MWP Roadmap for the development of RWE guidance

Joint HMA/EMA Big Data Steering Group workshop on RWE methods
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RWE Guidance from regulatory and HTA bodies

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

ICH, M14

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

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 topics covered by or susceptible of regulatory guidance

	EMA	FDA	HC	HAS	Swiss	MHRA	NICE	PMDA	NMPA
RWD quality and access:	✓		✓	✓	✓	✓	✓		
• EHR		✓							
• Claims		✓							
• Registries		✓							
Studies using RWD:									
• Non interventional studies (NIS):									
• Design aspects of NIS using RWD	✓ (RP)	✓	✓	✓	✓	✓	✓		
• 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?

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 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

Discussion

- Prioritization and scope of guidance on external controls
  - External controls from RWD or clinical trials
  - External data to supplement control arms in clinical trials
- Guidance on clinical trials using RWD (pragmatic trials)
- Other topics for RWE guidance development ?

Any questions?

Further information

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Back-up slides

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