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

Background

The journey towards a roadmap for regulatory guidance on real-world evidence began in 2022. The use of real-world data (RWD) and real-world evidence (RWE) in EMA regulatory procedures had been documented (Flynn et al, 2022), and the increasing availability of large health care data sources created opportunities for the generation of RWE to support regulatory decision making. This was reflected in the joint HMA-EMA BDSG workplan for 2022-2025, which envisaged the development of a roadmap for guidance development related to the use of real-world evidence in the regulatory setting. Since 2022, CHMP annual workplans have also included RWE-related activities. In the CHMP 2025 workplan, one such activity is to "*Develop a roadmap of RWE guidance to support high-quality RWE generation and continue strengthening the use of RWE for regulatory decision-making.*" Accordingly, this activity was reflected in the 2022-2024 workplan of the methodological working party (MWP) of the CHMP as well as in the current 2025-2027 workplan of the MWP.

A drafting group was appointed by the MWP to work on this objective. The drafting group included RWE experts from the MWP and the European Specialised Expert Community (ESEC) for Methodology. The project kicked off on 10 November 2022 with a review of existing regulatory guidance in the EU and other jurisdictions such as the US, Canada, UK, Switzerland or Japan. The review also included available guidance on RWE issued by health technology assessment (HTA) bodies in France, the UK and Canada.

This initial review exercise revealed that, while regulatory guidance covered several topics of interest, there was substantial focus on the use of RWD in non-interventional studies (NIS). Given the perceived need for EMA guidance on this topic, the drafting group decided to embark on the development of a reflection paper around the use of RWD in NIS, building on the regulatory experience already accrued from post-authorisation studies, from the development and regular revisions of the ENCePP guide on methodological standards in pharmacoepidemiology and from the development of the EMA guideline on registry-based studies. Furthermore, recommendations provided in those documents were in good alignment overall with the reviewed guidance from other agencies on key principles of regulatory interest in NIS using RWD.

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In parallel to the development of the reflection paper, the drafting group decided to continue updating the guidance review, as there was awareness of new RWE guidance under development by ICH (the M14 guideline on general principles on plan, design and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines) and by several regulatory agencies, including from countries that at the time had not yet released any guidance on RWE (e.g. Brazil or China). During 2023 and early 2024, numerous guidance documents related to RWD and RWE were published. By spring 2024, the drafting group completed the review and presented their conclusions from the review of RWD/RWE guidance issued by regulators, together with a proposal of topics for potential further guidance development. In what follows, we elaborate on these two points.

Outcomes of the RWD/RWE regulatory guidance review

The review of regulatory guidance, in the form of position papers, reflection papers and guidelines, identified four main target areas:

- RWD quality and access.
- Use of RWD in non-interventional studies (NIS).
- Use of RWD in clinical trials (CT).
- Submissions to regulatory agencies that include RWD.

RWD quality and access

While some minor differences were observed in the definitions of RWD across agencies, the quality of the RWD used to generate RWE for regulatory purposes was a topic systematically addressed. It was not surprising to confirm that data quality is a critical regulatory concern. However, the depth with which the subject was covered varied between agencies. Regulatory agencies with a single guidance document included the topic as a section of that document, whereas other agencies with various guidance documents published had one dedicated to RWD quality. An example of the latter was the HMA-EMA Data Quality Framework for EU medicines regulation, adopted by CHMP in October 2023, which built on data quality recommendations from TEHDAS and overarched over several existing data quality frameworks published in the literature. Other agencies such as the FDA, published more granular guidance for specific types of RWD, namely electronic health records (EHR), claims and registries. Data accessibility, including data governance and data protection issues, was also regularly addressed for the sake of transparency.

RWD considerations for CTs are included in the ICH E6(R3) Annex 2 Guideline for good clinical practice, which cover aspects related to data quality and format (e.g. terminologies and standards).

Use of RWD in NIS

Guidance from all agencies included in the review addressed aspects related to the design, analysis and reporting of NIS using RWD, with varying levels of detail. A clear description of the research question targeted by a study was a recurrent regulatory request, as the basis to subsequently choose study design, including type of design (e.g. cohort, self-controlled, etc.), inclusion/exclusion criteria, exposure and outcome definitions and measurements, confounders and effect modifiers, as well as strategies to mitigate the risk of bias and residual confounding, all of which are required to be clearly articulated and justified in the protocol by regulators. A rationale for the study size and a detailed description of the methods proposed for data analysis were also common requirements. For comparative NIS, regulators emphasised the importance of these methodological considerations to enable causal interpretation of the results. The drafting group took into consideration all these

elements in the development of the draft reflection paper on the use of RWD in NIS to generate RWE (see Section on future guidance development related to RWD/RWE).

Use of RWD in CTs

In contrast to the previous two areas, data quality and use of RWD in NIS, guidance on the use of RWD in the context of CTs was rather scarce in the countries included in the review.

Guidance on externally controlled CTs, where the external controls may come from RWD sources, was published by the FDA in the US and by NICE in the UK. The scope of the guidance clarifies the comparative nature of this type of CTs, aimed at comparing an active treatment to a control treatment or untreated patients, where data in the control arm may come from a previous CT or from RWD. This is unlike single-arm CTs, where the goal is to show the so-called *isolation of effect*, i.e. the observation of health outcomes in patients that could not occur without effective treatment (e.g. a reduction in solid tumour size). A fundamental aspect addressed by guidance is comparability of the external controls with participants recruited in the CT. This affects not only baseline characteristics due to lack of randomisation but also health outcomes and differences in the clinical management of patients. Guidance emphasises the need to minimise the risk of potential bias in the control arm, including the finalisation of the study protocol prior to initiating the CT and pre-specification of the strategies adopted to minimise risk of bias in the study design as well as in the analytic approach.

It is worth noticing that the scope of guidance documents on externally controlled trials excluded augmented CTs, i.e. CTs with a small control arm supplemented with external control data, which may be RWD. While this is an area susceptible to regulatory guidance, regulatory experience seems to be still limited.

The MHRA published guidance on prospective randomised CTs using RWD (pragmatic trials). Since these are CTs, albeit with a reduced burden for participants and physicians, this type of studies should follow general guidance for RCTs. Attention should be paid however, to data collection of safety and in settings where relevant endpoints come from assessments not commonly performed in routine clinical practice.

Submissions to regulatory agencies that include RWD

The FDA and the Swissmedic agencies provide guidance related to the identification of RWD/RWE in the regulatory submission. The FDA also published guidance on data standards for submissions with RWD, recommending to follow the data standards from the Clinical Data Interchange Standards Consortium (CDISC) and providing specific recommendations on file formats in which datasets should be submitted.

Potential future guidance development related to RWD/RWE

Details of guidance development in this area can be found in the MWP workplan 2025-2027, which is updated annually.

Of the four RWD/RWE-related topics where guidance development could be developed, the first two on RWD quality and use of RWD in NIS have already been addressed.

The HMA-EMA DQF, which provides general guidance to assess the quality of a data source, looking into foundational and intrinsic aspects of informing quality as well as specific dimensions and subdimensions of data quality with some suggestions on metrics for quantification of data quality. In addition, a draft chapter was developed in 2024 and was open for consultation till the end of January 2025, to provide further insights into how the general principles outlined in the DQF could be

implemented specifically to RWD. Together, these two guidance documents cover the first of the four topics susceptible of regulatory guidance identified in the review.

To address the second area identified during the guidance review, the drafting group developed the reflection paper on use of RWD in NIS to generate RWE for regulatory purposes. The objective of the reflection paper was to discuss methodological aspects of NIS using RWD to generate RWE for regulatory purposes. The main scope of the reflection paper was design, conduct and analysis of NIS using RWD. The reflection paper also discusses legal and regulatory requirements for use of RWD and RWE, governance and transparency, and data quality aspects. The reflection paper was open for public consultation between 3 May and 31 August 2024. Nearly 700 comments were received from numerous stakeholders including patient organisations, industry, public agencies, academia, professional societies. The drafting group reviewed those comments in Autumn and introduced revisions in the draft paper to address the feedback from the public consultation. The final version of the reflection paper was endorsed by the MWP and adopted by CHMP in March 2025.

The third topic, on the use of RWD in CTs, was proposed as the main area susceptible of future guidance development. Three potential subareas were considered:

- Use of RWD in externally controlled CTs.
- Use of RWD to augmented control CTs, i.e. CTs with a small control group supplemented with control data from RWD sources.
- Use of RWD in pragmatic CTs.

The proposal was discussed at the MWP, and the need for guidance on externally controlled CTs was considered a priority. Accordingly, it was agreed to include the development of a concept on externally controlled trials the MWP workplan for the period 2025-2027. Considering that external controls may also come from previous CTs in addition to RWD, the development of the concept paper will be a multidisciplinary effort with experts from RWD/RWE and biostatistics areas, as well as input from SAWP based on their experience assessing proposals involving external controls.

The development of guidance on the other two subareas, use of RWD in augmented controls and pragmatic trials, might be considered in the future.

Equally, the last of the four main areas identified during the review, related to guidance on data standards for submissions might be addressed in the future.

Annual revisions of the MWP workplan will reflect any plans for guidance development on the above topics if useful for the EU medicines regulatory network.