



The professional society for health economics and outcomes research

Improving healthcare decisions

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Dear Centers for Medicare & Medicaid Services (CMS):

ISPOR – the professional society for health economics and outcomes research - is pleased to respond on behalf of its membership to your guidance document entitled “Proposed Guidance Document: Study Protocols That Use 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 authors of the HARPER report. Comments were solicited from the ISPOR Real-World Evidence Steering Committee, and ISPOR Real-World Evidence Special Interest Group. 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

## Proposed Guidance Document: Study Protocols That Use Real-World Data

On behalf of the members of ISPOR – the professional society for health economics and outcomes research – we appreciate the Centers for Medicare & Medicaid Services’ efforts in preparing a guidance which provides clear and specific direction to the public on the critical elements of a study protocol that relies on real-world data (RWD). ISPOR supports RWD and real-world evidence (RWE) initiatives in many forms and stands firmly behind CMS’s efforts to require transparency in RWE studies. To that end, ISPOR is quite pleased to see that our good practices report, developed jointly in partnership with the International Society for Pharmacoepidemiology (ISPE), serves as the foundation for the guidance.

We noted that the guidance cites the *Pharmacoepidemiology & Drug Safety* article of the HARPER recommendations. Since its publication was subject to an agreement between ISPE and ISPOR that gives neither party first right of citation, we ask CMS to add the following *Value in Health* citation to the guidance:

Wang SV, Pottegård A, Crown W, et al. HARmonized Protocol Template to Enhance Reproducibility of Hypothesis-Evaluating Real-World Evidence Studies on Treatment Effects: A Good Practices Report of a Joint ISPE/ISPOR Task Force. *Value Health*. 2022;25(10):1663-1672. doi:10.1016/j.jval.2022.07.012.

In terms of the contents of the guidance, we reached out to the ISPOR RWE Special Interest Group leadership to gather comments that would improve its clarity and impact. Given that the guidance largely focuses on the existing good practices report, our comments are limited.

1. Because the guidance is built from existing work, members noted that there were sections which would benefit from more thorough references to the source material (HARPER). One such instance is to clarify the intended audience for using the HARPER+<sup>1</sup> template. As noted in the guidance section titled “Development of the RWD Study Template”, HARPER+ is intended for use by manufacturers or other sponsors. It should emphasize that it is not limited to those stakeholders alone. Templates like HARPER and HARPER+ promote visibility and transparency in studies and study data, which benefits a variety of stakeholders beyond regulators and manufacturers. For example, a payer organization informing their decision-making process, or a data provider curating a fit-for-purpose dataset. Another instance where explicit reference to HARPER would strengthen the guidance would be to highlight examples from the original HARPER, particularly for the guidance section on “Research Question and Objectives”.

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<sup>1</sup> Proposed guidance document: Study protocols that use real-world data. CMS.gov Centers for Medicare & Medicaid Services. January 2025. Accessed March 11, 2025. <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?mcid=39>.

2. In the Preamble, it is stated that CMS proactively published this guidance to “provide a framework for more predictable and transparent evidence development”. To that end, we suggest that CMS require sponsors to post their protocols on a credible RWE-specific protocol registry and add this requirement to the guidance document. Protocol registries that are posted before initiation of a research study are crucial for ensuring the transparency of RWE designs. ISPOR collaborated with ISPE, the Duke Margolis Center, and NPC to offer such a registry, which is freely available on the Center for Open Science<sup>2</sup> via this link: <https://osf.io/registries/rwe/discover>. Additional information about this registry, along with instructions for use, are here: <https://www.ispor.org/strategic-initiatives/real-world-evidence/real-world-evidence-registry>. We suggest that CMS include the registry and accompanying information as a resource in the final guidance. Note that users of this registry are asked to utilize HARPER as the template for their RWE protocols. A link to the protocol registry listing should also be included as part of the Title Page of protocols submitted to CMS, along with study contributors.

We acknowledge ISPOR members Shirley Wang and William Crown for their assistance in assembling these comments, as well as ISPOR staff Laura Pizzi, Kelly Lenahan, and Madeline Shipley.

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<sup>2</sup> OSF Real World Evidence Registry. OSF. Accessed March 11, 2025.  
<https://osf.io/registries/rwe/discover>.