Comment on CMS Coverage with Evidence Development Proposed Guidance Document

Submitted by:
Maryam Mooghali MD, MSc
Osman Moneer, BA
Nikhil Chaudhry, BA
Reshma Ramachandran, MD, MPP, MHS
Yale Collaboration for Regulatory Rigor, Integrity, and Transparency (CRRIT)
Yale School of Medicine

INTRODUCTION

Thank you for the opportunity to comment on the proposed guidance document for coverage with evidence development (CED). We are members of the Yale Collaboration for Regulatory Rigor, Integrity, and Transparency (CRRIT), an interdisciplinary initiative aligning research on medical product evaluation, approval, and coverage toward advancing policies that improve patient outcomes. On behalf of CRRIT, we commend CMS for developing the proposed guidance document, which comprehensively details the several factors CMS considers in making National Coverage Determinations (NCDs) using the CED paradigm. We found many points of agreement with the proposed guidance document, particularly in its emphasis on leveraging CED to expand patient access to promising technologies that would not otherwise meet the "reasonable and necessary" coverage standard, while requiring the generation of evidence that addresses specific areas of uncertainty identified in National Coverage Analyses. In our comments below, we offer suggestions to further clarify and strengthen the CED process in order to achieve its intended goal of ensuring robust data collection critical to patients and clinicians as well as CMS in determining whether coverage should be broadened for medical products when residual uncertainty is present at the time of FDA approval.

Section II – Purpose of this Proposed Guidance Document:

CMS has stated that "beneficiary participation in a CED trial is completely voluntary" such that beneficiaries must participate in an approved CED study in order to receive Medicare coverage for the medical product in question under the NCD. We recognize that Medicare patients who participate in these CED studies should participate knowingly with informed consent. However, we also believe that to enable the successful implementation of CED, CMS should help further facilitate study recruitment and ensure robust data collection to confirm that a promising item or service is reasonable and necessary for Medicare coverage.

Section V: Principles governing the application of CED

CMS has outlined several apt and specific principles around the application of CED including that "CED will require the generation of evidence that addresses specific evidentiary deficiencies identified in National Coverage Analyses." We would amend this principle to state that "CED will require the *timely* generation of evidence that addresses specific evidentiary deficiencies identified in National Coverage Analyses," thus signaling that data from approved CED studies will be made readily available such that CMS can re-evaluate its NCD with emerging evidence.

Additionally, CMS has stated that "CED will not duplicate or replace the FDA's authority in assuring the safety and effectiveness of drugs, biological products, and devices." However, while CMS will make its independent assessment as to whether a medical product is "reasonable and necessary" in its NCD, CMS should collaborate with the FDA to align CMS CED requirements and FDA's postmarketing requirements,[1] thus minimizing manufacturer burden and increasing the likelihood of CED and postmarketing studies being completed in a timely manner. Moreover, as with the Parallel Review program with medical devices that allows FDA and CMS to provide feedback on clinical trial designs and simultaneously review the pivotal clinical trial data before any regulatory decisions are made,[2] CMS could expand such a program to drugs and biologics to provide earlier clarity to sponsors around what evidence should be collected in clinical trials to also inform coverage decisions.

Section VI: Clinical Study Standards for CED under Section 1862(a)(1)(E)

CMS has proposed that it will expect sponsors or study sites to sign an agreement for voluntarily participating in a specific CED study under the NCD. We believe that these agreements between the agency and the stakeholders should be publicly available on CMS's website. As a part of the signed agreement, sponsors and study sites should also submit publicly available annual reports regarding the status of the CED study. If the sponsor or study fails to make these reports available, CMS should consider ending the CED and, thus, rescinding coverage of the medical product. Should sponsors or study sites wish to make changes to the protocol after the commencement of the CED study, the agreement should stipulate that they will publicly notify the CMS about the changes.

Milestones

CMS has proposed a written plan that describes the schedule for the completion of key study milestones, including results reporting. We believe that other key milestones, including study initiation, enrollment progress, and interim results reporting, should also be clearly described in the written plan. We recommend that sponsors or study sites provide updates and report outs of the status of the CED studies annually. Moreover, should sponsors or study sites wish to make changes to the schedule after the commencement of the CED study, CMS should ensure that the new timeline will be appropriate for fulfilling the NCD, and the change should be publicly announced within no more than 30 days of the CMS's decision.

Study design

CMS has proposed certain flexibility in terms of study designs. We believe that this flexibility could create challenges for conducting comparative analyses of key clinical outcomes across studies. Therefore, to ensure robust data collection across all CED studies, CMS could provide more guidance around the CED study design standards, as included in the Proposed CMS National Coverage Analysis Evidence Review,[3] and delineate the occasional situations where lower-quality study designs (such as observational or single-arm studies) may be allowed. For example, CMS has suggested that certain studies may not include contemporaneous comparison groups. In these cases, the agency should clarify how sponsors should leverage alternative data sources (e.g., historical controls) to conduct appropriate comparative efficacy and/or safety analyses and why these designs ensure sufficient rigor to determine benefits and harms in Medicare beneficiaries. In addition, there should be a detailed description of approaches that aim to minimize bias in both interventional and observational study designs. Moreover, given that a considerable portion of CED-approved studies are registries, CMS could clarify certain situations where registries are appropriate and identify specific criteria that could improve the quality of the evidence generated by registries. Moreover, should sponsors or study sites wish to make changes to the study design after the initial agreement, CMS should ensure that the new study design will be appropriate for fulfilling the NCD, and the change should be publicly announced within no more than 30 days of the CMS's decision.

Study population

To facilitate recruiting more generalizable study samples, CMS has proposed that study populations should reflect the demographic and clinical diversity, in terms of several factors including "relevant social determinants of health", among the Medicare beneficiaries. We believe that more clarity around "relevant social determinants of health" is needed. In addition to considering factors of racial and ethnic background, gender, age, disabilities, and comorbidities among the Medicare population, CMS could consider the diversity of geographic location (i.e., urban, rural, suburban) among beneficiaries. CMS often has certain criteria for CED studies, in terms of the eligible facilities or personnel providing the covered item or service to beneficiaries, which may create additional barriers to care access for patients not living in areas with those

eligible facilities or appropriate personnel and thus, could impede representative enrollment for the CED study. We recommend that sponsors and study sites provide plans for enrolling representative populations, including patients living in rural locations, as a part of the study agreement. CMS also could provide further guidance and assistance to define and ensure adequate representation within these studies.

Health outcomes

CMS has proposed that a validated surrogate outcome may be appropriate for some questions. We believe that CMS should clarify (1) the level of evidence sufficient for CMS to consider the surrogate outcome to be validated and whether this would be consistent with the FDA definition and (2) the specific indications in which surrogate outcomes are allowed to be used. Furthermore, we believe that the primary outcome(s) of the study should be pre-specified to ensure that the study fulfills the intent of the CED in determining whether the product is reasonable and necessary. CMS should also encourage sponsors to avoid changing the outcomes later in the process and, as noted above, if the sponsor proposes changing the outcomes, this should only be done with CMS's approval to ensure that the proposed new outcome will be appropriate for fulfilling the NCD. Finally, specific health outcomes collected as a part of the CED study should be paired with claims data to enable longitudinal assessments as well as objective measures of outcomes, such as hospitalizations, nursing home admissions, or deaths.

Objective Success Criteria

CMS has proposed that sponsors/investigators will establish an evidentiary threshold for the primary health outcome(s) in consultation with CMS and AHRQ. We believe that this evidentiary threshold for the primary health outcome(s) should be pre-specified. CMS should also encourage sponsors or study sites to not change the evidentiary threshold later in the process. Instead, sponsors or study sites should provide advance notice to the agency so that CMS can provide the necessary guidance that the proposed new outcome will be appropriate for fulfilling the NCD.

Sensitivity Analyses

CMS explicitly states that sensitivity testing needs to be "pre-specified". We believe that this requirement could be applied across the protocol, particularly to the health outcomes collected in the CED studies.

Reporting

CMS has required manufacturers to provide final results within 12 months of the primary completion date. We believe that this requirement could be further strengthened by requiring the submission of participant-level data in addition to the summary-level data as a condition of coverage under CED. Moreover, sponsors and study sites should also report annual results, in addition to final results, to the CMS. Moreover, the submitted data should be independently verified annually or at the time CMS revisits an NCD.

Sharing

CMS has proposed that the sponsors/investigators commit to sharing data, methods, analytic code, and analytical output with CMS or with a CMS-approved third party. We believe that CMS should have access to beneficiary-level data from all CED studies as part of the agreements with sponsors.

Section VII: Importance of Control Groups and Blinding in CED Studies

CMS has emphasized the importance of control groups and blinding in CED studies and has recognized that having control groups or blinding is not always feasible. We agree with the importance of including active control groups and blinding[4,5] and believe that further clarifications are needed regarding the situations where single-arm or open-label studies are allowed. Moreover, for cases with uncertainty about safety and efficacy among Medicare beneficiaries, such as when FDA approval was based on a trial population that was not representative of Medicare beneficiaries, CMS should encourage the inclusion of control groups and blinding as part of CED studies to ensure rigorous evidence generation.

Section VIII: Ending CED

CMS has provided guidance regarding ending CED when the evidence generated through CED studies supports a favorable coverage decision. We believe that further guidance is necessary for situations where the results of studies could not confirm the expected benefits (e.g., if the outcomes are negative or if sponsors do not report the interim results according to the agreement). In these cases, CMS's authority for ending the coverage of these products should be clearly stated. Moreover, CMS has proposed that the NCDs will be revised once the study results are published. Since there could be a significant lag from study completion to peer-reviewed publication of the results, we believe that CMS should instead consider revisiting their coverage decisions in a more timely manner, based on the data submitted by the manufacturers upon study completion. Additionally, the evidence generated through CED may raise additional questions about harms and benefits that were unanticipated when the CED decision was initially made (i.e., at an early stage of familiarity with a given item or service). CMS should acknowledge that CED may need to be modified or extended to address these new open questions.

Section IX: Transparency of CED

CMS has proposed several efforts to improve the transparency of CED, including that the results of all CED studies will be published in the public domain, preferably in peer-reviewed journals. We believe that in cases where sponsors do not publish their results upon study completion, CMS should publicly publish their evaluation of any submitted data for re-evaluation of the coverage decision. Moreover, there is a need for a more comprehensive publicly available database where all the items and services covered under the CED program are listed, even after CED coverage is removed. Thus, the current CMS's CED webpage could be improved by including

a separate section listing the products that have previously been covered under the CED program. The database should include all updated decision memos and CED-approved studies to enhance transparency and facilitate data gathering and analysis for research purposes.

References

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