RE: Coverage and Evidence Development Proposed Guidance Document

Dear Coverage and Analysis Group,

The Robert J. Margolis, MD Center for Health Policy at Duke University (“the Duke-Margolis Center” or “the Center”) appreciates the opportunity to comment on the Coverage and Evidence Development Proposed Guidance Document published on June 22, 2023.

The Duke-Margolis Center generates and analyzes evidence across the spectrum of health policy and supports the triple aim of better care, better health, and lower cost. A core mission of the Center is to focus on increasing the value of biomedical innovation to patients. Center experts are engaged in policy research and development efforts to improve the processes and infrastructure needed at the Centers for Medicare and Medicaid Services (CMS) to ensure efficient access to new and innovative technologies.

These comments describe opportunities to ensure that Coverage with Evidence Development (CED) studies that meet the proposed new requirements produce sufficient evidence to inform CMS’s assessment that a novel technology is reasonable and necessary for Medicare beneficiaries. These comments are informed by the Center’s independent analysis of the proposed guidance, participation in the recent Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) panel on the “Analysis of Coverage with Evidence Development (CED) Criteria,” and engagement with a diverse group of stakeholders, including manufacturers, real-world evidence experts, providers, researchers, and payers.

The Duke-Margolis Center is supportive of the CED proposed guidance. Separating existing compound requirements into distinct, thematic criteria allows for more specificity and clarity of study guidance, which will better inform study design and facilitate downstream assessments of study results. The revisions also reflect evolving evidence needs for novel technologies including “fit-for-purpose” (FFP) study designs and a greater reliance of real-world data (RWD) collection methods allowing CMS to reevaluate efficient and appropriate coverage of novel technologies for Medicare beneficiaries in a timely manner. In order to ensure the effectiveness and the impact of the CED guidance, Duke-Margolis recommends CMS:

- Require interim results reporting as part of the proposed CED criteria 2: “Milestones”;
- Clarify when there is scope for multi-stakeholder engagement to inform CED study objectives and designs;
• Provide specific guidelines and examples on the types of data generation strategies, data sources, and study designs that support CMS Medicare coverage in the forthcoming FFP guidance;
• Clarify how CMS will evaluate specific CED study designs relative to related guidance on clinically meaningful endpoints for that disease area and applicable data generation strategies, data sources provided from the forthcoming FFP guidance; and
• Increase CMS resources and capacity to support Medicare coverage activities, including implementing the proposed revisions to the CED requirements and guiding evidence generation for new technologies.

Background
The CED policy was developed to provide access to novel technologies that did not have sufficient evidence to substantiate the Medicare’s coverage standard of reasonable and necessary. For a product to be reasonable and necessary, it must be: (1) safe and effective, (2) not experimental or investigational, and (3) appropriate for use in Medicare beneficiaries. An item or service is “appropriate” in this context if it is furnished according to the medical practice standards for the diagnosis or treatment of a condition, in a setting of care that can meet patient needs, by a qualified provider, whether a product meets the medical needs of the patient, and whether it is as least as beneficial as an existing alternative.

The CED proposed guidance is part of broader initiatives of modernizing Medicare coverage processes to be more timely, transparent and predictable. Advances in biomedical innovation and the growth of expedited FDA regulatory processes have accelerated the pace at which novel technologies reach market authorization. Many of these novel new technologies, while promising, may have limited evidence on health outcomes for Medicare beneficiaries, long-term adverse events, and the treatment durability at the time of approval, which suggests greater reliance on CED as a means to provide access. Concurrent with the growing pace of medical innovation are the growing importance of RWD and real-world evidence (RWE) as a means to evaluate health outcomes for Medicare beneficiaries. Traditional clinical studies are not generally designed to evaluate the impact of novel technologies in real world settings with the variety of patients reflective of the diverse Medicare populations. As such, RWD sources and methods are becoming a more relevant means of generating the evidence that could substantiate the reasonable and necessary coverage. The CED proposed guidance presents an opportunity to further allow for greater use of RWD and RWE to support Medicare coverage. Another broad trend that has been driving the assessment and evaluation for novel technologies is the principle of FFP study methodologies as determined by both evidence questions and the endpoints and outcomes evaluated. The proposed CED guidance allows for these new methods to qualify and quantify the impact of novel technologies on Medicare beneficiaries.

Through the CED proposed guidance, CMS aims to provide a more transparent and predictable evidence generation framework to facilitate Medicare coverage; allow for broader range of FFP study designs; and accelerate beneficiary access to new items and services. The first part of this comment letter will evaluate how the proposed criteria support CMS’s aims. The second part of the comments will address how additional guidance could strengthen the overall CED processes.
Providing a more Predictable and Transparent Evidence Generation Framework

The CED proposed guidance provides more specificity regarding the evidentiary expectations and populations of interest than the previous guidance to create a more predictable and transparent framework for CED studies. For example, criteria 6: “Study Population,” explains a threshold for which factors sponsors must consider for reflecting the diversity among intended Medicare beneficiaries, namely attention to the racial and ethnic backgrounds, comorbidities, gender, age, and disabilities within the user population. Criteria 10: “Objective Success Criteria” does not define the objective thresholds for all studies to meet, but notes that sponsors will establish an evidentiary threshold for primary outcomes with CMS and AHRQ. This engagement will add an element of certainty that the primary outcomes for CED studies are the most appropriate and relevant for answering the CED research question. Additionally, criteria 14: “Reporting” lays out a timeline for when final results must be submitted to publication, as well as potential avenues for publication, which may help sponsors develop an appropriate publication plan and add to framework predictability. CED studies should also be registered with ClinicalTrials.gov for additional transparency, and the statistical analysis plans delivered to CMS, per criteria 3: “Study Protocol.” Publishing the study design and the study results will help inform providers and patients of the risks and benefits of a product or service, as well as indicators of treatment success to better inform decision-making.

The proposed guidance also addresses predictability of the overall CED process. Since the CED policy was first implemented, there have been 26 National Coverage Determinations (NCDs) requiring CEDs. Per CMS’s analysis, only 3 CED NCD topics have had the CED requirement removed following an NCD reconsideration and have received national coverage. According to the most recent updates on the CMS website, there are four NCDs with CED requirements for which no studies have been approved. Accordingly, stakeholders have voiced concerns in the past over the lack of predictability around timing of CED reconsiderations and a lack of definitive ending of CED. A first step towards addressing these issues is defining key study milestones including interim results and study finalization. The proposed criteria 2: “Milestones” will require sponsors to give CMS a plan for key study milestones, which will include results reporting. This plan could include both start and end dates, as well as a final results reporting date. Interim results could help CMS better understand the state of the evidence and allow them to plan for the NCD reconsideration process. Final reporting should initiate a discussion for plan for NCD reconsideration. This will also allow sponsors to have a more precise timeline for long term Medicare coverage.

Recommendation: CMS should require interim results reporting as part of proposed CED criteria 2: “Milestones” to ensure timely reconsiderations and increase pathway predictability.

Allow for Broader Range of Fit-For-Purpose Studies

Past CED studies have utilized a number of different study designs, including both traditional clinical trials and fit-for-purpose designs that analyze secondary use of real-world data (RWD). More traditional studies have ranged from randomized, prospective, multi-blinded designs to prospective, longitudinal, non-blinded designs, depending on the nature of the CED research question and the rigor required to show improvement in health outcomes. Other CED studies have utilized data collected in real-world
settings through CMS-approved registry data\textsuperscript{9,10,11} and analyses of claims data.\textsuperscript{12,13} Thus, CMS has been moving towards using FFP study designs and data sources to address CED questions.

The CED proposed guidance could encourage a broader range of FFP studies leveraging RWD sources. Depending on the research question, studies leveraging RWD may be an effective avenue for answering evidence questions for CED. This proposed CED guidance includes criteria that may make it easier to design studies that capitalize on existing data sources, such as Medicare claims or electronic health records. As cited by the AHRQ analysis of CED criteria,\textsuperscript{14} the Duke-Margolis framework for regulatory use of real-world evidence states that RWD must be valid, high-quality, reliable, and relevant and to be conclusive. To this end, proposed criteria 5: “Study Design” is flexible enough to allow for FFP studies that utilize any type of RWD to fill evidentiary gaps, so long as the study generates valid evidence to infer causal inference. The data also must meet the threshold for data quality as required by the CED research question (11: “Data Quality”). It will be important for CMS to work with study sponsors to clarify expectations for the various aspects of quality highlighted in the “Data Quality” criteria. Sponsors must show CMS how the data collected or gathered from existing sources will be valid and contribute to a better understanding of identified health outcomes of interest (12: “Construct Validity”). Finally, the proposed criteria that requires data to come from expected sites of care when applicable (8: “Care Setting”) will help contribute to the relevance of the RWD to Medicare intended users.

**Accelerate Beneficiary Access to New Items and Services**

The proposed guidance may help extend access to underserved populations, which supports CMS’s mission to advance health equity. While traditional trials may offer ideal conditions for determining causal inference, they often have smaller sample sizes, are shorter, and have strict enrollment criteria. RWD over a larger, more diverse cohort can provide key insights into what constitutes “appropriate” use of a product by allowing investigators to observe how a product performs in different patient populations, with different provider experience or site capacity. The proposed criteria requires study populations to reflect the demographics of the intended Medicare users (6: “Study Population”), and study sponsors will be required to consider and discuss the subpopulations and underrepresented groups in the study, how the enrollment criteria will affect trial diversity, and plans for population retention (7: “Subgroup Analyses). Both of these criteria will not only help CMS have confidence that the study data is generalizable to the intended users and help determine the proper context of care for the item or service, but also potentially expand item or service access to populations that may not otherwise be included.

The proposed criteria may likely increase the predictability and transparency of the CED process, which could accelerate beneficiary access to new items and services. Future guidance on the types of RWD and data collection methods that CMS finds most rigorous will further help inform CED study design and objectives, which will allow manufacturers to begin earlier planning for post-market studies that would support Medicare coverage. Efforts to accelerate beneficiary access to new items and services may benefit from early and sustained engagement between CMS, manufacturers, and other stakeholders engaged in evidence generation that can support CED. Sponsors may need additional CMS guidance on outcomes of interest, study duration, and data collection efforts to design an effective study that would address CED questions. Early engagement between CMS, sponsors, FDA, and other stakeholders may enable CMS to more efficiently identify the evidence gaps relevant to Medicare beneficiaries. This will then have an effect on criteria 4: “Study Context,” which requires that CED studies have rationales
supported by available scientific evidence, which may be supplemented by engagement with providers, specialty societies, or data experts. Earlier multi-stakeholder engagement will also assist with developing primary health outcomes of interest and thresholds that can demonstrate clinically meaningful differences (9: “Health Outcomes;” 10: “Objective Success Criteria”). Finally, earlier engagement between FDA, sponsors, and CMS may help prevent overlaps and duplication in CED and post-market evidence collection efforts.

**Recommendation:** CMS should clarify when there is a scope for multi-stakeholder engagement to identify outcomes of interest or align on CED research questions and study design.

### Future Directions for Supporting Proposed CED Guidance

CMS appears to be incrementally moving towards a CED framework that utilizes FFP study designs, reflecting the advancing methods for collecting and utilizing RWD and RWE. Accordingly, CMS has indicated that there is forthcoming guidance on FFP studies. CMS states that CED studies should be as rigorous as possible, employing a study design and using data sources appropriate to answer the research question, whether by developing a randomized controlled trial, utilizing advanced study designs to simulate randomization with an active comparator (for example, compare to current standard of care). CMS also notes that studies should minimize confounding and bias. While the CED proposed guidance may help investigators design FFP studies to answer CED research questions, additional specificity in forthcoming FFP study guidance could ensure that studies meet CMS’s standards for study rigor to increase the degree of confidence that CMS can derive from study results while capitalizing on secondary uses of RWD. Additional guidance on the types of FFP study designs, types of data, and data collection methods that CMS would find most rigorous, as well as the outcomes of interest in different disease areas will provide additional transparency and predictability to the framework.

The success of this proposed CED guidance document will also depend on the strength and thoroughness of Clinical Endpoints Guidance for specific disease areas. Concurrent with the CED proposed guidance, CMS published a proposed Clinical Endpoints guidance document which illustrates, using Knee Osteoarthritis as an example, how CMS evaluates clinically meaningful endpoints and their clinically meaningful differences in specific disease areas. CMS has indicated they will publish different clinical guidance documents for different diseases areas. The availability of clinical guidance would favorably impact the extent to which a study sponsor could design a CED study. In particular, the effectiveness of proposed criteria 4: “Study Context” and 9: “Health Outcomes” are going to be highly dependent on whether there is published CMS guidance on the current state of the evidence for a particular disease space and the endpoints that can fill evidentiary gaps within that space. Criteria 4 states that “The rationale for the study is supported by scientific evidence and study results are expected to fill the specified CMS-identified evidence deficiency and provide evidence sufficient to assess health outcomes.” Criteria 9 then outlines that health outcomes for the study must be “important to patients and their caregivers [and] clinically meaningful.” These CED proposed criteria are indicative of the interaction with the forthcoming Clinical Endpoints guidance documents.

**Recommendations:** CMS should provide specific guidelines and examples on the types of data generation strategies, data sources, and study designs that support CMS Medicare coverage in future fit-for-purpose guidance. Accordingly, CMS should clarify how CMS will evaluate specific CED study designs relative to
related guidance on clinically meaningful endpoints for that disease area and applicable data generation strategies, data sources provided from the forthcoming FFP guidance.

The CED proposed guidance aims to provide more clarity around the process that will be needed to support predictable, timely, and productive interactions between CMS, manufacturers, and investigators to meet CED expectations. With the growing pace of novel technologies, the ratio of CED to total coverage decisions continues to increase, and the number of interactions needed to reach consensus on the types of evidence that would support fit-for-purpose studies increases, CMS will need more resources to engage with sponsors and provide guidance on important outcomes of interest. Any new CED criteria will have the greatest impact if accompanied by steps to ensure adequate resources and capacity for CMS for implementation. CMS could leverage additional resources to work with other agencies and subject matter experts to discuss evidence needs and the types of trial designs that would most effectively and efficiently answer evidentiary questions for a given product. This would allow for an earlier understanding of the types of evidence infrastructures needed to develop evidence for coverage, making it easier and less costly to develop the necessary post-market evidence. We believe the resource requirements to support expedited coverage and the new CED criteria will be modest relative to their impact on innovation and Medicare patients’ health outcomes.

**Recommendation:** Increase CMS resources and capacity to support Medicare coverage activities including implementing the CED proposed guidance and guiding evidence generation for novel technologies.

**Conclusion**

The Duke-Margolis Center supports the CED proposed guidance and encourages CMS to consider the importance of additional elements that encourage transparent and predictable early engagement between stakeholder and encourage innovative study designs and CED approaches. Adequate resourcing will ensure CMS is equipped to support these changes and ensure the impact of the proposed guidance are all the more effective. The Duke-Margolis Center appreciates CMS’s consideration of our comments, and the Administration’s support for advancing high-value, affordable healthcare.

Sincerely,

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References


7 LivaNova, “A Prospective, Multi-Center, Randomized Controlled Blinded Trial Demonstrating the Safety and Effectiveness of VNS Therapy® System as Adjunctive Therapy Versus a No Stimulation Control in Subjects With Treatment-Resistant Depression,” Clinical trial registration (clinicaltrials.gov, September 2, 2022), https://clinicaltrials.gov/study/NCT03887715.

8 Medical College of Wisconsin, “A Multi-Center Biologic Assignment Trial Comparing Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients With Intermediate-2 & High Risk Myelodysplastic Syndrome (BMTCTN1102),” Clinical trial registration (clinicaltrials.gov, March 1, 2023), https://clinicaltrials.gov/study/NCT02016781.


