ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

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Dear the 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 "**Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence - Scientific guideline.**"

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 100 countries globally; nearly 20% (1 in 5) of our membership resides within the European Union. Members across our organization come from 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. We solicited comments from several ISPOR Special Interest Groups (Real-World Evidence and Statistical Methods in HEOR), the ISPOR Institutional Council, and the ISPOR Health Science Policy Council. 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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Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence - Scientific guideline.

We applaud The European Medicines Agency (EMA) for their recently released "Reflection paper on use of real-world data in non-interventional studies (NIS) to generate real-world evidence" which discusses the methodological aspects of NIS using real-world data (RWD) to generate real-world evidence (RWE) for regulatory purposes. We find this guidance well written and will help further the field of RWD generation and use of RWE in decision making.

ISPOR's membership submitted the following comments:

1 Introduction (Lines 44-87)

Clarification: We would recommend that the introduction be clarified to explain what it means by non-interventional studies. Suggested wording might be: "non-interventional studies using real-world data for regulatory purposes are observational studies where treatment is not assigned by the study protocol." In addition, in line 58, "NIS are often used in post-authorisation safety assessment" is not entirely accurate because there are examples of both effectiveness and safety-focused NIS.

Line specific comments: In line 56, we recommend introducing efficacy (focus of clinical trials) and effectiveness (focus of RWE).

2 Scope (Lines 88-119)

We believe it is worth noting in this section that there is a considerable amount of RWD coming from tokenization (eg, RWD coming from patient-level linked datasets). This section also describes data quality as including data relevance; however, these are two different concepts that should be separately noted. Further, the quality of data doesn't matter if the data chosen for the study is not relevant to the research question at hand.

Additions/Clarifications: Please add a line about each of the following:

1) a clear statement regarding limitations/non-acceptance of regulatory RWE without a comparator. (line 117)
2) At the end of paragraph on lines 110-119: "To meet causal objectives, the NIS study protocol should be framed within an accepted causal framework (ex. Target Trial Emulation [TTE], Directed Acyclic Graphs [DAGs], Single World Intervention Graphs). Currently, TTE is the most intuitive approach for clinical researchers and easiest to employ."

3 Legal obligations and regulatory requirements (Lines 120-151)

On lines 124-125, we suggest this be clarified to "The regulatory assessment does not mandate a specific study design, but the design must be appropriate to answering the research question and utilize fit-for-purpose (FFP) data, such that the evidence generated is sufficiently reliable to support the regulatory objective."

4.2 Feasibility Assessment (Lines 166-189)

On line 177 the term "sufficient precision" is vaguely used. We suggest providing a bit more guidance on how precision may be assessed such as reporting of confidence intervals around effect estimates. Investigators should describe how precise they estimate their study will be and whether this precision is sufficient for the purpose of the study in terms of its ability to contribute meaningful evidence.

4.3 Studies with descriptive objectives (Lines 190-213)

We suggest adding to lines 191-213 a line about representativeness in descriptive studies – and later sample selection bias in causal studies – that researchers should cross-reference the sample with a properly

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weighted national survey to gain a better understanding of the sample selection. Many countries have implemented such surveys.

We also suggest clarifying “representative of the real-world target population” by modifying it to say, “representative of a meaningful target population or adjacent populations, making it meaningful for the real-world population of interest”. It may also be useful to state in this section that the requirements for studies with descriptive versus causal objectives will be different.

4.4 Studies with causal objectives (Lines 214-245)
We appreciate the discussion surrounding how a Target Trial Emulation (TTE) framework should be considered, as we believe this is currently the most intuitive approach for RWD studies with causal objectives.

We suggest referencing the following 2 manuscripts on the GRACE Checklist in this section, derived from an empirical study that showed that sensitivity analyses were the single best indicator of quality in observational studies of comparative effectiveness:

- Dreyer NA, Bryant A, Velentgas P. The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness. J Manag Care Spec Pharm. 2016 Oct;22(10):1107-13.
- Dreyer NA, Schneeweiss S, McNeil BJ, et al.. GRACE principles: recognizing high-quality observational studies of comparative effectiveness. Am J Manag Care. 2010;16(6):467-71.

We also suggest referencing the ISPOR Good Practice Report series on comparative effectiveness research using real world data in this section:

- Berger ML, Mamdani M, Atkins D, Johnson ML. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report—Part I. Value Health. 2009;12(8):1044-52.
- Cox E, Martin BC, Van Staa T, Garbe E, Siebert U, Johnson ML. Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary data sources: the International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report—Part II. Value Health. 2009;12(8)1053-61.
- Johnson ML, Crown W, Martin BC, Dormuth CR, Siebert U. Good research practices for comparative effectiveness research: analytic methods to improve causal inference from nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report—Part III. Value Health. 2009;12(8):1062-73.

4.5 Bias and confounding (Lines 246-359)
<u>General Comment:</u> The entire section discussing Bias and Confounding needs more detail about appropriate methods. However, we recognize that such detail may be out of scope for this reflections paper. A more detailed methods review would be useful as a subsequent document or appendix. We also want to emphasize that a main priority should be that the study needs to be designed to answer the research question(s), ie, that correcting for bias cannot fix study results if the design itself is not appropriate.

<u>Clarifications:</u>

- Lines 256-257: A comment about the phrase “later in the design of the study.” Some elements of study design, eg, the key PICOTs, as well as the basic approach such as TTE, should be identified first to be able to think about selection mechanisms and conduct a feasibility assessment, The feasibility assessment and selection concerns help to fine-tune parts of the study, but the sequencing

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implied in this first sentence is unclear.
- Lines 267-270: The text is about exploratory analyses on a preliminary dataset to inform the protocol/statistical analysis plan (SAP), rather than the final SAP. A message encouraging such exploratory analyses could be made more explicit.
- Lines 339-340: While pre-specification to address confounding is primary, it would be realistic to recognize that "modifications may be needed during the operationalization of the analysis", stipulating that any such modifications must be described subsequently and may be the basis for sensitivity analysis.
- Line 340: Add "Recognizing that modifications may be needed during operationalization of the analysis plan".
- Line 341: Some studies involve multiple comparators; suggest revising this sentence to say "one or more comparators".
- Lines 348 – 359: In the discussion of negative controls, for completeness, it may be useful to mention that negative controls can be useful for identifying issues like recall bias or reverse causality.

5.2 Transparency (Lines 383-397)
We strongly agree that transparency is critical for trusting RWE and understanding what analyses have been done. However, the sentence on line 384 would be clearer if it said "Transparency is essential to support the evaluation…" ie, delete "study information" since the term "study information" is unclear. Alternatively, in the bullet points in this section, EMA may wish to add more detail about what study information should be shared, and EMA's position on whether the data itself should be shared. It may not be possible to share the data itself due to the boundaries set by data use agreements and ethics boards. However, you may also want to state that, where possible, investigators should make the analytical dataset itself available.

Clarifications:
- Lines 396-397: The last bullet could be clarified to include the programming code used to create the analytical dataset as well as programming code used for the analysis, and any relevant meta data. either by sharing directly or by providing access through secure portals/servers
- Line 396: reword to state, "make publicly available **the logic** and the codes used for the creation of the analytical data set and the programming code for the statistical analyses." The logic behind decisions is also important.

6.2 Relevance (Lines 423-438)
We appreciate the recognition and citation of HARmonized Protocol Template to Enhance Reproducibility (HARPER) of Hypothesis Evaluating Real-World Evidence Studies on Treatment Effects as a very useful template that helps standardize and summarize the presentation of protocol information for both researchers and those who will use the research. However, we have one clarification, the use of "adequate" in line 429 is vague; we suggest replacing it with "large enough to be informative to address key research questions or to contribute to filling evidence gaps".

6.4 Data Linkage (Lines 452-459)
Line Specific Comments:
- Line 454: Please add "wearables and other digital health technologies" after "genetic data".
- Line 457: Please add "privacy-preserving record" before "linkage methodology"
- Line 459: Add one more bullet stating "any metrics that support the accuracy and precision of such linkages".

6.5 Data Quality Frameworks (Lines 460 – 470)
While the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and EMA have produced a very useful data quality framework, the US Food and Drug Administration (FDA) has

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produced a slightly different one. We encourage efforts to harmonize them, perhaps after some user feedback on both, to standardize frameworks for international researchers.

7.3 Stratified analyses (Lines 495 – 508)
It may be prudent to ensure that stratified analyses should be pursued when clinically relevant or necessary to examine study hypotheses.
There is considerable overlap with this section and **7.6 Heterogeneity (Lines 529 – 542)** in that both deal with potential differences in effects between subpopulations, with consideration of multi-database studies. In both cases any such analysis should be pre-specified and based on clinically relevant characteristics and/or specific hypotheses about potential differences. The bullet points in the Heterogeneity section mostly apply to Stratified Analysis and vice versa. Consider combining the two sections for a more coordinated approach to this topic.

7.5 Missing data (Lines 519 – 528)
It is a standard research reporting principle to reveal the extent of missing data for key variables. While full detail may not be necessary in the study protocol and SAP, some information about the extent of missing data would be useful there to help put the management of it in context. We suggest changing the language in line 521 to "… describe the extent and management of missing data …".

7.6 Heterogeneity (Lines 529 – 542)
Please see our comments noted above under **7.3 Stratified analyses**

We acknowledge the following ISPOR members Marc Berger, Mark Cziraky, Nancy Dryer, and Dick Willke for their assistance in assembling these comments, as well as ISPOR staff Laura Pizzi, Kelly Lenahan, and Madeline Shipley.