ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

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February 28, 2025

Dear European Medicines Agency (EMA):

ISPOR – the professional society for health economics and outcomes research - is pleased to respond on behalf of its membership to your consultation entitled "Data Quality Framework for EU medicines regulation: application to Real-World Data."

ISPOR is a scientific and educational society with many of its members engaged in evaluating health technologies, including pharmaceuticals, medical devices, and other interventions. We have a large membership living and working in 110 countries globally, across a range of disciplines, including health economics, epidemiology, public health, pharmaceutical administration, psychology, statistics, medicine, and more, from a variety of stakeholder perspectives, such as the life sciences industry, academia, research organizations, payers, patient groups, government, and health technology assessment bodies. The research and educational offerings presented at our conferences and in our journals are relevant to many of the issues and questions raised in this request for information.

The response to this consultation was led by the ISPOR Real-World Evidence Steering Committee. Comments were solicited from the ISPOR Real-World Evidence Steering Committee and ISPOR Real-World Evidence Special Interest Group leadership. The attached document provides a summary based on their comments. We hope they prove useful.

ISPOR would be happy to answer any questions about our response, to serve as a partner, or to participate in any follow-up consultations on the relevant program items mentioned within the report.

Sincerely,

Robert Abbott
CEO & Executive Director
ISPOR

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Data Quality Framework for EU medicines regulation: application to Real-World Data

On behalf of the members of ISPOR – the professional society for health economics and outcomes research, we appreciate the European Medicines Agency's efforts in preparing a document which describes the Real-World Data (RWD) specific recommendations derived from the existing Data Quality Framework (DQF) for EU Medicines and commend the comprehensive nature of the document. This is of particular interest to ISPOR in our pursuit of improving standards and practice for the collection and analysis of RWD. Our members had several comments that we felt would further strengthen the document.

Need for practical examples and context

Although the framework addresses the many relevant aspects of RWD quality assessment, including secondary data use challenges, such as incomplete records or data collected for different purposes, there is a lack of practical examples and use cases that could illustrate how the guidelines could be applied in real-world scenarios. For example, in Section 4.3, *Considerations for the Implementation of RWD DQ Metrics*, the section could benefit from real-world examples that demonstrate how metrics are applied at each stage of implementation, such as how quality assurance metrics are automated in a large-scale RWD system. Table elements of Section 5.3 appear to provide input rather than guidance for making a fit-for-purpose determination. Without accompanying examples, it is difficult to ascertain whether data previously found to be fit-for-purpose in a specific use case would still be considered quality data under these criteria.

In the section where an example is present, in Lines 426-427, we found it to be confusing, wondering what the "timing of a causal effect occurring after its effect" meant. The wording should be improved to clarify the provided example.

Additionally, while the document clearly defines Real-World Data and highlights the distinction between primary and secondary data, additional context is needed about how secondary use affects data quality, for example, due to the lack of original research intent and its design and original purpose. It would also be helpful to explain how the criteria in the guidance document would be used to evaluate secondary data versus primary data.

Extensiveness and representativeness

In reference to data quality control on secondary use of data, Lines 190-192 state, "For instance, DQ control on secondary use of data often cannot adequately detect missing information, especially when this relates to an outcome or event that is not necessarily expected to be present." We suggest adding the following to Line 192 as it refers to event data: "As well as events that are expected to be present, but whose absence may indicate that the test, for example, was never performed despite being ordered or that a medication was not filled, and not because of poor data quality or flawed data linkage." It is important that the nature of missing event data is defined for quality evaluations.

For section 1.4.2, in lines 200-203, we suggest changing "biased outcomes in some studies" (Line 201) to, "outcomes that may not be broadly generalizable." It is important to keep in mind

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that there are few databases that include underrepresented populations, particularly indigent, transient, and migrant groups. Referring to findings from a study as “biased outcomes” can lead to distrust and downgrade the value of important datasets that can be meaningful, even if they are not fully representative.

Responsibility for data quality

This section would benefit from EMA articulating who the responsible parties are and how they should be involved at each step of the data quality process. To this end, ISPOR members suggest that specific roles and responsibilities be defined for each stakeholder responsible for data quality in RWD, including providing clarity as to which stakeholders are responsible for completing data quality checks and applying quality measures that meet the needs of the specific problem at hand. As processes are important in regulatory settings, the framework should also provide guidance as to when a sponsor and/or stakeholder should interact with EMA during their data quality evaluation.

Scope and relevance

The databases listed in Section 2.2 are understandably out of scope in our view but also bring up the question of just how prospective this framework is, and if it is applicable to types of innovative RWD sources, like synthetic data. As synthetic data grows in prominence, we see it potentially being used for regulatory purposes and thus it could be helpful to specify EMA’s current position regarding synthetic data. Also, with respect to patient reported outcome (PRO) data, ISPOR members note that it is an important source of secondary data. If it is collected as part of a registry with clear data collection rules, it can provide valuable outcomes evidence. Therefore, we believe that the document may be going too far in ruling all PRO data out of scope, especially as other types of data become more readily available and acceptable.

Metrics for assessment

Data quality requires a focus on variables that answer the study question. We suggest reconsidering Line 469 which states that these metrics would apply to “all records”. The implication that checks should be performed for all the data under consideration is a significant amount of work that will also generate information irrelevant to the study purpose. The introduction of the section should instead state that assessments should be conducted for variables intended to be used to address the research question.

Generalizability and support

The approach of generalizing question-specific aspects is promising, especially for large-scale studies or multi-site studies. However, further elaboration on how these elements can be automated and standardized across various types of research could improve practical applicability, as fit-for-purpose data is often not generalizable. Lastly, as the document discusses in Line 653 the granular data information that should be made public, EMA should consider developing and maintaining a website that would contain this information. This information would be publicly available for stakeholders to access and understand how previous data quality issues have been managed, supplementing the lack of real-world use cases which

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was highlighted earlier in this response.

We acknowledge the following ISPOR members Sandipan Bhattacharjee, Gracy Crane, Nancy Dreyer, Tuhin James Paul, and Dick Willke for their assistance in assembling these comments, as well as ISPOR staff Laura Pizzi, Kelly Lenahan, and Madeline Shipley.