

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

January 17, 2025

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Preamble

Section 1862(l)(1) of the Social Security Act (the Act) requires the Secretary of Health and Human Services (the Secretary) to make available to the public the factors that are considered in making national coverage determinations (NCDs) of whether an item or service is reasonable and necessary. The Centers for Medicare & Medicaid Services' (CMS) procedures for issuing guidance documents under this authority are set forth in 69 Fed. Reg. 57325 (September 24, 2004).

NCDs concerning whether a particular item or service is reasonable and necessary under section 1862(a)(1)(A) of the Act are based on information including clinical experience, and medical, technical, and scientific evidence.ⁱ The NCD process also considers public comments. The public is afforded the opportunity to comment on a proposed determination as set forth in section 1862(l) of the Act. When we make an NCD, we provide a clear statement of the basis for the NCD as well as responses to the comments received from the public.

To encourage innovation and accelerate beneficiary access to new items and services, CMS is proactively publishing this proposed guidance document to provide a framework for more predictable and transparent evidence development.

This proposed guidance represents CMS' current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind CMS or the public. Where warranted by circumstances, CMS may consider an alternative approach if it satisfies the requirements of the applicable statutes and regulations. Individuals interested in discussing an alternative approach are encouraged to contact CAGInquiries@cms.hhs.gov and reference this guidance.

CMS is seeking public comment on this proposed Real-World Data Study Protocol Guidance. CMS will review the public comments and respond to the comments in the final document.

Questions and comments may be submitted to CAGInquiries@cms.hhs.gov. Alternatively, written comments may be submitted to the Coverage and Analysis Group, Centers for Medicare & Medicaid Services, mailstop: S3-02-01, 7500 Security Blvd. Baltimore, MD. 21244. Please refer to this proposed guidance document when submitting comments.

To ensure consideration, comments must be received by March 18, 2025.

Purpose of Proposed Guidance Document

This proposed guidance document aims to provide clear and specific guidance to the public on the critical elements of a study protocol that relies on real-world data (RWD) sources for an NCD using the coverage with evidence development (CED) paradigm. This protocol template is primarily intended for studies that exclusively analyze RWD. The CED may be part of the Parallel Review Program or the Transitional Coverage for Emerging Technologies (TCET) pathway, both of which are coverage mechanisms specific to devices, when an NCD with CED requirements is anticipated or CMS approval for

ⁱ Section 1862(a) of the Act, in the material following (25). ("[I]n making the [national coverage] determination, the Secretary has considered applicable information (including clinical experience and medical, technical, and scientific evidence) with respect to the subject matter of the determination[.]")

https://www.ssa.gov/OP_Home/ssact/title18/1862.htm

a clinical study under an existing NCD with CED requirements is sought. This document does not discuss specific factors CMS considers in making NCDs using the CED paradigm. We refer readers to our Coverage with Evidence Development Guidance Document for discussion of the specific factors CMS considers in making NCDs using the CED paradigm. The most recent CED Guidance is located here: [Coverage with Evidence Development](#).

Background

In general, in order for an item or service to be covered under Medicare, it must meet the standard described in section 1862(a)(1)(A) of the Act – that is, it must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. When the available evidence is insufficient to demonstrate that the items and services are reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member under section 1862(a)(1)(A) of the Act, coverage with evidence development (CED) has been used to support evidence development for certain items and services that are likely to show benefit for the Medicare population.ⁱⁱ CED has been a pathway whereby, after a CMS and AHRQ review, Medicare covers items and services on the condition that they are furnished in the context of clinical studies or with the collection of additional clinical data.ⁱⁱⁱ CED relies primarily on the statutory exception in section 1862(a)(1)(E) of the Act, which effectively permits Medicare payment for items and services that are reasonable and necessary to carry out research conducted pursuant to section 1142 of the Act.

This guidance is part of a broader CMS modernization initiative to provide a more transparent and predictable evidence-generation framework to facilitate Medicare coverage. For a more complete discussion of this effort, we refer readers to [Coverage with Evidence Development](#) and [CMS National Coverage Analysis Evidence Review](#).

Through these guidance documents, CMS has indicated interest in considering a broader range of fit-for-purpose study designs for CED. This guidance document provides detailed and specific information about CMS standards for fit-for-purpose study designs using RWD to the public and potential study sponsors. We intend that providing this guidance will lead to more efficient approval of proposed CED studies by reducing the need for multiple rounds of review. We also intend for this guidance to reinforce public confidence that CMS is applying rigorous standards to RWD studies.

CMS recommends that an Evidence Development Plan (EDP) be submitted with all CED study protocols. The EDP frames the overall evidence generation strategy, of which an RWD study may be one component, and defines a timeline for reconsideration. Generally, a CED study may be one component of the evidence-generation strategy. Studies should be designed, and protocols should be written and submitted to CMS before study outcomes are available to those designing the study or writing the protocol.

Rationale for a Standardized RWD Protocol Template

ⁱⁱ CMS CED Guidance Document, 2, 3.

ⁱⁱⁱ CMS CED Guidance Document, 4.

On August 7, 2024, CMS released an updated CED guidance document to address the factors CMS considers in making NCDs, the principles governing the application of CED, and the clinical study standards for [CED](#). We intended to allow for a range of fit-for-purpose study designs to satisfy CED requirements. Provided that the study design, analysis plan, and data sources are appropriate to the research question, CED studies may incorporate RWD. As CMS has reviewed protocols utilizing RWD submitted as part of CED, we have found that the proposed research protocols vary significantly in terms of the level of detail and content provided. Often, the protocols submitted are missing key details. Others may include more detail but may not be focused on the most critical aspects. This slows the study approval process – something that all parties want to avoid.

To help draft protocols, potential study sponsors have requested that CMS provide specific information about expectations for RWD studies and examples of strong study protocols. In response, CMS has drafted a standardized template for RWD study protocols. The methodology for developing the template is discussed below, and a completed example is included in [Appendix B](#). We invite public comment on the draft template and will respond to comments in the final version of this guidance. Once finalized, the RWD study protocol template will be available for download by study sponsors and other members of the public on the CMS website. CMS strongly encourages prospective study sponsors to use the template. Departures from the requested format and content may lead to delays in the study approval process.

Development of the RWD Study Template

CMS has drafted a standardized RWD study protocol template, called the HARPER+, to be used by manufacturers or other sponsors when creating study protocols using RWD ([Appendix A](#)). The HARPER+ framework is based on the HARmonized Protocol Template to Enhance Reproducibility (HARPER),¹ but adapted for medical devices and Medicare coverage criteria. In developing the HARPER+, CMS reviewed several academic guidelines and templates for studies using observational data, including the International Society for Pharmacoepidemiology (ISPE) and ISPOR - The Professional Society for Health Economics and Outcomes Research (ISPOR)'s HARPER framework for developing replicable observational studies that use RWD. We chose the ISPE-ISPOR HARPER framework as the basis for CMS' recommended template because it was developed: 1) with a focus on protocols using RWD for post-market studies; 2) through an international task force that contained highly regarded epidemiologists and stakeholders from multiple professional societies, regulatory agencies, and industries; and 3) included the majority of elements CMS deemed essential to determine if the proposed study will meet the clinical study standards for CED.

The HARPER+ includes all of the elements in the HARPER. However, CMS added sections for study sponsors to provide additional information to confirm that all CED study standards are met. For example, a section entitled "CMS-identified evidence gaps" was added to the HARPER+ to help align the research objectives with the evidence gaps. In addition, CMS expanded the helper text to provide more examples related to medical devices. The protocol information requested and the rationale for the request in the HARPER+ are discussed below.

In developing the HARPER+, CMS has solicited feedback from industry, government, and academia. CMS has cross-referenced and aligned the HARPER+ with the Food and Drug Administration's guidance for using real-world evidence to support regulatory decision-making for medical devices and the National

Evaluation System for Health Technology Coordinating Center's Research Methods Framework.^{2,3} We urge interested parties who intend to submit a CED study protocol using RWD for CMS approval to adhere to the template and provide all requested information to the best of their ability. The standardized format will facilitate efficient review of the protocol. Departures from the requested format and content may lead to delays in the study approval process. We invite public comment on the draft protocol template.

CMS has completed the HARPER+ using publicly available study details of the Safety Assessment of Femoropopliteal Endovascular Treatment with Paclitaxel-coated Devices (SAFE-PAD study) ([Appendix B](#)).⁴⁻⁶ This example was constructed to aid protocol submitters by illustrating the information requested in specific sections.

The following section provides a rationale for each component of the HARPER+. It includes context for each element of the proposed research to help readers understand how RWD will be used to develop evidence.

RWD Study Template Components

- 1. Title Page:** The title page captures basic information about the protocol for identification purposes. Basic information includes the title of the protocol and central research question/objectives. The protocol version and last update date are meant to distinguish different protocol drafts and ensure that all parties are primarily focused on the most recent version. Additional identifying information includes names and contacts for protocol contributors (i.e., authors), names and contacts for the sponsoring organization, information linking the protocol to [clinicaltrials.gov](#), and statements of any real or perceived conflicts of interest.
- 2. Abstract:** The abstract provides a concise overview of the protocol. This is intended to improve communication by framing the subsequent detailed content. This abstract could also be re-used as part of information on this protocol that is entered into [clinicaltrials.gov](#).
- 3. Amendments and Updates:** All protocols will likely undergo revisions based on discussions between the sponsor and CMS. The Amendments and Updates section provides a concise overview of the protocol's evolution over time, including version numbers, associated dates, sections changed, and rationale for changes/updates. Documenting this information supports a common understanding of the current protocol version's form and content.
- 4. Milestones:** A key aspect of Coverage with Evidence Development is determining the timing of reconsidering a coverage decision. The estimated study milestones enable both the sponsor and CMS to know when to expect certain important events, such as the presentation of interim data quality checks. They may also help define the appropriate timing of an NCD reconsideration.
- 5. Rationale and Background:** This section is intended to provide the information needed to understand why a Coverage with Evidence Development study is necessary. This information includes a basic understanding of the health condition being addressed, current standard of care and associated

shortcomings, past research that bears directly on the approach included in the protocol, and remaining gaps in the evidence base that could affect coverage decisions.

6. Research Question and Objectives: This section provides a concise statement of the primary and secondary research questions/objectives underlying the protocol. The high-level summary allows readers to quickly frame and better understand the details that follow in subsequent sections of the protocol.

7. Research Methods

7.1. Study Design: A brief statement of the type of study design (e.g., retrospective cohort study) allows protocol readers to more quickly understand and assimilate the following details. The requested rationale is intended to illustrate, at a very high level, how the protocol authors have translated their research objectives/questions into an action plan.

7.2. Study Design Diagram: A study diagram can helpfully summarize many protocols' details in one easy-to-remember image, including data observability, definition of exposure, outcome windows, etc. It is useful to both protocol authors and readers to clarify basic aspects of the proposed research design.

7.3. Setting

7.3.1. Context and Rationale for Definition of Time 0 (and Other Primary Time Anchors) for Entry to the Study Population: This section includes the context, rationale, and operational definition of Time 0. Time 0 is a critical study component. It establishes a “starting point” for each participant, allowing researchers to more easily track and analyze observed phenomena over time, especially exposures and outcomes. It ensures comparability across study participants, enabling meaningful comparisons. It can minimize bias by ensuring that participants are at a similar stage of the condition under study. A clear operational definition of Time 0 can support future replication efforts.

7.3.2. and 7.3.3 Context and Rationale for Study Inclusion and Exclusion Criteria: These sections include the context, rationale, and operational definitions of the study inclusion and exclusion criteria. Clearly-explained and specified inclusion/exclusion criteria are critical for ensuring that the study population is properly scoped so that the observed effects can potentially be attributed to the exposure or intervention of interest (internal validity). They also help reviewers assess the external validity of the proposed study, i.e., whether the study results are likely to generalize to the target population. The operational definitions contribute to a clear understanding of the study population, making data analysis and interpretation easier and facilitating future replication efforts. Finally, clearly defined and explained inclusion/exclusion criteria allow reviewers to consider the safety and ethical aspects of the study, e.g., ensuring that participants can provide informed consent when applicable and are not exposed to unnecessary risks.

7.3.4. Generalizability of Study Population: A crucial consideration in studies that may impact CMS coverage decisions is whether the results of a proposed study are likely to generalize to the Medicare population. This section allows protocol authors to demonstrate that their results from their study population can be reasonably expected to apply to the Medicare population.

7.4. Variables

7.4.1 and 7.4.2 Context and Rationale for Exposure(s) and Outcome(s) of Interest: These sections include the context, rationale, and operational definition for the exposure(s) and outcome(s) of interest. The rationale sections allow protocol authors to connect aspects of the detailed study protocol to the overall

objectives and research questions defined previously; specifically, why the exposure(s) and outcome(s) are important to investigate and how further research using these exposure(s) and outcome(s) will address identified evidence gaps. A clear definition of the exposure(s) and outcome(s) helps authors and readers evaluate the appropriateness of the study design, the proposed study population, the statistical analysis plan (Section 7.5.1), and whether the study will likely have internal and external validity. Finally, a clear operational definition of the exposure(s) and outcome(s) of interest can support future efforts at replication.

7.4.3. Context and Rationale for Follow-Up: The context and rationale for the follow-up period are important to assess anticipated data completeness and outcome ascertainment. Follow-up period information includes censoring events that may influence observability and suggest informative censoring. A censoring event (such as a new medical problem or loss to follow-up) may prevent the study participant from reaching the study outcome. In addition, the length of the follow-up period has implications for whether the proposed outcome will be observed reliably, given the exposure.

7.4.4. Context and Rationale for Covariates (Confounding Variables and Effect Modifiers, e.g., Risk Factors, Comorbidities, Comedications): The context and rationale for the covariates allows reviewers to understand which confounders and effect modifiers will be considered in the study. “Covariates” are attributes of the study participant that might potentially be associated with the outcome and/or exposure. Examples of covariates include age, gender, health conditions/diagnoses, prior treatments, insurance status, and other socioeconomic factors. Details of the covariates help CMS assess whether the variable will have construct validity and can be reliably abstracted from the RWD.

7.5. Data Analysis: The data analysis section provides reviewers with details on the proposed hypothesis, analytical program(s), statistical model(s), confounding adjustment method, missing data methods, and subgroup analyses. These details allow CMS to ascertain whether the proposed data analysis can answer the research question. In addition, protocol submitters are recommended to describe the proposed sensitivity analyses in this section.

7.5.1. Statistical Analysis Plan: A statistical analysis plan (SAP) outlines the statistical methods and procedures for analyzing data in the study. It includes details on the statistical aspects of the trial design, the criteria for selecting data for analysis, and the procedures for analyzing various data items. It also defines included populations and describes how the results will be presented.

7.5.2. Context and Rationale for Analysis Plan: A clear description of the purposes and aims of the sensitivity analyses will enable CMS to understand how the sensitivity analyses will test the robustness of the results from the main analyses.

7.6. Data Sources: CMS requests information about the data sources to understand the reasons for selection and their strengths and limitations. For example, it is important to provide a description of the data source (e.g., number and demographic characteristics of included patients, geographic distribution of the data sample, and description of important individual variables). The credibility of data sources is higher when study sponsors can also demonstrate with published citations that the data source has been successfully used in a similar context. This information enables CMS to assess whether the data is fit-for-purpose to answer the research question.

7.6.1. Context and Rationale for Data Sources: There is a range of potential data sources used in RWD studies. These include electronic health records (EHR), insurance claims, pharmacy benefit claims, and patient registries. Much of the data is created by clinicians during care. Additionally, claims data is contributed to by coders and billing personnel in the claims management process. Clinical registries often contain data from abstractors who are reading clinical records, and in some cases, registries may have data input directly from patient surveys. The Coordinated Registry Networks developed by clinical specialty societies bring together many sources in highly granular and curated data sets that have been used by regulatory agencies.^{iv} Understanding why researchers recommend using specific data sources is fundamental to the likelihood of success of the research proposal.

7.7. Data Management: The data management section requests information about the procedures, policies, and infrastructure for data storage, transfer, data updates, backup, and information security. CMS will review this section to appraise whether the study sponsor has appropriate data management practices to reduce the risk of unforeseen events influencing the completion of the study.

7.8. Quality Control: The quality control section requests that study sponsors state the steps to ensure data quality, including quality assurance and quality check procedures, double programming, source data verification, validation of endpoints, data transformation and linkages, and assessment of the data's reliability. CMS requests this information to assess whether the study sponsor has the appropriate quality control procedures to prevent errors in the study results.

7.9. Study Size and Feasibility: This section provides projected study sizes to minimally detect a pre-specified effect with a pre-specified statistical precision. CMS will review this section, including the assumptions used in the statistical power calculations, to determine if the study will be statistically powered to answer the research question.

8. Limitation of the Methods: The limitations of methods section requests a discussion of the potential limitations of the study design, variable identification and measurement, and analytic methods. CMS requests this information to have a shared understanding of the study's limitations and steps to reduce their potential impact.

9. Top Threats to Successful Completion of the Study Objectives: CMS requests that study sponsors explicitly state their views on the top threats to successfully completing the study objectives. This information helps CMS rank the risks and prioritize the mitigation strategies.

10. Protection of Human Subjects/Governance: The protection of human subjects and governance section requests study sponsors describe the information governance, privacy, and data security provisions that have been established to satisfy Federal privacy and security regulations issued pursuant to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and codified in 45 CFR Parts 160 and 164 (Subparts A, C, and E), United States Department of Health and Human Services (HHS) regulations at 42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient Records (as appropriate) and HHS regulations at 45 CFR Part 46, regarding informed consent for clinical study involving human

^{iv} Gressler, Laura Elisabeth, et al. "A Comprehensive Framework for Evaluating the Value Created by Real-World Evidence for Diverse Stakeholders: The Case for Coordinated Registry Networks." *Therapeutic Innovation & Regulatory Science* (2024): 1-11.

subjects. CMS requests this information to assess whether the study sponsors will follow appropriate security and human subject requirements. If the study is an FDA-regulated clinical investigation, this section should also address compliance with applicable FDA regulations, including 21 CFR Parts 50 and 56.

11. Reporting of Adverse Events: This section describes the procedures for collecting, managing, and reporting adverse events/adverse reactions in the published report. CMS requests this information to understand how new information might influence the evaluation of the product's benefit-risk balance while the study is being conducted.

12. Applicable Federal Regulations: CMS requests that study sponsors confirm compliance with CED requirements and applicable federal regulations on privacy and patient protections which are not addressed in component 10.

13. Protocol Signatures: CMS requests that an appropriate representative from the study sponsor's organization sign the protocol to signify adherence to the applicable statutes and regulations.

14. References: CMS requests that the appropriate references be listed in this section to allow reviewers to assess supporting information sources.

15. Appendix A. Additional Statistical Considerations: The Additional Statistical Considerations appendix contains additional details related to the protocol's analysis plan. CMS will review these additional details and the statistical analysis descriptions in the main protocol to assess if the statistical methods are appropriate for the study objectives.

15.1. Directed Acyclical Graph: A Directed Acyclical Graph (DAG) visually depicts the relationships between multiple variables and exposure and outcomes. Arrows show a causal relationship between nodes representing the variables and illustrate potential confounding effects. Understanding these relationships will inform researchers which variables need control in the analysis.

15.2. Interim Analyses and Data Monitoring (As Applicable)

15.2.1. Purpose of Interim Analyses: In observational studies carried out prospectively, issues will likely arise which need to be evaluated once the study is underway and should be reported in an interim analysis. Data monitoring refers to activities related to collecting and pooling data in a standardized manner. Depending on the duration and complexity of the study, researchers might plan on having more than one interim analysis. Data monitoring activities are needed throughout the study to ensure a high-quality research data set and an informative study. An independent data monitoring committee may be established to review the interim analyses for some complex studies. An independent committee is comprised of experts who are not otherwise involved in the study.

15.2.2. Scope of Adaptations: Based on knowledge of the data sources and the study risks (identified elsewhere in the protocol), researchers should indicate what aspects of the protocol most likely need adaptation. For example, enrollment issues, data availability, and data quality may lead to adjustments in the study timeline, sample size targets, and analytic approach.

15.2.3. Stopping Rules: Major issues could potentially arise which lead to the early stopping of the research study. For example, if the treatment being studied is found to be no longer clinically useful, the

product supply is cut off, or enrollment in the treatment group is not met, it may be reasonable to stop the research project. Researchers should describe the risk of such events and the thresholds they recommend for potentially stopping the study.

15.2.4. Analysis Methods to Minimize Bias from Naïve Interim Analysis: Naïve Interim Analysis conducts data analysis before the full data set is complete. This introduces the possibility of bias leading to wrong conclusions. Researchers should describe methods to be used to limit this risk while still producing an informative interim analysis.

15.2.5. Adjustment of Confidence Intervals and P-Values for Interim Analyses: Target P-values and confidence intervals specify the criteria that will be used to determine whether a treatment effect is statistically significant and should be specified in the statistical analysis plan. In the rare case where these criteria are changed during the study, it is important to pre-specify when and how such an adjustment might be considered.

15.2.6. Interim Analysis for Sample Size Adjustment: Sample size targets are set in the initial protocol but may be subject to adjustment based on findings from an interim analysis. Researchers should specify criteria and methods when considering sample size changes.

15.2.7. Practical Measures to Minimize Bias from Unblinding During Interim Analyses: Blinding refers to the information available to researchers enrolling patients and statisticians analyzing which patients received which treatments. To minimize bias, it is important to specify at the beginning of the study who will perform the interim analysis, to what information they will have access, and what information, if any, might be released to the general public or other groups after the interim analysis and other study milestones.

15.2.8. Documentation of Interim Analyses: Snapshots of the data available at each interim analysis should be preserved, as should all documentation of analysis plans, programming code, and reporting provided at each interim. Recreating the decision process from the study archive at any time should be possible. Record what documents will be created and stored in the archive. Describe data management plans for each expected interim analysis, including how data snapshots will be managed.

15.3. Multiple Testing: Multiple testing or multiple comparisons is the potential risk of calculating false positive results simply by chance. This can result from running a statistical test multiple times on the same data set. Specific methods can reduce this risk (e.g., Bonferroni correction). The analysis plan should address how the risk of multiple testing will be handled.

15.4. Statistical Plan Deviations: The statistical analysis plan (see Section 7.4.1.) is written in advance and critical to the research protocol. Any deviation from the plan should be documented in detail, including the rationale for any changes and the decision-making process.

15.5. Randomization and Blinding (If Applicable): In observational studies, it is desirable to withhold interim results from the enrolling physicians to avoid changes in their enrollment practices as the study progresses. In this case, the physicians are “blinded” from the interim analysis, so they don’t change which treatment they recommend to patients based on that new knowledge.

16. Appendix B. Data Validation Output: “Data quality” refers to the characteristics of the research data set that make it believable and reliable. While this is not a comprehensive list of characteristics

needed to assess data quality. Ideally, the data set is complete without missing data and conforms to expectations of format and minimum/maximum values. Researchers should report on these characteristics for key study variables (e.g., inclusion characteristics, and outcome variables). The [Kahn Framework](#) provides industry-standard guidance for data validation terminology.

17. [Appendix C. Data Use Agreement](#): Data use agreements (DUA) provide contractual language on the expected uses and limitations of use for a data set. They are made between stakeholders related to a research project, including data vendors, researchers, collaborators from participating institutions, etc. Modifications to a DUA can be made only with formal review and agreement between the parties and may require the Institutional Review Board (IRB) approval.

18. [Appendix D. Data Dictionary](#): The data dictionary provides the agreed-upon definitions, including code language, format, and categories for each variable used in the research data set. It may also reference expected data sources, minimum/maximum values, and other characteristics. As an example, please see: <https://www.ahrq.gov/research/findings/final-reports/ssi/ssiapc.html>

19. [Appendix E. Value Sets](#): Value sets are the specific lists of healthcare terminology codes allowed for a specific variable in the research data set for a specific research protocol. Each value set is drawn from well-defined code sets such as SNOMED, ICD-10, CPT, and LOINC for concepts such as diagnosis/conditions, procedures, test results, etc. Adhering to these standard definitions is important for interoperability within the project, future reproducibility of the study, and generalizability of the findings.

Revision History.

This is the first version of this guidance document.

References

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