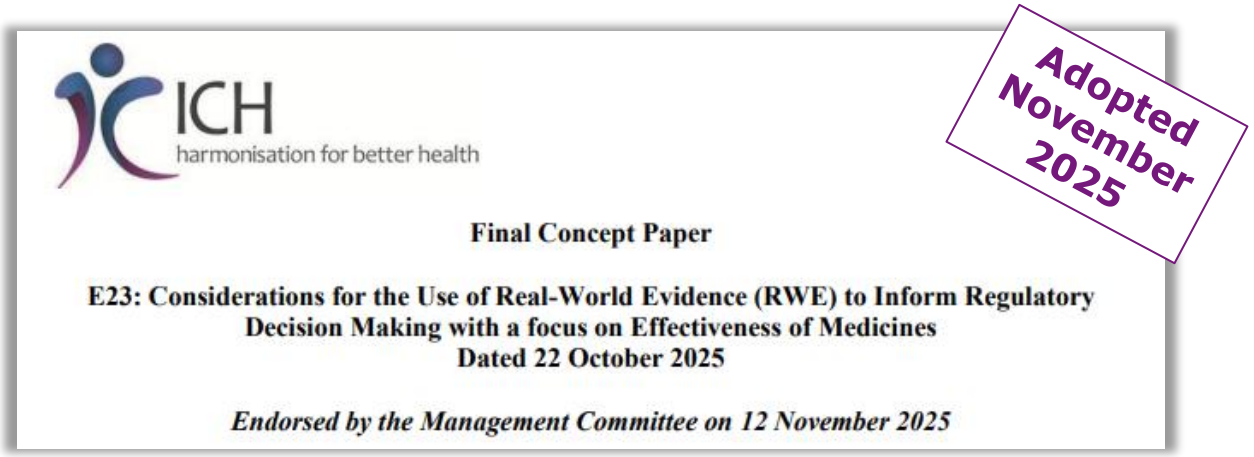
- Proposed by EC, Europe and Health Canada (HC), Canada / co-sponsored by EFPIA
- Convergence on:

  1) RWE terminology, metadata and assessment principles (GL1)

  2) format of study protocols and reports, study transparency (GL2)

ICH E23

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

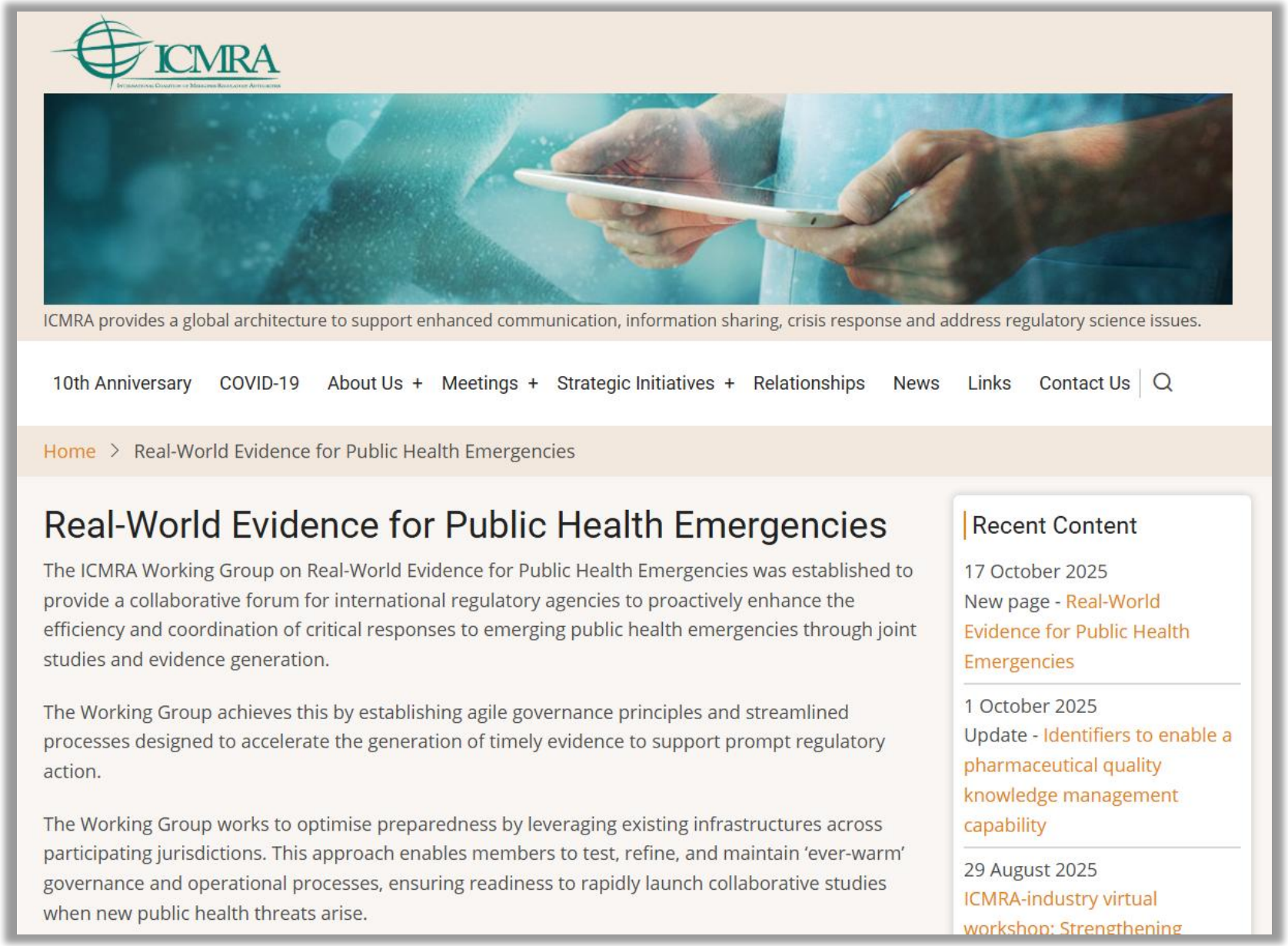
Andrew E. Beck, Melissa Kampman, Cindy Huynh, Craig Simon, Kelly Plueschke, Catherine Cohet, Patrice Verpillat, Kelly Robinson, Peter Arlett

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



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

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Thank you

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