REAL-WORLD EVIDENCE ALLIANCE

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Coverage and Analysis Group
Centers for Medicare & Medicaid Services
Mailstop: S3-02-01
7500 Security Boulevard
Baltimore, Maryland 21244-1850

**Re: Proposed Guidance Document: Study Protocols That Use Real-world Data**

To the Centers for Medicare & Medicaid Services ("CMS"):

The RWE Alliance appreciates the opportunity to comment on the Proposed Guidance Document: Study Protocols That Use Real-world Data ("Proposed Guidance").[1] We are a coalition of real-world data ("RWD") and analytics organizations with a common interest in harnessing the power of real-world evidence ("RWE") to inform regulatory decision making to improve the lives of patients. Our members have deep knowledge and experience working with healthcare data across disease areas and patient populations, and we aim to bring these collective insights to bear in support of RWE policies.[2]

The RWE Alliance commends CMS for issuing the Proposed Guidance that describes critical elements for fit-for-purpose studies involving RWD and for providing a standardized template for sponsors to use when creating study protocols using RWD. CMS's rationale for each section will help facilitate a researcher's understanding of how the template is expected to be used. Moreover, we appreciate CMS aligning its Proposed Guidance with FDA's guidance for use of RWE in regulatory decision making. We agree with CMS's efforts to share clear expectations for the design, selection of data sources, and analysis methods for any studies using RWD intended for submission to CMS. We provide the following general comments for any approach that CMS considers for reviewing studies that incorporate RWD, including but not limited to potential updates to this Proposed Guidance.

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[1] CMS, Proposed Guidance Document: Study Protocols That Use Real-world Data (January 17, 2025), https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?mcdid=39.

[2] For information about our members, please see our website, https://rwealliance.org/who-we-are/.

- First, we agree with the general approach of using the HARmonized Protocol Template to Enhance Reproducibility ("HARPER") framework as the basis for a modified framework (i.e., "HARPER+"). Given that many researchers use the HARPER framework for multiple submissions (e.g., regulators, health technology assessments), we suggest that the Proposed Guidance more completely document the modifications and additions introduced in HARPER+ to facilitate the identification and implementation of changes necessary for CMS studies.

- Second, we suggest that CMS move away from the terms "retrospective" and "prospective" when describing real-world studies. As FDA explains, these terms are "commonly but variably used"[3] and can have multiple meanings that add unnecessary confusion. To align with FDA, we suggest that CMS instead use the terms "primary data collection" and "secondary data collection" to distinguish the purpose for which the data were collected. Specifically, CMS should use "primary data collection" to refer to data that are collected de novo, i.e., directly from clinical sites, patients, or health care providers, for the purposes of the study at hand. CMS should use "secondary data collection" to refer to data that are obtained from an existing data source and were collected for a purpose other than the study. We recommend that CMS describe how the data collection type may influence the application of different parts of the Proposed Guidance, such as on the reporting of adverse events.

- Third, we ask that CMS clarify why the completed template example in Appendix B for the SAFE-PAD study states "N/A" under "Data source provenance/curation." Specifically, it would be helpful to understand if "N/A" is listed because no such information is available from CMS on the claims datasets used in the study or because an explanation is not needed because the AHA Annual Survey Database does not provide patient-level data. Generally, we recommend that CMS provide more complete discussions of data provenance and curation in the Proposed Guidance and any future publications to help sponsors describe data provenance for secondary uses of RWD.

- Fourth, we find the formatting of the appendices to be difficult to navigate. The Proposed Guidance labels two separate documents as Appendix A and two other documents as Appendix B. We recommend that CMS clarify the formatting of the documents and/or sections currently labeled as appendices. For example, if the HARPER+ template and the completed example were labeled as Annex 1 and Annex 2, it would preserve the term "appendix" to apply to the five items currently listed as appendices to the HARPER+ template.

The comments in this letter focus on scientific methods related to developing study protocols and managing real-world data for clinical research. Our comments do not

[3] FDA, Draft Guidance for Industry: Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products at 4, n.14 (Mar. 2024), https://www.fda.gov/media/177128/download.

address the Transitional Coverage for Emerging Technologies pathway, Coverage with Evidence Development, or other CMS policies. The RWE Alliance appreciates the development of the Proposed Guidance and similar efforts to inform the design of studies involving RWD submitted to CMS. Thank you for considering these comments, and please let us know if you have any questions. We welcome the opportunity to discuss further.

Best regards,

The RWE Alliance