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European Medicines Agency

Outcome of public consultation on the Reflection Paper *Use of real-world data in non-interventional studies to generate real-world evidence for regulatory purposes*.

Summary report of comments received during the public consultation and next steps

1. Background and consultation

The European Medicines Agency (EMA) conducted a public consultation on the revised reflection paper titled "Use of Real-World Data (RWD) in Non-Interventional Studies (NIS) to Generate Real-World Evidence (RWE)." This reflection paper aims to provide guidance on the use of RWD in NIS to support regulatory decisions.

The draft reflection paper built on the discussions from the Multi-stakeholder workshop on Real World Data (RWD) quality and Real World Evidence (RWE) use organised by the EMA on 26th June 2023.

In addition to the comments provided during the public consultation, the revision of the draft reflection paper benefited from discussions held at the Joint HMA/EMA Big Data Steering Group workshop on real-world evidence (RWE) methods on 14th June 2024.

The draft reflection paper was adopted by CHMP on 15th April 2024 for public consultation. The open consultation period lasted from 3rd May 2024 to 31 August 2024.

In this document, we provide an overview of the comments received during the public consultation and how they were implemented.

2. Contributors

In total, 695 comments were submitted by 39 stakeholders, including:

- Regulatory Authorities
- Pharmaceutical Industry
- Academia
- Healthcare Professionals' Associations

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- Patients' Associations
- International Societies
- Individuals

The EMA wants to express their gratitude to stakeholders for the careful review and useful comments provided during the public consultation.

3. Summary of the main points raised during the consultation

Overall Expression of Comments:

- The majority of comments were supportive of the initiative, with some expressing concerns on specific topics, requesting additional details, or suggesting potential improvements.
- Many valuable editorial comments were received and are not detailed here. Many of those were implemented in the revised version.

Main Topics Identified:

General and specific comments were provided. Below, we summarise those by topic, including a brief description of the comment(s) and how they were addressed in the revised version of the manuscript.

1. **Definitions of RWD and RWE:**
    - **Comments:** Various proposals were made to amend the definitions of RWD and RWE to better reflect their scope and application.
    - **Decisions:** The definitions were retained as originally proposed. RWD describes patient characteristics (including treatment utilisation and outcomes) in routine clinical practice, while RWE is derived from the analysis of RWD.
2. **Clinical Trials vs. NIS:**
    - **Comments:** Stakeholders requested a more detailed elaboration on the strengths and limitations of clinical trials (CTs) versus non-interventional studies (NIS), and the role of both in regulatory decisions.
    - **Decisions:** The suggested discussion on strengths and limitations was not included. However, text in the Introduction Section was amended to emphasize that CTs are the primary source of evidence for evaluating the benefits and risks of medicines in marketing authorization procedures. NIS using RWD can complement CTs by addressing knowledge gaps and reducing uncertainties about a product's safety and effectiveness.
3. **Efficacy vs. Effectiveness:**
    - **Comments:** It was suggested that NIS using RWD should focus on assessing effectiveness rather than efficacy.
    - **Decisions:** This suggestion was implemented. Instances of "efficacy" were replaced with "effectiveness" throughout the document.
4. **Regulatory Applications:**

- **Comments:** Clarification was requested on when NIS using RWD should be submitted in regulatory applications.
- **Decisions:** The case-by-case basis for including NIS using RWD was maintained. The text was reinforced to recommend early dialogue between Marketing Authorization Holders (MAHs) or Applicants (MAA) and EMA through scientific advice and protocol assistance procedures.

5. **Primary Data Collection:**
    - **Comments:** Stakeholders requested additional considerations for cases where RWD is collected through primary data collection.
    - **Decisions:** This was implemented. Text regarding primary data collection was added in several chapters, including Scope, Feasibility Assessment, Bias and Confounding, Governance, and Data Quality.
6. **Artificial Intelligence (AI), Machine Learning (ML), Natural Language Processing (NLP):**
    - **Comments:** Recommendations on the use of artificial intelligence (AI), machine learning (ML), and natural language processing (NLP) technologies were requested.
    - **Decisions:** This was partly implemented. The field is not mature enough for comprehensive recommendations. However, text was added in the Data Quality Section stating that, if these technologies are used to collect and process RWD included in a NIS, the methodologies applied to evaluate the performance, risk of bias, and impact on results should be detailed in the study protocol. A reference to the Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle was included as well.
7. **Study Design:**
    - **Comments:** The dichotomy of studies with descriptive versus causal objectives was considered oversimplified. It was suggested to add predictive studies and other types.
    - **Decisions:** This suggestion was not implemented as as the text provides methodological definitions for each type of studies and these definitions apply to a very wide range of studies. However, text was added to clarify that studies with descriptive objectives may include risk assessment, prediction, and service evaluation. Furthermore, it was clarified that the recommendations provided for studies with descriptive objectives should also be considered for studies with causal objectives.
8. **Research question in studies with causal objectives**
    - **Comments:** There were comments suggesting to consider other frameworks to increase the causal interpretation of results in this type of NIS. Furthermore, there were comments requesting clarification on how the target trial emulation and the estimands frameworks could be used jointly.
    - **Decisions:** The text was amended to state that, while the EMA acknowledges other frameworks could be used to clearly specify the research question of a NIS and to enhance the causal interpretation of the results, from a regulatory perspective there is value in the exercise of designing a hypothetical clinical trial that would be address the research question of interest, followed by designing a NIS that emulates it as closely as possible.

Equally, the use of the estimands framework in ICH E9(R1) will help define clearly and unambiguously the research question of the hypothetical trial as per current regulatory guidance. The use of concepts and terminology from ICH E9(R1) will help bridge meaningfully between the hypothetical clinical trial and the NIS.

9. **Governance:**

- **Comments:** Recommendations on ethical aspects, data privacy, and informed consent were requested. The need to consult patients and patient associations was also highlighted.
- **Decisions:** This was implemented. Text was added based on the Guideline on registry-based studies - Scientific guideline | European Medicines Agency (EMA) to include ethical considerations, data privacy, and patient consultation.

10. **Confounding:**

- **Comments:** Methods to assess and control for confounding, such as Directed Acyclic Graphs (DAGs), Propensity Score Matching (PSM), and Instrumental Variables, were requested.
- **Decisions:** This was not implemented as the aim of the reflection paper is to discuss principles of regulatory interest and not specific methods, which evolve over time with new methodological approaches replacing existing ones.

11. **Bias**

- **Comments:** Suggestion to refine the issues with the choice of "time 0" to avoid time-related bias.
- **Decisions:** This was implemented by amending the corresponding text, which now emphasises the importance of defining and aligning, at the design stage, for all included individuals the timepoint of eligibility, treatment initiation and start of follow-up to prevent the occurrence of time-related bias.

12. **Data Quality:**

- **Comments:** Recommendations on validating algorithms to extract and code data were requested. Also, concerns were expressed on whether requesting high level of data quality for each database will discourage multi-database studies thus reducing sample size.
- **Decisions:** Recommendations on data quality and validation of algorithms were included. However, data quality is paramount from a regulatory perspective and not susceptible of a trade-off with quantity.

13. **Transparency:**

- **Comments:** It was suggested to remove the recommendation to make publicly available the codes used for creating the analytical dataset and the programming code for statistical analyses.
- **Decisions:** This was not accepted. It is important to make codes publicly available for the replicability of studies and reproducibility of results.

14. **Statistical Analysis:**

- **Comments:** A distinction between the role of sensitivity analyses and supplementary analyses was requested.
- **Decisions:** This was implemented. The distinction was made based on ICH E9(R1), with sensitivity analyses assessing the impact of bias and assumptions made in the primary analysis, and supplementary analyses providing additional contextual information (e.g. to choices made in the study design such as the definition of exposure or outcome).

4. Next steps

Following the public consultation, the MWP revised and agreed on the final reflection paper "Use of Real-World Data (RWD) in Non-Interventional Studies (NIS) to Generate Real-World Evidence (RWE) for regulatory purposes", which was adopted by CHMP on 17th March 2025 and published on the EMA website on 3rd April 2025.

The final reflection paper is available on the EMA website: Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence for regulatory purposes