CMS National Coverage Analysis Evidence Review

Proposed Guidance Document, Issued June 22, 2023

Summary of Comments Received (received June 22, 2023 – August 21, 2023)

CMS received 16 comments on the proposed guidance posted on June 22, 2023. This Appendix to the final guidance summarizes and responds to the major themes of the public's comments. Comment sources included eight device manufacturers, two trade associations, one commercial real-world data analytics company, three advocacy organizations (one organization sent two sets of comments), and a nonprofit research organization. In general, commenters appreciated CMS' efforts to "provide a framework for more predictable and transparent evidence development." Most commenters requested greater clarity on some aspects of the guidance and requested that CMS provide greater flexibility.

GENERAL SUPPORTIVE COMMENTS

Comments: The nonprofit research organization reviewed all sections of the NCA Evidence Review guidance document and expressed support for fundamental principles and priorities throughout all sections of the document. The real-world data analytics company generally supported the methodological principles outlined in the coverage document. Six device manufacturers expressed eagerness to receive the forthcoming fit-for-purpose (FFP) studies guidance document referenced in the Transitional Coverage for Emerging Technologies (TCET) notice.

> Response: CMS appreciates the supportive feedback and looks forward to issuing and receiving public comment on the forthcoming proposed guidance regarding FFP studies.

CONCERNS

Methodological Principles

Comment: One commenter considered guidance limited to a "broad framework of the issues we consider when reviewing the clinical evidence" insufficiently helpful if, as the document states, "each NCD has its unique methodological aspects." The commenter also requested an explanation of the rationale for the evidence questions that guide each NCA and clarification of what constitutes "sufficient" evidence. One real-world evidence company objected to the listing of "reporting bias" among examples of internal validity and offered substitute language.

> Response: The general principles outlined in the guidance document must be applied thoughtfully to each NCA because the necessary evidence may vary considerably. The most robust study designs may not be feasible for some technologies and health conditions. Criteria for applicability or generalizability to the Medicare population will depend on the health condition. Long-term follow-up will matter more for some technologies and health conditions than others.
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> 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 Social Security 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 making coverage determinations, CMS policies

have long considered whether the item or service is not just safe and effective but also whether the item or service is not experimental or investigational and is appropriate for Medicare beneficiaries.[1] While we appreciate the commenter's request for more specificity, describing all potential variations in the application of the principles outlined in the guidance document is not possible because of the breadth of items and services that may be subject to CMS review.

CMS has revised the guidance to clarify the distinction between assessing the internal validity of individual studies and publication bias in a body of evidence.

Review of Individual Studies

Comments (unpublished studies): Four device manufacturers urged CMS to limit its systematic reviews of the evidence to studies published in the peer-reviewed literature. Others suggested that completed but yet to be published studies and analyses may be presented to CMS and should be included as milestones in the Coverage with Evidence Development (CED) process.

Response: CMS follows an open and transparent process when conducting NCAs, and the public has at least one opportunity (and often two) to submit comments before an NCD is finalized. CMS understands that not all potentially relevant evidence resides in the peer-reviewed literature. As stated in the NCA Evidence Review Guidance Document, "high-quality findings from other *publicly reported* results, such as pre-market studies that supported FDA market authorization, may also be used." To make a meaningful comment, the public must have access to the evidence considered in an NCA. Since public reporting generally entails peer review and acceptance or rejection by an entity without a vested interest in the CMS coverage decision, this provision also contributes to the objectivity of the NCA process.

Comments (more clarity needed on types of evidence required): Some device manufacturers and the real-world evidence company requested more explicit guidance on CMS' requirements of the evidence. One commenter noted that the guidance document does not mention specific analytic methods that can justify causal inference in observational studies, e.g., instrumental variables and regression discontinuity design, and methods such as sensitivity analyses for assessing the potential effect of unobserved confounders. One commenter pointed out that observational studies can be especially useful for showing the impact of device iteration and operator learning curves.

Another commenter found the following assertions in the guidance document to be confusing: that 1) randomized controlled trials (RCTs) are generally the most credible sources of evidence, but 2) observational studies may more accurately reflect clinical practice and answer questions that RCTs cannot answer, and 3) CED observational studies may have higher credibility because of consultation with the Agency for Healthcare Research and Quality (AHRQ) and CMS before study execution.

Response: CMS appreciates the reference to specific analytic methods that can be used in observational research to correct the lack of randomized treatment assignments. The proposed and final guidance documents state, "New study design approaches and analytic techniques that handle bias continue to evolve and may improve the reliability and validity of observational study results. FFP [fit-for-purpose] observational studies aim to emulate the strengths of RCTs by

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[1] For more information see the CMS Program Integrity Manual, Chapter 13.5.4, available at https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/pim83c13.pdf.

taking advantage of these newer approaches and techniques." Discussion of specific approaches and techniques is reserved for a separate forthcoming guidance document on FFP studies.

Drugs and devices often have distinctive evidence development requirements. CMS agrees that devices are often iteratively refined aftermarket, and there may be a learning curve for furnishing providers. Both of these factors illustrate how observational studies can supplement the premarket evidence base as new devices become more widely used outside of tightly controlled clinical studies.

CMS has added clarifying language about the value of RCTs versus observational studies in the final guidance document. The guidance document also describes the kinds of evidence that may be given greater weight for different questions according to well-established criteria for evaluating clinical and epidemiological research. CMS has clarified in the final guidance that traditional RCTs may demonstrate benefits and harms of an intervention under ideal circumstances. At the same time, various kinds of postmarket studies may be needed to address evidence gaps that conventional clinical studies may be unable to address. CMS has also added language to clarify that CED observational studies may also achieve high standards of credibility through a review of study proposals with AHRQ and CMS before study execution, complete transparency of the study protocol, faithful execution, and clear public reporting of results. Additional information on CED, including CMS' response to public comments on CED, can be found in the CED guidance document.[2]

Comments (methodological challenges): Many commenters referred to the practical challenges of conducting methodologically rigorous RCTs for devices. For example, in some cases, blinding may not be possible, and sample size may be limited in circumstances where the eligible clinical population is small (as with rare disorders) or procedures occur in low volume. Commenters also cited challenges in interpreting results from RCTs involving patients with heterogeneous and progressive diseases. One commenter objected to the provision for multiple studies with findings in the same direction (reproducibility), given the difficulties associated with conducting a single rigorous study. Another commenter asserted that patients with rare diseases and few treatment options would be satisfied with greater uncertainty about the benefits and harms of a promising treatment.

Response: In general, the Medicare statute bars payment for items and services that are not reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member. When assessing whether items and services are reasonable and necessary, CMS considers the totality of the evidence, which may include fit-for-purpose studies that demonstrate the performance of items and services in real-world use. CMS has revised the guidance to clarify that NCAs generally seeks the most robust feasible study designs that may establish the benefits and harms of an item or service for the intended Medicare population.

CMS recognizes that ideal study designs are impossible for some technologies and health conditions. Regardless of study design, disease characteristics may preclude a straightforward

[2] CMS' guidance documents can be accessed here: https://www.cms.gov/medicare-coverage-database/reports/national-coverage-medicare-coverage-documents-report.aspx?docTypeId=1&status=all

interpretation of results. These factors are accounted for when conducting individual NCAs but do not change the principles that govern a strength of evidence evaluation broadly.

Comments (requirements for devices versus medications): One trade association stated that CMS requires more substantial evidence for devices than medications.

Response: CMS strongly disagrees with this assertion but notes that drugs and devices often have distinctive evidence development requirements. As noted previously, devices are often iteratively refined aftermarket, and there may be a learning curve for furnishing providers and institutions; both factors may have important impacts on the risks and harms of treatment. These postmarket changes generally cannot be addressed in premarket studies.

Comments (methods for evaluating rare disease studies): One organization cited several publications on assessing studies of treatments for rare diseases, primarily for developing practice guidelines, and encouraged CMS to consult this literature. Another organization referred to the Heart Act and its encouragement of FDA to consult experts on the science of studies in small populations.

Response: CMS appreciates these comments on unique methods for research in rare disease populations. CMS has added language in the final guidance to clarify considerations for planning and evaluating research in rare disease populations. CMS has commented elsewhere in this document (Applicability/External Validity) on the representation of patients with rare disorders in clinical studies. We do not address the comment that references the Heart Act as it is beyond the scope of this guidance.

Risk of Bias:

Comments (noncomparative studies): A device manufacturer, a trade association, and an advocacy organization maintained that in some circumstances, non-comparative sources of data such as single-arm trials or registries might be adequate for determining whether a device is reasonable and necessary.

Response: The commenters are correct in pointing out that non-comparative studies can usefully contribute to the evidence base for an item or service. The guidance document acknowledges this point in the section on Evaluating the Quality of the Evidence. The guidance notes "While non-comparative studies may not be as useful, they may help demonstrate that treatments can be provided safely in particular settings, and they may allow for longer-term follow-up than is often possible in RCTs." Nonetheless, studies with an active comparator are often necessary to credibly establish a causal relationship between a treatment and improved health outcomes. CMS has added a sentence that clarifies the role of non-comparative studies in the guidance document's discussion of the risk of bias. CMS states that "once effectiveness and safety have been demonstrated through comparative studies, case series and single-arm studies may provide supplemental information on issues such as the absolute frequency of rare adverse events or the durability of a device."

Precision of Estimates:

Comments (power analyses): One device manufacturer recommended that CMS defer to best practices when evaluating effect estimates because power analyses may not always be appropriate, particularly in nonrandomized studies using real-world data.

Response: The commenter is correct that in some real-world studies, neither an a priori power analysis nor a prespecified sample size is appropriate. Nonetheless, CMS recommends an a priori power analysis, where feasible, to estimate the time required to complete a study with adequate precision to address the research question posed. Coverage decisions consider the precision of effect estimates, not whether or not a power analysis was performed. CMS has clarified this point in the finalized guidance document by stating that "CMS recommends that proposals for studies with a comparison group include a power analysis where feasible and appropriate in order to increase the chances of precise estimates of benefit or harm. However, CMS' ultimate evaluation of the evidence takes into account the precision of findings, not whether a power analysis was conducted."

Comments (GRADE system): One device manufacturer recommended that the GRADE system be used only when robust pooled estimates are possible.

Response: CMS notes that the precision of estimates principle of the GRADE system is most readily applied to bodies of evidence where studies use homogeneous measures for assessing the outcomes of interest and pooled estimates through meta-analysis are possible. Even so, the concept can be applied when evaluating the overall evidence without pooled estimates.

Comments (industry sponsorship): While acknowledging that potential conflicts of interest and funding sources should be acknowledged and managed, five device manufacturers objected to the notion that industry-sponsored research might be automatically considered lower-quality evidence.

Response: CMS appreciates these comments. The guidance states that "CMS carefully considers both the funding source and potential conflicts of interest for study investigators." It does not imply that industry-sponsored studies are necessarily of lower quality in terms of methodological rigor or study execution. However, CMS sees the potential that the source of funding or conflicts of interest among investigators might influence the parameters of an investigation, i.e., the populations and clinical settings, the outcomes to be measured, and the duration of follow-up. CMS' various guidance documents are meant to help avoid the potential for evidence gaps by clarifying the study populations, settings, and outcome measures that are considered to be the most relevant to Medicare coverage decisions.

Applicability/External Validity

Comments (generalizability to Medicare beneficiaries): All advocacy organizations expressed concerns about applicability/external validity. One submitter requested a definition of "representative" in the context of applicability to the Medicare population and another requested that it not be a default assumption that the benefits of a therapy would differ between Medicare beneficiaries and other populations. Some submitters pointed to the difficulties in recruiting patients with rare disorders who are also eligible for Medicare, not only because clinical populations are small but also because these individuals often have disabilities that interfere with their ability to travel to trial centers. Others referred to the "inherent heterogeneity of the diseases" that can "often confound results and endpoints."

Response: When making coverage determinations, CMS policies have long considered whether the item or service is not just safe and effective but also whether the item or service is not

experimental or investigational and is appropriate for Medicare beneficiaries.[3] When making this determination, CMS generally requires that evidence from clinical studies apply to the intended recipients of the Medicare population(s). Applicability assessment depends on whether a new technology's effectiveness would reasonably be expected to vary between the populations studied in clinical trials and Medicare recipients, who are often older and have more comorbidities.

CMS recognizes that it may not be possible to recruit enough patients with the same disorder to achieve statistical power because of the rarity of the disorder. When that is the case, study groups should represent the mix of patients a device is intended to help.

Comments (pivotal trials versus studies in community settings): One advocacy organization referred to the document's "derogation of the nature of clinical trials" in describing the factors that might lead to different results from those achievable in community settings. The submitter describes the care given in these pivotal trials as "high quality."

Response: CMS recognizes the importance of early clinical trials that are intended to demonstrate evidence of the safety and effectiveness of interventions under the ideal conditions of clinical trials. However, CMS notes that the balance of harms and benefits in real-world use may differ. In some instances, CMS requires additional evidence to demonstrate how potential benefits and harms are observed in real-world use.

Comments (follow-up and surrogate endpoints): Some commenters asserted that short-lived benefits and surrogate outcomes (rather than health outcomes) may be meaningful for patients with terminal illness or severe illness, especially when there are no other good treatment options.

Response: CMS agrees that meaningful study endpoints might differ from those for other populations in studies involving patients with terminal illness and short life-expectancy. Nonetheless, in general, there are many instances in which studies that have relied on short-term follow-up and intermediate outcomes have failed to ultimately demonstrate improved health outcomes in subsequent studies. CMS believes that the CED pathway may be valuable in extending early access to such treatments while further evidence of improved health outcomes is generated.

Strength of Evidence Assessment

No concerns specific to this section of the guidance document were expressed.

Other Comments Unrelated to Document Headings

Comments (statistical methods): One device manufacturer requested that the document include CMS' view of the Finkel-Schoenfeld method of creating hierarchical composite endpoints, which creates greater statistical power for smaller sample sizes but prioritizes the components of the endpoint according to clinical importance. This commenter also asked that CMS comment on Bayesian statistics.

[3] For more information see the CMS Program Integrity Manual, Chapter 13.5.4, available at https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/pim83c13.pdf.

Response: CMS understands the commenter's desire for guidance on these specific statistical issues. A detailed discussion of these particular statistical methods is beyond the scope of this guidance document, which was meant to provide an overview of general principles. However, CMS will consider addressing these methods in future guidance.

Comments (various data sources): One device manufacturer asked about CMS' view of using claims data to establish a control group for studies within the proposed Transitional Coverage for Emerging Technologies (TCET) pathway, either as an adjunct to other data collection methods or as a sole means of data collection. One trade association urged CMS to consider real-world evidence and patient-reported outcomes.

Response: To address any evidence gaps for coverage purposes that persist at the time of FDA market authorization, CMS recognizes the potential value of claims data, alone or in combination with other real-world data sources, in generating evidence to address important research questions. However, CMS endorses the concept that CED studies must be fit-for-purpose, that is the study design, analysis plan, and study data must be appropriate to address the research question. Administrative claims alone include a limited range of patient characteristics and outcome measures, and patient reported outcome measures are rarely available unless data are intentionally collected. We intend to provide more information on acceptable use of real-world data in a future fit-for-purpose study proposed guidance document.

Comments (coverage process clarification): One device manufacturer and one advocacy group expressed a strong desire for CMS to outline the process and timelines that could be expected for the completion of an NCD or a CED NCD, similar to the process and timeline details that were provided for the proposed Transitional Coverage for Emerging Technologies (TCET) pathway. One commenter also requested clarification regarding opportunities for a coverage requestor to consult with CMS or CMS' third-party reviewers about the clinical evidence during the NCD process.

Response: The NCA Evidence Review Guidance articulates the principles and process that CMS uses when assessing the strength of evidence to demonstrates that an item or service improves health outcomes for the intended Medicare population(s). A discussion of the process and timeframes for completing an NCD are beyond the scope of this document. More information on the NCD process may be found at 78 FR 48164.

Comments (FDA versus CMS): Several advocacy and manufacturer organizations encouraged greater alignment on evidence requirements between FDA and CMS. One advocacy organization noted FDA's efforts to encourage a more representative mix of patients in pivotal studies through such strategies as decentralized trials improving generalizability; the submitter urged CMS to support FDA in these efforts and for CMS and FDA to standardize their respective requirements.

Response: CMS and FDA have long-standing initiatives intended to enhance collaboration and alignment wherever possible. The proposed new TCET pathway includes plans for enhanced FDA-CMS collaboration for certain FDA Breakthrough Devices. However, CMS and FDA must consider different legal authorities and apply different statutory requirements when making coverage decisions and marketing authorization, respectively. Generally, FDA makes marketing authorization decisions based on whether the relevant statutory standard for safety and effectiveness is met,

while CMS generally makes NCDs based on whether an item or service is reasonable and necessary for the diagnosis and treatment of an illness or injury for individuals in the Medicare population. For coverage decisions, CMS generally looks for evidence of benefit in the Medicare population, which often is older, has more complex medical needs, and is inadequately represented in clinical studies used to obtain FDA market authorization.

Comments (application of guidance to other CMS programs): A real-world evidence company recommended that the principles in the NCA Evidence Review document be applied to other CMS functions and programs.

Response: CMS notes that the NCA Evidence Review Guidance is not specific to any coverage pathway. Instead, the document articulates principles and processes generally applicable to CMS evidence reviews for national coverage determinations.