Methodology Working Party (MWP) Workplan

ENCePP Plenary – Session 2
22 November 2024

Olaf Klungel, University of Utrecht

Workplan May 2022- Dec 2024

Goals with regards to RWE:

1. Reflection paper on the use of Real-World Data to generate Real-World Evidence in non-interventional studies
2. Roadmap for the development of RWE guidance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 April 2024
EMA/CHMP/150527/2024
Committee for Human Medicine Products (CHMP)

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	3 May 2024
End of consultation (deadline for comments)	31 August 2024

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

Public consultation - RP on Use of RWD in NIS to generate RWE

- Public consultation ended on 31st August
  - 695 comments from 39 institutions: 89 general comments, 605 specific, 1 other
  - Comments provided by: Industry, CROs, Regulatory Authorities, HTA, Professional associations, patient associations
- A separate review was arranged with RWE SIA
  - 15 comments from 3 members

27 stakeholders providing ≥10 comments

Institution	Number of comments
European Federation of Pharmaceutical Industries and Associations (EFPIA)	79
Medicine Evaluation Board	52
Cohort Coordination Board (CCB) and Trial Coordination Board (TCB)	33
EuropaBio	33
ISPOR - The professional society for health economics and outcomes research	33
RTI Health Solutions (RTI-HS)	32
Fondazione per la Ricerca Farmacologica Gianni Benzi Onlus	30
European Society of Cardiology	29
Research Quality Association (RQA)	29
Vaccines Europe	24
European Organisation for Research and Treatment of Cancer	22
IQVIA	22
Medicines for Europe	21
Lymphoma Coalition (represented by Natacha Bolanos)	20
EUCOPE	19
Alliance for Regenerative Medicine (ARM)	18
Krka, d. d., Novo mesto	18
Parexel International	18
OM Pharma SA	17
Coalition for Epidemic Preparedness Innovations (CEPI)	15
European Hematology Association (EHA)	15
Institute for Quality and Efficiency in Health Care (IQWiG)	14
Takeda Pharmaceuticals International AG	13
CHU Dijon-Inserm CESP	12
EVERSANA	11
AESGP	10
Medsavana SL	10

Development of roadmap for RWE Guidance

FDA, USA

2017 - Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

2018 - Use of Electronic Health Record Data in Clinical Investigations

2021, draft - Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products

2021, draft - Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

2021, draft - Data Standards for Drug and Biological Product Submissions Containing Real-World Data

2022 - Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products

2023, draft - Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

2023 - Considerations for the Use of RWD and RWE To Support Regulatory Decision-Making for Drug and Biological Products

2024, draft – RWE: Considerations regarding NIS for Drug and Biological Products

EMA, EU

2021 – Guideline on registry-based studies

2023 – Data Quality Framework for EU medicines regulation

ENCePP, EU

2023 – Guide on Methodological Standards in Pharmacoepidemiology, Rev. 11

Swissmedic, CH

2023 - Swissmedic position paper on the use of real world evidence

HAS, FR

2021 - Real-world studies for the assessment of medicinal products and medical devices

MHRA, UK

2021 – Guidance on the use of RWD in clinical studies to support regulatory decisions

2021 – Guideline on randomized controlled trials using RWD to support regulatory decisions

NICE*, UK

2022 – NICE RWE Framework

Health Canada

2018 - Use of Electronic Health Record Data in Clinical Investigations

Canada's D&HTA* (+ Health Canada)

2023 – Guidance for reporting RWE

PMDA, Japan

2014 – Guidelines for the conduct of pharmacoepidemiological studies in drug safety assessment with medical information databases

2017 – Basic Principles on the use of medical information databases in post-marketing pharmacovigilance

2020 – Points to consider for ensuring the reliability of post-marketing database study for regenerative medical products

2021 – Basic Principles on utilization of registry for applications

NMPA, China

2021 – Guidance for Real-World Data Used to Generate Real-World Evidences (Interim)

2022 – Guidance on the Use of Real-World Evidence to Support Drug Development and Regulatory Decisions

2023 – Guidance on Communication with Regulatory Agency on Real- World Studies to Support Product Registration

2023 – Guidance on the Design and Protocol Development of Real-World Studies for Drugs

* Health Technology Assessment Agency

RWE Guidance from international non-EU RAs (list not exhaustive)

EUROPEAN MEDICINES AGENCY

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 Prod

EMA, EU

Guideline on registry-based studies

Data Quality Framework for EU medicines regulation

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

MFDS, Rep. of Korea

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

MHRA, UK

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

Guideline on randomized controlled trials using RWD to support regulatory decisions

Health Canada

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, CH

Swissmedic position paper on the use of RWE

SFDA, Saudi Arabia

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

PMDA, Japan

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

NMPA, China

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

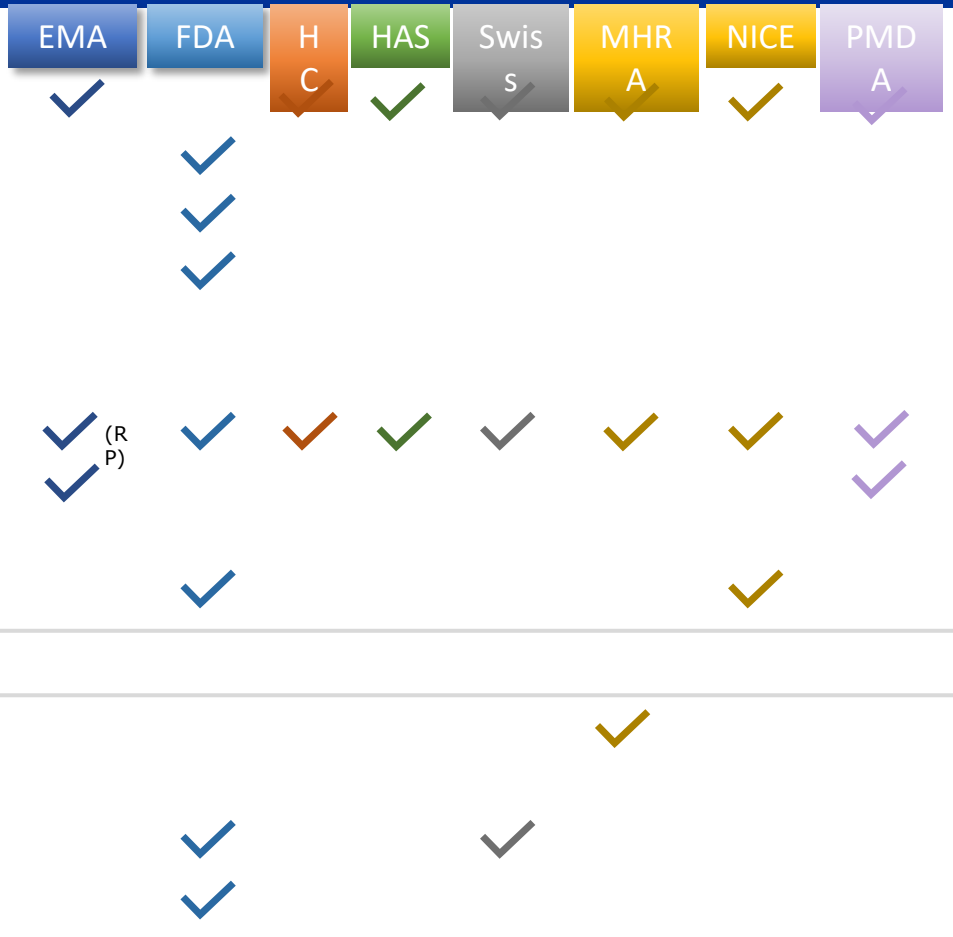
Guidance on the Use of Real-World Evidence to Support Drug Development and Regulatory Decisions

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

* Health Technology Assessment Agency

RWE topics covered by or susceptible of regulatory guidance



RWD quality and access:

- EHR
- Claims
- Registries

Studies using RWD:

- Non interventional studies (NIS):
  - Design aspects of NIS using RWD
  - Registry-based NIS
- Clinical trials
  - Externally controlled CTs
  - External control data to supplement control arm in CTs
  - Clinical trials using RWD (pragmatic CTs)

Submissions that include RWD:

- Identifying RWD/RWE in reg. submissions
- Data standards for submissions with RWD

EMA guidance on RWE

Areas covered

RWD quality:

- *Data Quality Framework for EU medicines regulation*
  - *With a follow-up RWD deep-dive chapter*

Studies using RWD:

- Non interventional studies (NIS):
  - *Reflection paper on use of real-world data to generate real-world evidence in non-interventional studies*
  - *Guideline on registry-based studies*

Areas of potential interest

Studies using RWD:

- Clinical trials (CTs):
  - Externally controlled CTs
    - Using patient-level data
    - Using group-level summaries
  - External control data to supplement control arm in CTs
    - Using patient-level data
    - Using group-level summaries
  - Clinical trials using RWD (pragmatic CTs)
  - Others?

Workplan Jan 2025- Dec 2027

Goals with regards to RWE:

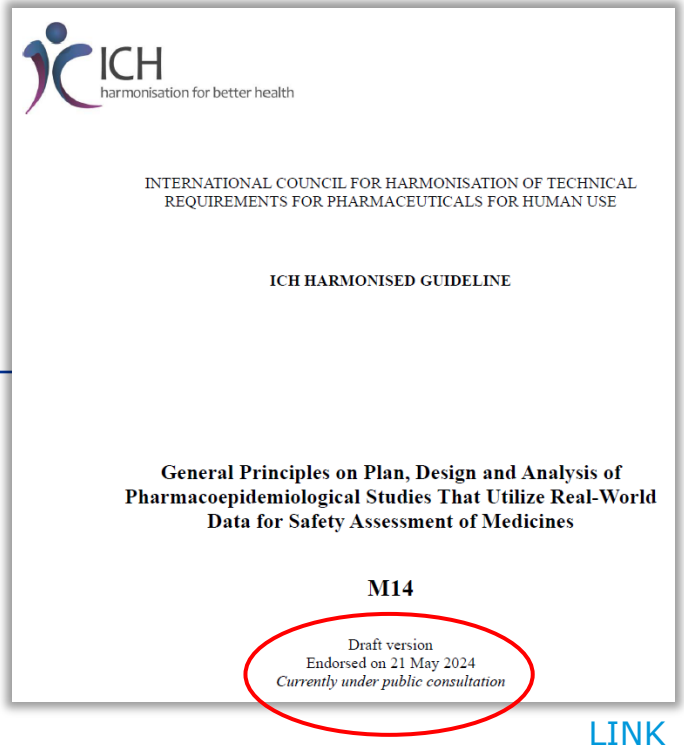
1. Concept paper on external controls (joint activity with Biostatistics)
2. Concept Paper on the use of pragmatic trials in regulatory decision making (joint activity with Biostatistics)

ICH & regulatory guidance update

ENCePP Plenary – Session 2
22 November 2024

ICH M14

General principles on plan, design and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines

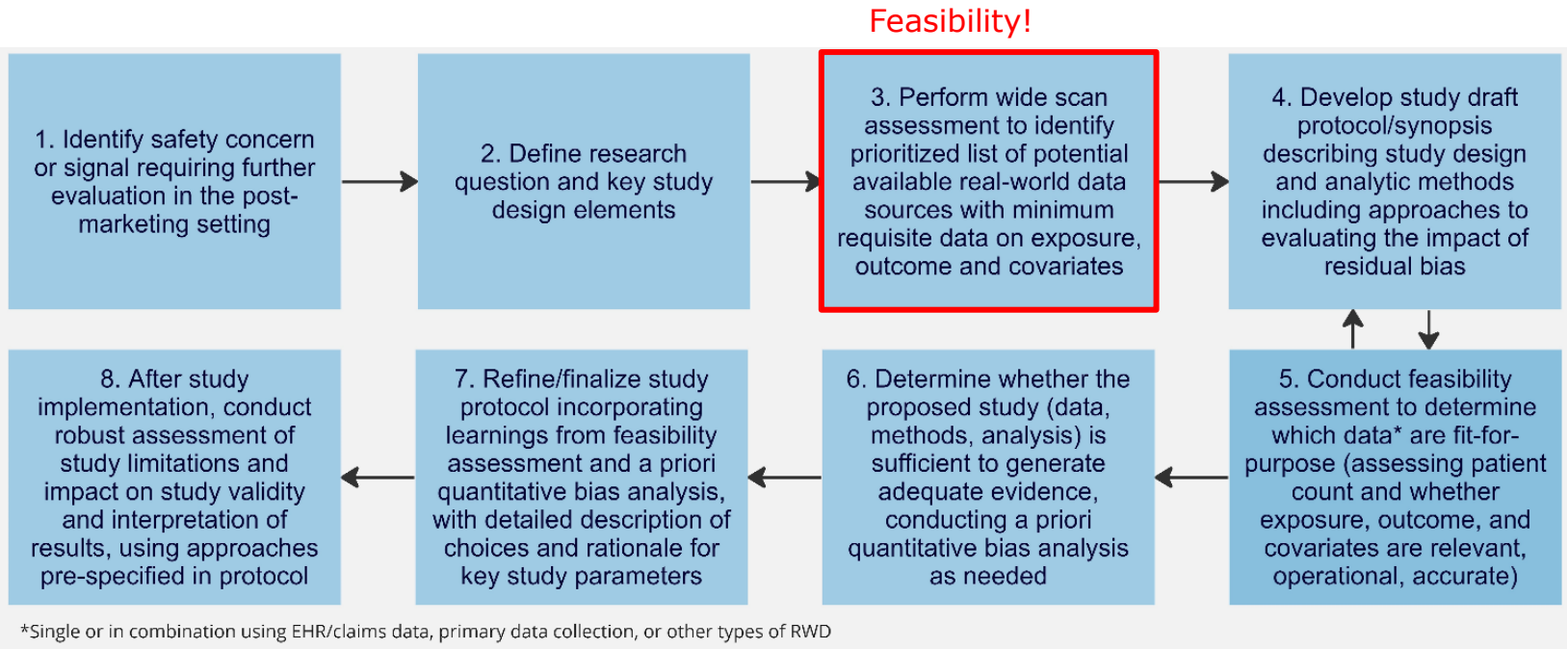


LINK

Last update: 2022 ENCePP Plenary

Contents

Framework for generating adequate evidence using fit-for-purpose RWD to address regulatory questions



Key aspects

- Focus on **post-approval NIS** of **drugs, vaccines, other biologics**
- **Iterative approach** to develop high-quality evidence suitable for **regulatory submission**
- Robust evidence relies on **reliability** and **relevance** of the data and application of sound pharmacoepidemiological methods
- Not intended as a comprehensive resource for pharmacoepidemiological methods
- Streamline sponsor **development** and regulatory **assessment** of protocols/reports and increase **transportability** across regulatory jurisdictions
- May be **applicable** to studies with purpose other than safety, e.g. **drug utilisation** and **effectiveness**
- **Out of scope**
    - Use of spontaneous reports (pharmacovigilance)
    - Studies involving treatment assignment (principles may be applicable to these studies when RWD elements included)
    - Studies collecting and analysing patient experience data (PED)

Timelines/ICH steps

Step 5: Implementation & post-hoc evaluation plan		Guideline establishment ~~January 2025~~ June 2025
Step 4: Adoption of ICH Harmonized Guideline		
Step 3: Regulatory Consultation and Discussion	Planned June 2024	October 2024 – May 2025*
Step 2a: ICH Parties Consensus Step 2b: Draft guideline adoption (Public Consultation)	Planned January 2024	May 2024 – October 2024
Step 1: Consensus Building- Technical Document	Planned December 2023	Completed May 2024

Following public consultation May-October 2024

→ Total all regions/jurisdictions: N=1,280 comments, incl. **Europe: N=755**

Other updates relevant for ENCePP

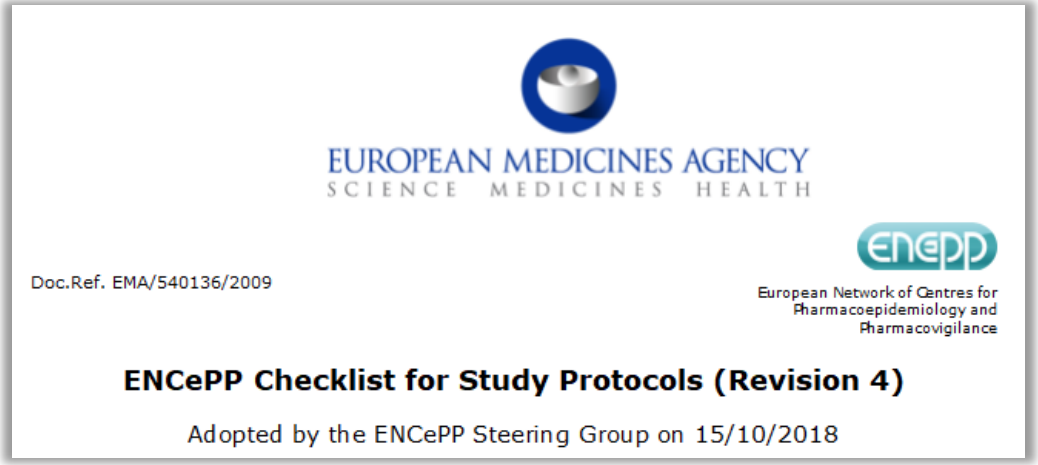
- GVP **Module VIII** revision – public consultation Q1 2025 (will be announced on the ENCePP website). Updates: study feasibility, selection of fit-for-purpose data sources for PASS
- Update of the ENCePP **Checklist for Study Protocols** (Q2 2025)
- **ICH new topic** on '*Considerations for the Use of Real-World Evidence (RWE) to Inform Regulatory Decision Making with a focus on Effectiveness of Medicines*' (EMA, FDA, Health Canada). High-level contents: harmonised operational definitions of RWD/RWE; use of metadata; assessment principles

Back-up

GVP Module VIII revision – key aspects

- Text of Appendix I (**Methods** for post-authorisation safety studies) replaced by referring to the **ENCePP Guide** on Methodological Standards in Pharmacoepidemiology
- Addition of text recommending to conduct a **feasibility assessment** to investigate fit-for-purpose data source(s) and their generalisability for the EU population (not mandatory)
- Recommendation to use data from **EU data sources** in priority; however, does not preclude data collection from **other regions** based on the justification that epidemiology of the disease, patient characteristics, or medicinal product use, are similar
- **PRAC** consulted for the update
- **Public consultation** planned Q1 2025 (will be announced on the ENCePP website)

Update of the ENCePP Checklist for Study Protocols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Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

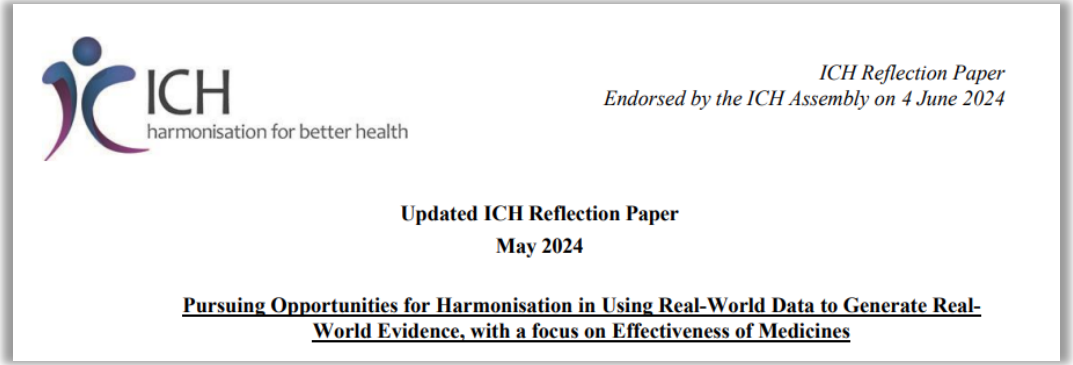
Adopted by the ENCePP Steering Group on 15/10/2018

- **Process** - review by WG of existing regulatory/non-regulatory guidelines, e.g., HARPER, ENCePP Guide, ICH M14, EMA Reflection paper on RWE, FDA Guidance on RWD…
- Recommend in **GVP VIII** as relevant guidance and to support feasibility assessments
- **Timelines** - Q3 2024 to Q2 2025 (TBC)

ICH topic proposal:

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

EC, Europe
FDA, United States
Health Canada, Canada


ICH
harmonisation for better health

ICH Reflection Paper
Endorsed by the ICH Assembly on 4 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

Scope & goal

	Topic	Objective	Deliverables	Tentative timeframe
1.	**RWD/RWE terminology, metadata, and assessment principles**	• Promote a common understanding of the types and scope of RWD/RWE • Guide the discoverability, identification, and description of RWD • Inform the assessment of RWD/RWE for regulatory purposes	• Common operational definitions of RWD and RWE, with clear scope, breadth of potential RWD sources, and level of granularity (e.g., pertaining to RCTs and non-interventional studies)[3] • Core list and use of metadata • General principles for assessment of RWD/RWE	Submit new ICH topic proposal in Dec 2024
2.	**RWD/RWE protocol & report format, and study transparency**	• Agree on common principles regarding formats for RWD/RWE protocols and reports of study results submitted to regulators • Promote transparency by encouraging registration of study protocols and study reports in publicly available registries	• Principles for structure and content of protocols and reports (for medicines developers) • Recommended "best practices" for registration of study protocols/results	Initiate work after the first guideline reaches *Step 4* of the ICH Procedure

- Expected timing: ≈ three years
- Apparent benefits anticipated at early stage (Step 2, public consultation)
- Interface with ICH E6(R3), ICH M14
- Foundation for subsequent work, with additional proposal on protocol/report format for studies using RWD and study transparency → to be submitted once first guideline reaches ICH Step 4

Use of RWD in clinical trials (1/3)

Externally controlled clinical trials

- Highlighted by industry as a priority area for guidance development
- FDA draft guidance available on this topic (see summary in back-up slides)

Use of RWD in clinical trials (2/3)

External control data to supplement control arm in CTs

- Applicable to situations where there's comparable control data from another CT or a RWD source
  - CT design will recruit less subjects in the control arm (e.g. randomisation ratio 2:1)
    - More attractive to participants because of the smaller chance to be allocated to control arm
    - Shorter trials
    - Increased feasibility
  - CT analysis combines (in a scientifically sound manner) historical and current control data
- No regulatory guidance available on this topic (yet)
- Related to the concept of extrapolation of information from 'source' population to 'target' population
  - ICH E11A – Paediatric extrapolation
- It's likely that many aspects related to study design, data comparability and analysis are shared with externally-controlled trials

Use of RWD in clinical trials (3/3)

CTs using RWD (pragmatic CTs)

- Available MHRA guidance on this topic

2. Scope

This guideline provides points to consider when planning a prospective randomised trial using RWD sources with the intention of using the trial to support a regulatory decision. This guideline covers clinical trial authorisation (if applying for approval to run such a trial wholly or in part in the UK), and clinical trial design including choice of endpoints and safety data requirements. For requirements relating to the trial database quality and inspection please see 'MHRA Guidance on the use of Real-World Data in Clinical Studies to Support Regulatory Decisions'.

- An example mentioned in the guideline: imagine approved add-on treatment approved for a severe version of some disease. A CT using RWD could be used to investigate efficacy of SoC+treatment vs Soc in patients with a mild version of disease

Summary of FDA draft guidance on external controls

Scope: patient-level data. Summary-level estimates are out of scope

A. Study design considerations:

- Study populations
- Treatment attributes
- Index date (time zero)
- Assessment of outcomes

B. Data considerations for the external control arm:

- Data from RCT
- Data from RWD
- Comparability of data across arms

C. Analysis considerations:

- General considerations
- Missing data
- Misclassification

Summary of FDA draft guidance on external controls

A. Study design considerations:

- Study populations: baseline characteristics of external and trial arms; eligibility criteria
- Treatment attributes: adherence, dose, timing of initiation, duration; use of additional treatments; influence of external factors such as health-seeking behaviour or insurance coverage
- Index date (time zero): may be challenging or even not possible to assign
- Assessment of outcomes: availability of endpoints of interest; risk of bias due to lack of blinding, assessment method and timing; occurrence of intercurrent events

Summary of FDA draft guidance on external controls

B. Data considerations for the external control arm:

- Data from RCT: comparability regarding eligibility criteria, treatment administration, care patterns (e.g. sites), concomitant medications, assessments of outcomes and adverse events; time gaps
- Data from RWD: comparability of participant characteristics, timing and frequency of data collection, patterns of care; missing data (e.g. loss to follow-up); availability of relevant clinical characteristics
- Comparability of data across arms: Time periods, geographic region, diagnosis, prognosis, treatments, concomitant/additional treatments, follow-up, intercurrent events, outcome, missing data

Summary of FDA draft guidance on external controls

C. Analysis considerations:

- General considerations: analysis plan before trial starts; method assumptions made explicit; assessing and accounting for comparability between the external control and treatment arms for important covariates; considerations to anticipated effect size
- Missing data: explicit strategy to deal with missing data in the analysis; if due to intercurrent events, addressed with an appropriate estimand and analysis plan
- Misclassification: when involving the drug, covariates, or outcomes of interest can introduce bias and make difficult the interpretation of the drug-outcome association
- Additional analyses: sensitivity analyses to assess the impact of assumptions on study results; pre-specified supplementary analyses to gain further insights on the treatment effect (e.g. subgroup analysis by prognostic factors)

Summary of FDA draft guidance on external controls

A. Communication with FDA

- Recommendation to consult early with FDA: provide justification of proposed study design, data sources and fit-for-use, planned statistical analysis and data submission

B. Access to Data and Documents

- Relevant patient-level patient data for both treatment and external control arms must be included in MAAs