Duke | MARGOLIS CENTER *for* Health Policy

VIA ELECTRONIC SUBMISSION
Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244
March 18, 2025

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

Dear Coverage and Analysis Group,

The Robert J. Margolis, MD Institute for Health Policy at Duke University ("the Duke-Margolis Institute" or "the Institute") appreciates the opportunity to comment on the "Proposed Guidance Document: Study Protocols That Use Real-world Data," published on January 17, 2025.

The Duke-Margolis Institute generates and analyzes evidence across the spectrum of health policy and supports the triple aim of better care, better health, and lower cost. The Center focuses on transforming health care delivery and increasing the value of biomedical innovation through evidence-based solutions to the most pressing, relevant health care delivery and payment policy questions. Center experts are engaged in policy research and development efforts to improve both care delivery and the processes and infrastructure needed at the Centers for Medicare and Medicaid Services (CMS) to ensure efficient access to new and innovative technologies.

The comments below describe opportunities for strengthening the proposed guidance document to more closely align with CMS's goals of improving the transparency, predictability, and timeliness of Medicare coverage processes. These comments are informed by the Institute's independent analysis of the guidance document and engagement with the Institute's Value for Medical Products Consortium, a diverse group of stakeholders, including manufacturers, real-world evidence experts, providers, researchers, and payers.

The Institute commends CMS for their continued efforts towards the goals of more transparent, predictable, and timely coverage processes. The template presented in this guidance document offers greater transparency into how CMS will evaluate studies that use RWD for Coverage with Evidence Development (CED). This guidance document is one important step to ensure clear communication regarding study protocol expectations. Noting that there are many potential data sources and collection strategies that could be used to collect RWD for studies that answer CMS-identified evidence questions, this template will be a helpful operational tool for manufacturers as they create and submit study protocols. The Institute provides below recommendations for language clarifications within the proposed guidance document to ensure that the template is as clear and effective as possible. Additionally, the Institute offers comments on further actions and steps that CMS can take beyond this template to support effective and efficient real-world evidence (RWE) generation in the post-market setting and further their goals of increasing the transparency, predictability, and timeliness of Medicare coverage processes.

The Institute recommends that CMS:

- Clarify the preferred process for updating the study protocol;
- Clarify how the new HARPER+ framework may be applied across studies that include primary and secondary data collection;
- Publish guidance on fit-for-purpose (FFP) studies that can support Medicare coverage; and
- Consider utilizing early, multi-stakeholder engagement to inform evidence thresholds and evidence generation strategies.

The comments below detail these recommendations.

Areas for Clarification

For this guidance document, CMS prepared a standard template for study sponsors to complete such that CMS can more efficiently and effectively review study designs for approval. This new template is based on the International Society for Pharmacoepidemiology (ISPE) and The Professional Society for Health Economics and Outcomes Research (ISPOR)'s HARmonized Protocol Template to Enhance Reproducibility (HARPER) framework, as well as the Food and Drug Administration (FDA) guidance on RWE use to support regulatory decision-making for medical devices.[1, 2] The new template, the HARmonized Protocol Template to Enhance Reproducibility Plus (HARPER+), builds on these frameworks, with the following additions: a note that studies should seek to answer CMS-identified evidence questions, a section on generalizability to Medicare beneficiary populations, a section identifying threats to study completion, and language that aligns with CED criteria around protection of human subjects.

Protocol Updates

In the proposed template, there is a section on the title page that indicates the protocol version and the most recent update date. There is thus an opportunity for sponsors to update and edit the study protocol within this template. The types of changes that would warrant a manufacturer to update the study protocol, however, are unclear. There may be several appropriate junctures and study updates for which a manufacturer may want to submit an update to CMS. The threshold for considering what constitutes a "minor" change that may not require providing an update to CMS, as well as the appropriate timeframe for notifying CMS of a major change, is a point for clarification. Considering that recent process reforms have focused on helping manufacturers to navigate coverage processes, additional clarity around when and how to submit a study protocol update to CMS could provide further predictability. The Institute recommends that **CMS clarify the preferred process for updating the study protocol.**

Primary and Secondary Studies and HARPER+

The HARPER framework, as the foundation for HARPER+, is a standardized template designed to ensure reproducibility for RWE studies, specifically studies that make secondary use of RWD. Whereas primary data are collected directly from a population being studied for a specific study, secondary data are data collected for a non-research purpose that are then leveraged for a study (such as EHR data or administrative claims). CED studies may use either primary data collection, through prospective studies, or use secondary data to answer CMS-identified evidentiary questions. For example, some studies that

support CED have been prospective and use primary data collection through registries, such as for amyloid PET imaging.[3] Studies for Leadless Pacemakers and Autologous Platelet-rich Plasma have used existing Medicare claims data, which is a secondary use of RWD.[4, 5] CMS may intend that HARPER+ be used for both studies that rely on primary or secondary data collection and analysis, though the distinction between studies that use primary and secondary data is not clear in the current guidance. Since the precursor to HARPER+ focused on secondary use of RWD, the Institute recommends that **CMS clarify how the new HARPER+ framework may be applied across studies that include primary and secondary data collection.**

Areas for Future Actions and Guidance

The recent guidance documents from CMS have provided insight into how CMS may evaluate what constitutes "reasonable and necessary," what is the strength and level of evidence needed to support coverage, and an example of how CMS will determine clinical endpoints of interest for a therapeutic area. These guidance documents were designed to add predictability and transparency into CMS processes. This guidance document on Study Protocols That Use Real-world Data adds an additional level of clarity into how CMS will review study protocols and the template that should be used. HARPER+ could further support timeliness of coverage processes by enabling CMS and manufacturers to communicate more effectively.

These reforms are intended to offer greater transparency around the strength and level of evidence needed in studies and the technical elements of data protocols submitted to CMS. However, there are still outstanding questions regarding the transparency and predictability around the types of data collection strategies and study designs that are most suitable for evidence generation to support Medicare coverage. Through this guidance document, CMS has the opportunity to inform studies that utilize RWD, even beyond studies for supporting Medicare coverage. This will ultimately increase CMS' influence over the types of study designs, data collection methods, and RWE generation methods that are used in FFP studies more broadly.

One step that CMS could take to provide further clarity into their expectations for evidence generation strategies would be to propose a guidance document on FFP study designs. The updated CED guidance document outlined the key principles for CED studies, including expected level of evidence, and the recently published HARPER+ template details the study elements that CMS will review in a study protocol. CMS also provided an example of how they will determine clinical endpoints of interest in different therapeutic areas. A remaining area of uncertainty is how CMS will consider what is an appropriate evidence generation strategy, given the types of evidentiary questions CMS may have at the time of product approval.

CMS has expressed their interest in publishing a FFP guidance document, and the Institute supports this endeavor to clarify evidence expectations. CMS noted in their National Coverage Analysis Evidence Review Guidance Document that CMS "endorses the concept that studies should be fit-for-purpose" and lists the broad methodological principles that CMS uses to assess studies. CMS also expressed that one of the values of FFP post-market studies is that they can be more representative of the clinical experience, and in this recent guidance document on study protocols that use RWD, CMS reiterated their openness to FFP studies that support coverage. A guidance document for FFP study design could

detail the types of data sources and evidence generation strategies that might be appropriate for supporting coverage based on the type of evidence questions that CMS identifies. For example, CMS could clarify how they might determine what types of causal inference study designs or data sources might be most suitable for answering questions regarding appropriate patient criteria for the product or service. This could help provide clarity into how CMS would evaluate studies that utilize novel RWE generation methods without being overly prescriptive, and would allow sponsors to think about potential data collection strategies earlier in the coverage process.

The Institute facilitated a series of expert stakeholder roundtables to determine evidence generation strategies for specific outcomes of interest or evidence questions for a particular product category, with the goal of making post-market evidence generation more streamlined and efficient. The Institute's roundtable series focused on tricuspid valve interventions (TVIs). Participants included providers, researchers, RWE experts, commercial payers, FDA, and CMS. Participants identified potential evidentiary questions, the outcomes of interest for different stakeholders that may affect patient access and product uptake, the data sources that may be best suited to gathering data based on these identified outcomes, and data collection strategies that would support coverage without being overly burdensome or costly. The Institute created a preliminary framework for considering the data sources and evidence generation strategies that would best support coverage for TVIs given identified evidence questions.

A similar framework or guidance document from CMS could provide transparency into how they may evaluate the appropriateness of FFP studies for categorical evidence questions across different therapeutic areas. In conjunction with this Study Protocols that Use RWD guidance document, the evidence expectations for Medicare coverage would be more transparent and the coverage process more predictable. The Institute recommends that **CMS publish guidance on FFP studies that can support Medicare coverage**. CMS could also consider publishing an example of how they may evaluate FFP studies based on their evidentiary questions and expectations for one coverage determination, similar to the approach taken with the example Clinical Endpoints Guidance Document for Knee Osteoarthritis, or the example pre-populated HARPER+ template.

Early, multi-stakeholder engagement—in conjunction with FFP guidance—can support the development of efficient and novel RWD collection strategies that lower the burdens and cost of post-market evidence generation. For example, novel trial designs—such as decentralized trials that use remote patient monitoring devices or studies that utilize synthetic data—have the potential to produce rigorous evidence at a lower cost than traditional randomized control trials. As these take time to develop, any early guidance on FFP studies will allow manufacturers to streamline evidence generation.

CMS can facilitate early engagement with a variety of stakeholders to inform both the relevant outcomes of interest for a given disease or therapeutic area (which can be incorporated into clinical guidelines guidance documents) and the relevant considerations for FFP studies that support coverage. For instance:

- Experts in RWD and RWE could offer feedback into the relevant considerations of implementing innovative evidence generation strategies, as well as ideas for how to ensure rigorous analysis for different sources of RWD, including patient-generated data.

- Patients can elaborate on the outcomes that are most important to them as end users of a given product or service.
- Providers can identify outcomes of importance that impact product uptake and how data collection methods may impact burden and clinical workflows.

For therapeutic areas for which there are a lot of novel products in development, CMS could consider implementing strategies to facilitate multi-stakeholder engagement to discuss evidence thresholds based on evidentiary questions and outcomes of interest to inform future guidance documents. Such efforts can inform the development of forthcoming Clinical Endpoints guidance documents and further clarify how manufacturers can use FFP guidance to inform their evidence planning.

This engagement could look similar to CMS' Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meetings, which serve to provide expert guidance to CMS on clinical topics. These meetings, similar to MEDCAC meetings, could also be public to offer greater transparency into not only the processes, but the outcomes of these meetings. To support early and efficient data collection infrastructure development, the Institute recommends that **CMS consider utilizing early, multi-stakeholder engagement to inform evidence thresholds and evidence generation strategies**.

Conclusion

The Duke-Margolis Institute supports CMS' continued efforts to make Medicare coverage processes more transparent, predictable, and timely. The proposed guidance document on Study Protocols that Use Real-world Data offers greater transparency into how CMS will evaluate elements of studies that support Medicare coverage. CMS can continue to pursue their goals through publication of a FFP study guidance document and through early engagement with a variety of stakeholders.

The Institute appreciates CMS' consideration of our comments.

Sincerely,

Hannah Graunke – Senior Policy Analyst
Beena Bhuiyan Khan – Research Director of Payment and Coverage Policy

Disclosures
Beena Bhuiyan Khan is a former employee and shareholder of Abbott Laboratories.

References

[1] Shirley V. Wang 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," *Pharmacoepidemiology and Drug Safety* 32, no. 1 (January 2023): 44–55, https://doi.org/10.1002/pds.5507.

[2] Food and Drug Administration, "Use of Real-World Evidence To Support Regulatory Decision-Making for Medical Devices, Draft Guidance for Industry and Food and Drug Administration Staff; Availability," *Federal Register* 88, no. 242 (December 19, 2023), https://www.federalregister.gov/documents/2023/12/19/2023-27852/use-of-real-world-evidence-to-support-regulatory-decision-making-for-medical-devices-draft-guidance.

[3] Centers for Medicare & Medicaid Services, "Coverage with Evidence Development Amyloid PET," CMS.gov, September 10, 2024, https://www.cms.gov/medicare/coverage/evidence/amyloid-pet.

[4] Centers for Medicare & Medicaid Services, "Coverage with Evidence Development Leadless Pacemakers," CMS.gov, September 10, 2024, https://www.cms.gov/medicare/coverage/evidence/leadless-pacemakers.

[5] Centers for Medicare & Medicaid Services, "Coverage with Evidence Development Autologous Platelet-Rich Plasma," CMS.gov, September 10, 2024, https://www.cms.gov/medicare/coverage/evidence/plasma.