ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

505 LAWRENCE SQUARE BLVD SOUTH
LAWRENCEVILLE, NJ 08648

P +1-609-586-4981
F +1-609-586-4982

info@ispor.org

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Notice Number: NOT-OD-23-180

Dear NIH:

ISPOR – the professional society for health economics and outcomes research (HEOR) - is pleased to respond on behalf of its membership to your request for information entitled "Inviting Comments and Suggestions on Opportunities and Challenges for the Collection, Use, and Sharing of Real-World Data (RWD) including Electronic Health Records, for NIH Supported Biomedical and Behavioral Research."

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 Real-World Evidence (RWE) Steering Committee of ISPOR, comprised of experts in the field of RWD/RWE. 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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Inviting Comments and Suggestions on Opportunities and Challenges for the Collection, Use, and Sharing of Real-World Data (RWD) including Electronic Health Records, for NIH Supported Biomedical and Behavioral Research.

ISPOR is a multidisciplinary scientific association focusing on health economics and outcomes research (HEOR), with substantial membership from health economists, epidemiologists, health psychologists, and biostatisticians – fields where use of real-world data (RWD) has long been a fundamental part of research. Our members are very experienced in the use of administrative claims data, electronic health records, registries, large- and small-scale surveys, and other sources of RWD. They use RWD for comparative effectiveness and safety research, cost and burden of illness analyses, and studies of adherence, treatment patterns, and health preferences, as well as other areas of work as appropriate. Many of our members also work closely with biomedical researchers conducting randomized clinical trials (RCTs) and other work traditionally in the domain of NIH.

Due to the importance of scientific quality, transparency, and ethical conduct in RWD-based work in HEOR, ISPOR has had a major focus on promoting excellence in this area. Over the last 20 years, we have assembled a sequence of task forces that published Good Practice Reports relating to the use of RWD [1-10]. Use of RWD, both in research and in decision-making, has been regularly featured in our conferences, summits, and journals; it is also an important aspect for several of our ongoing Special Interest Groups and some other working groups. In 2018, we joined forces with the International Society for Pharmacoepidemiology (ISPE), the Duke-Margolis Center for Health Policy, and the National Pharmaceutical Council (NPC), to form the RWE Transparency Initiative, whose objective is to establish a culture of transparency for study analysis and reporting of hypothesis evaluating real-world evidence studies on treatment effects [11].

We thank NIH for the opportunity to comment on this RFI.

1. **Scientific value and quality considerations for collection, use, and sharing of RWD in biomedical and behavioral research.**

   ISPOR's Good Practices Reports address some of these topics, notably:
   - Defining, reporting, and interpreting RWE [1-3, 6]
   - Bias and confounding in the design of RWE studies [4]
   - Causal inference [5]
   - Assessing relevance and credibility [7]

While we have not written a Good Practices Report specifically relating to data quality, we held a Summit in May 2023 that focused on this topic; a summary of that Summit is available [12]. We also recommend the work on this topic led by Duke-Margolis, in which a number of ISPOR members have participated [13,14]. ISPOR members have also been involved in a recent publication that proposes a data quality evaluation tool [15].

Regarding underrepresentation of populations in data, there has been considerable interest in using RWD to address the lack of diversity in clinical trial populations, as the general assumption is that RWD are more representative of the target population for medical treatments. However, some vital variables remain uncaptured (eg, socio economic status) or the variables have a large degree of missingness (race/ethnicity for specific populations such as Hispanic, Latino, etc.). If these variables are not populated appropriately, there is a barrier to the use of RWD in research. A recent publication has highlighted that anonymization techniques affect some aspects of the original data such as baseline characteristics, and outcomes [16]. Such technical issues with anonymization have been highlighted by regulators and will need further investigation, as anonymization plays a role during data linkage.

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ISPOR also has an active Special Interest Group focused on Health Equity Research which is very interested in social determinants of health in RWD. They have paper in the publication process entitled "Primer on Health Equity Research in Health Economics and Outcomes Research: An ISPOR Special Interest Group Report."

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3. 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; 12:1044-52.
4. 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 non-randomized studies of treatment effects using secondary data sources: The ISPOR good research practices for retrospective database analysis task force–Part II. Value Health 2009; 12:1053-61.
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6. Berger ML, Dreyer N, Anderson Fred, et al. Prospective Observational Studies to Assess Comparative Effectiveness: The ISPOR Good Research Practices Task Force Report. Value Health 2012; 15:217-230.
7. Berger M, Martin B, Husereau D, et al. A questionnaire to assess the relevance and credibility of observational studies to inform healthcare decision making: an ISPOR-AMCP-NPC good practice task force report. Value Health 2014; 17:143-156.
12. Willke RJ. Real-world evidence: From frameworks to practice - Summary of the May 2023 ISPOR/ISPE/Duke-Margolis Summit. Value & Outcomes Spotlight 2023; Sept/Oct. https://www.ispor.org/publications/journals/value-outcomes-spotlight/vos-archives/issue/view/developing-tomorrow's-heor-leaders/real-world-evidence-from-frameworks-to-practice
13. Duke-Margolis Center for Health Policy. Characterizing RWD Quality and Relevancy for Regulatory Purposes 2018. https://healthpolicy.duke.edu/sites/default/files/2020-03/characterizing_rwd.pdf
14. Duke-Margolis Center for Health Policy. Determining Real-World Data's Fitness for Use and the Role of Reliability 2019. https://healthpolicy.duke.edu/sites/default/files/2019-11/rwd_reliability.pdf
15. Berger ML, Crown WE, Li JZ. et al. ATRAcTR (Authentic Transparent Relevant Accurate Track-Record): a screening tool to assess the potential for real-world data sources to support creation of credible real-world evidence for regulatory decision-making. Health Serv Outcomes Res Method (2023).
16. Mehtälä, J, Ali, M, Miettinen, T. et al. Utilization of anonymization techniques to create an external control arm for clinical trial data. BMC Med Res Methodol 2023: 23, 258.

2. **Using RWD as part of the scientific paradigm, including open science, scientific rigor and reproducibility, and team science.**

Several Good Practices Reports, written jointly with ISPE, are relevant to open science, transparency, and reproducibility:

- Transparency (joint with ISPE) [8,10]
- Reproducibility (joint with ISPE) [9,10]

To encourage study process transparency via pre-registration of RWD study protocols, our Transparency Initiative created an RWE Registry on Open Science Forum, designed for efficient registration of RWD studies, particularly cohort and case-study designs [11].

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3. **Administrative and logistical considerations for collecting, using, and sharing RWD for biomedical research.**

   While these topics have been discussed in a number of our conference sessions, we do not have a published ISPOR report that covers these considerations in depth.

4. **Ethical considerations for using RWD for biomedical and behavioral research.**

To respond to these points, we copy relevant summary points from ISPOR's Code of Ethics, with full details available in that article [17]:

- When a database (from primary data collection and/or secondary data use) is analyzed, members should provide a description of approaches, tools, and technologies used to store the data and maintain patient privacy/confidentiality and de-identification.
- Personal data should be maintained securely and adequate back-up should be maintained. Data access should be limited to authorized individuals. Control systems should be put in place to ensure authenticity, integrity, and confidentiality of data records when transmitted electronically.
- Researchers should offer the right to access to the anonymized, group-level data used in their research. If data access is restricted by proprietary or contractual considerations, those considerations should be disclosed. If journal reviewers deem it important that statistical review of proprietary data be conducted, authors should work with both the data owners and the reviewers to find appropriate confidential arrangements for such review whenever feasible.
- Members' hypotheses and research designs should be defined a priori, reported transparently, defended relative to alternatives, and planned to recognize and minimize all types of bias.
- Members should fully disclose the identity of sponsors of their research.
- Members should strive to avoid bias and the appearance of bias in conducting research, such as in the choice of methods and data inputs, or in the selective reporting of results.
- Members should be aware of conflicts of interest and the appearance of conflicts of interest. As a point of reference, members should look to the rules on disclosure of potential conflicts of interest laid down by major peer-reviewed journals and their own institutions.
- Members should maintain their professional autonomy and objectivity in conducting and reporting, in writing or verbally, research findings.
- Methods sections of papers should identify and justify all departures from the a priori analysis plan.
- Members should maintain and protect the integrity of data used in their studies as well as on any other aspect of their research, as previously discussed, e.g., respect for patient autonomy such as informed consent and data privacy.
- Members should not draw conclusions beyond what their data would support and discuss any limitations in a transparent manner.

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17. Santos J, Palumbo F, Molsen-David E et al. ISPOR Code of Ethics 2017 (4th Edition) Value Health 2017; (20) 1227-1242.

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