CMS Coverage with Evidence Development
Proposed Guidance Document, Issued June 22, 2023

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

CMS received 30 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 ten advocacy organizations, eight device or drug manufacturers, three trade associations, two medical specialty societies, one pharmacy professional society, four academic medical centers, one nonprofit research organization that maintains an extensive outcomes registry, and one nonprofit organization. Some comments addressed issues or expressed concerns that were beyond the scope of the proposed guidance and will not be summarized and included in our responses below.

GENERAL FEEDBACK

Comment: Several commenters representing different perspectives expressed support for the goals of the CED paradigm. An advocacy group comprised of physician members agreed with CMS' statutory authority to implement CED for technologies that do not yet meet the reasonable and necessary standard.

Response: CMS appreciates the support for CED.

Comment: A few commenters described the document as being generally consistent with the Agency for Healthcare Research and Quality's (AHRQ) report on "The Analysis of Requirements for CED" and the public comments made at the February 13-14, 2023 Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) meeting where the AHRQ report was presented. Commenters called for strengthening some of the provisions, such as those regarding study protocols, study designs and health outcomes. Many commenters asked for greater clarification of specific issues such as the use of noncomparative studies and CMS expectations regarding validating a surrogate endpoint as a predictor of clinical benefit.

Response: CMS appreciates these comments. We agree that the guidance document is generally consistent with the AHRQ report and was informed by the public comments we received at the MEDCAC meeting. We note that the CED guidance applies to the full spectrum of potential study designs. A detailed description of considerations for study protocols, study designs, and applicable health outcomes is beyond the scope of this CED guidance. CMS expects to publish proposed fit-for-purpose study guidance soon to address many of these concerns in greater detail, particularly for studies that rely on real-world data.

Comment: Organizations representing industry and patient interests had concerns that CED would unduly limit patient access and innovation.

Response: We disagree. Coverage under CED can expedite beneficiary access to innovative technologies while increasing the likelihood of positive health outcomes by ensuring that systematic patient safeguards—including assurance that the technology is provided to clinically appropriate patients—are in place that reduce the risks inherent to new technologies, or to new applications of older technologies.

If the evidence supporting an item or service does not meet the reasonable and necessary standard under section 1861(a)(1)(A), CMS would likely either non-cover the item or service or substantially restrict its use to the limited contexts where the evidence is sufficient to satisfy the reasonable and necessary standard. Under CED, the item or service could be more broadly covered while collecting information to answer key evidentiary questions for patients, caregivers, and their providers.

Comment (statutory authority): A manufacturer, a trade association, two advocacy organizations, and an academic medical center questioned whether CMS has the statutory authority to use CED.

Response: We disagree with the commenters' suggestion that CMS does not have statutory authority to use CED. Congress has established an exception in section 1862(a)(1)(E) that authorizes the Medicare program to pay for items and services in the case of research conducted pursuant to section 1142, so long as the items or services are reasonable and necessary to carry out the purposes of that section. Section 1142(a)(1)(A) authorizes the Secretary, acting through the AHRQ Director, to "conduct and support research with respect to the outcomes, effectiveness, and appropriateness of health care services and procedures in order to identify the manner in which diseases, disorders, and other health conditions can most effectively and appropriately be prevented, diagnosed, treated, and managed clinically[.]" In this subsection the word "support" is not necessarily limited to financial backing. "Support" pursuant to this subsection may also take the form of an appropriate AHRQ endorsement.

Under CED, AHRQ has endorsed and supported research for various items and services that were of particular importance to the Medicare population, but where the existing medical evidence was not sufficient to permit coverage under section 1862(a)(1)(A). AHRQ's endorsement has occurred when AHRQ officials have used staff resources to identify the general characteristics and attributes that are necessary for any Medicare sponsored clinical trial. The general AHRQ recommendations have been included in both the proposed guidance document and our prior CED guidance documents. [1] AHRQ officials have also reviewed each NCD where CED has been proposed or finalized, focusing on the specific methodological approach that would be necessary for coverage in each specific CED NCD. AHRQ's support has been documented and included in the record for each CED NCD. As other commenters have noted, AHRQ has also been substantially involved in reconsidering changes to current CED guidance document. AHRQ has developed a comprehensive report about CED, and recommended changes in the scientific standards to improve the process and to make it more efficient. AHRQ representatives attended the February 13-14, 2023 MEDCAC meeting and recommended additional changes after considering public comments. AHRQ's expertise has been essential to support CED under sections 1142 and 1862(a)(1)(E) of the Social Security Act.

The Department of Health and Human Services (HHS) has recognized that AHRQ's endorsement of standards for qualifying clinical trials under section 1142 can provide the statutory authority

[1] National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development (July 12, 2006); Coverage with Evidence Development (November 20, 2014). https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27

for Medicare coverage for items and services under the Medicare program in circumstances outside of the CED policy. The Medicare clinical trial policy, now established at section 310 of the Medicare National Coverage Determinations Manual,[2] relies on the same statutory authority and has been effective since September 19, 2000.

Subsequently, CMS, then known as the Health Care Financing Administration, requested AHRQ convene a multi-agency Federal group to develop readily verifiable criteria by which to identify trials that meet an appropriate standard of quality. On October 20, 2000, AHRQ held a public meeting to gather pertinent information and views that would contribute to defining the qualifying criteria used to identify sound clinical trials appropriate for Medicare coverage. The qualifying criteria was developed under the authority to support health care research in §1142 of the Social Security Act (Act).

We note that other public commenters have recognized CMS' statutory authority to implement CED.

Comment: Some commenters objected to the guidance document's claim that its "principles for CED studies . . . are supported by the Agency for Healthcare Research," citing an Advisory Opinion from the former General Counsel for HHS that *support* is usually used to mean funding. One commenter asked for clarification of why this particular Advisory Opinion no longer appears on the HHS website with no explanation for the removal.

Response: We acknowledge that an Advisory Opinion from a former HHS General Counsel has been removed from the Department's website as that opinion no longer reflects the agency's interpretation of the relevant statute. Advisory Opinions can be revised, modified, or eliminated as necessary to reflect changing circumstances.

Comment: Some commenters suggested that when CMS issues national coverage decisions using CED, the agency is usurping or duplicating FDA authority. These commenters cited the recent CED NCD for Monoclonal Antibodies Directed Against Amyloid for the treatment of Alzheimer's Disease and recommended that on-label uses of drugs and biologicals be excluded from CED to ensure patient access.

Response: A discussion regarding the specifics of the NCD for Monoclonal Antibodies Directed Against Amyloid for the treatment of Alzheimer's Disease is beyond the scope of this document. However, we do not agree that CMS is usurping or duplicating FDA's important role when we issue an NCD using CED to cover an item or service for Medicare beneficiaries, including for on-label uses of drugs and biologicals. When we find that the medical evidence is insufficient to permit Medicare payment under section 1862(a)(1)(A), we often consider whether an item or service may be clinically beneficial to patients within the Medicare population. The coverage that we provide to beneficiaries that elect to participate in clinical trials through CED does not interfere with FDA's role under that agency's separate statutory authority.

[2] https://www.cms.gov/regulations-and-guidance/guidance/manuals/downloads/ncd103c1_part4.pdf

Comment: Some commenters suggested that through CED, CMS is acting as a research institute and has no mandate to play this role.

> Response: We do not agree with the suggestion that CMS is acting as a research institute when the agency issues an NCD using CED. As noted above, AHRQ plays an essential role in supporting NCDs using CED and establishing the researched methodologies needed for specific NCDs. AHRQ's mission is to produce evidence to make healthcare safer, higher quality, more accessible, equitable, and affordable, and to work within HHS and with other partners to make sure that the evidence is understood and used. CMS is also interested in determining whether items and services would be clinically beneficial for Medicare beneficiaries. Too often, individuals who are older, or disabled are not selected to participate in the initial clinical trials. The evidence developed in CED trials helps to fill the important information gap. One of the guiding principles of CED, however, is that CED will not be used to interfere with NIH's role in fostering, managing, or prioritizing clinical trials. CMS is not an NIH research institute. Still, Congress has recognized that Medicare payment for routine costs in certain clinical trials is important for Medicare beneficiaries. See § 1862(a)(1)(E); § 1862(m). In addition, Congress has authorized the Secretary to make NCDs with respect to whether or not an item or service is covered nationally under Title XVIII. CMS's role in making NCDs is consistent with the agency's statutory authority.

Comment: Several commenters pointed to the CED pathway's history of achieving additional data collection and noted that CMS reconsidered CED NCDs in only a few instances.

> Response: CMS and AHRQ have made iterative refinements to the CED coverage pathway over time, and while we believe CED has reduced barriers to innovation and expanded beneficiary access to new technologies and therapies, our experience over the last several years indicates that further improvements can be made to the CED process. Working in conjunction with AHRQ, our goal is to improve CED so that it fulfills its potential as a mechanism that simultaneously reduces barriers for innovation and enables CMS to make better informed decisions on coverage for medical devices that improve health outcomes for Medicare beneficiaries. We believe it is essential to provide a more predictable and transparent approach to facilitate evidence development. Our updates to the CED guidance document, the NCA Evidence Review guidance and the Clinical Endpoints guidance are some of the first steps we are taking to provide a more predictable and transparent evidence generation framework that, when appropriate, not only develops reliable evidence for patients and their physicians to make health care decisions but also provides safeguards to ensure that Medicare beneficiaries are protected and continue to receive high-quality care.

COMMENTS ON SPECIFICS OF THE GUIDANCE DOCUMENT

Background

Comment (sufficiency of early studies): Some comments from the device or drug manufacturing perspective challenged the guidance document's statement that "For new technologies, it is rare that there is sufficient clinical evidence to support broad national coverage under section 1862(a)(1)(A)" and asked that the statement be amended to state that *some* new technologies have insufficient evidence to support an NCD. However, one academic medical center explicitly agreed with the CMS statement. One

academic medical center and a medical specialty society called for a definition of "sufficient [clinical] evidence" to support national coverage under section 1862(a)(1)(A) of the Act.

> Response: CMS has modified the guidance to state that "New technologies often lack sufficient clinical evidence to support broad national coverage under section 1862(a)(1)(A) of the Act." CMS evaluates the available evidence when assessing whether an item or service satisfies the reasonable and necessary standard for coverage under 1862(a)(1)(A) of the Act.[4] We have found that sufficient evidence is often not available to support national coverage for Medicare patients when novel technologies first receive market authorization.

V. Principles governing the application of CED

Comment: An academic medical center recommended revising one of the guiding principles to add the word "timely" before "generation of evidence."

> Response: We are exploring options to ensure timely evidence generation. The Transitional Coverage for Emerging Technologies (TCET) pathway illustrates one new approach to time-limited CED that we believe will help to achieve that aim.[5] Although we aspire to generate timely evidence, CED trials may take time, so we are not adding the word "timely" to this principle.

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

Comment (voluntary participation): Several commenters, specifically advocacy organizations, device/drug manufacturers, and trade associations questioned the statement "participation in CED studies is voluntary both for beneficiaries and trial sponsors and participating study sites" since a CED NCD requires that study sponsors provide the technology only in the context of CED studies and patients receive the treatment only by participating in CED studies.

> Response: Items and services may be covered through a CED NCD when they do not satisfy the reasonable and necessary standard required for coverage under 1862 (a)(1)(A) and therefore have no Medicare coverage. CMS may cover certain items and services under the CED pathway that would otherwise not satisfy the reasonable and necessary standard because they are covered in the context of a CMS-approved clinical study. Receipt of an item or service under a CED NCD is voluntary.

Comment: One commenter claimed that CMS' reliance on Institutional Review Board (IRB) oversight was insufficient to protect the rights of patients participating in CED studies. This commenter stated that CED should be subject to the Federal Policy for the Protection of Human Subjects (Common Rule) since the individuals who do not participate in the CED studies become "an additional, albeit unintentional and non-consenting 'control' population." The commenter further urged CMS to inform patients that self-pay is an alternative path to access treatment and to create a process allowing patients to appeal CED NCD decisions related to their condition.

---

[4] CMS, Medicare Program Integrity Manual, Chapter 13, 13.5.4, *available at* https://www.cms.gov/regulations-and-guidance/guidance/manuals/downloads/pim83c13.pdf

[5] See 88 FR 41633.

Response: The Secretary has authority to establish human research subject protections under 5 U.S.C. 301; 42 U.S.C. 289(a); and 42 U.S.C. 300v-1(b). The Common Rule defines required research subject protections, including informed consent standards, within clinical studies (45 CFR 46). All CED studies are required to undergo IRB review; this includes a detailed description on the use and source of data sources. IRBs make determinations that research studies are in compliance with the Common Rule and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements See §46.102(h).

The majority of CED studies are observational studies that have no impact on the care received by Medicare beneficiaries. Observational studies that make secondary use of real-world data are generally exempted from informed consent requirements because patient privacy protections are established through the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the risk of participation is *de minimus,* and consent for participation in retrospective analyses is impractical or impossible to achieve. In rare circumstances where a CED study is an interventional study where patients are allocated to a particular treatment, informed consent is generally required for all study subjects.

The Medicare statute does not prevent beneficiaries from paying for any item or service that is not covered. Patients may access care outside of Medicare coverage through self-pay.

Comment (specificity of the guidance): One advocacy organization regarded most of the guidance in this section to be too vague and asked for standard definitions of health outcomes, representative study populations, sufficiency of sample size, adequacy of data, and robustness of results. Conversely, one device manufacturer asked for flexibility in interpreting clinical study standards, given the variability across technologies and their intended uses. One academic medical center asked that CMS prioritize requirements so study sponsors could focus on the most important ones and provide more precise criteria for determining whether studies are "fit-for-purpose."

Response: This guidance document describes characteristics that CMS recommends for CED studies generally. The forthcoming guidance on fit-for-purpose studies will offer more specific recommendations for real-world data studies. In addition to publishing CMS National Coverage Analysis Evidence Review guidance, this CED guidance, and topics in clinical endpoints guidance series, CMS routinely engages with manufacturers to clarify evidence expectations at all points in the product lifecycle. Since each NCD analysis has unique methodological aspects determined by the item and service being evaluated, it is impossible for CMS to provide standard definitions of health outcomes, representative study populations, sufficiency of sample size, adequacy of data, and robustness of results that could apply to every CED study. Additionally, we disagree that the clinical study standards outlined in the guidance document should be prioritized. CMS believes all of the standards are important to ensure that CED studies are designed to answer the evidence questions at hand.

Comment (2. Milestones): Two academic medical centers and one medical specialty society recommended CMS require more granular reporting of study milestones such as study initiation, enrollment progress, *interim* results reporting, and annual progress reports. One device manufacturer

asked CMS to confirm that submission to Clinicaltrials.gov would suffice for the "schedule for completion of key study milestones, including results reporting" as detailed in the CED guidance document.

> Response: CMS appreciates these suggestions to expand the guidance regarding milestones. We have updated the final guidance document by adding study initiation, enrollment progress, and interim results reporting as milestones. The information needed for a Clinicaltrials.gov posting would only partially satisfy the CED Milestones requirement; the more detailed plans needed by CMS will be discussed in early meetings with study sponsors.

Comment: One academic medical center recommended that CMS consider ending CED if the specific reporting conditions outlined in the guidance document are not satisfied.

> Response: We appreciate the comment. CMS can remove CED by reconsidering the NCD. A CED NCD remains in place until it is reconsidered. It is in the manufacturer's best interest to satisfy the reporting standards outlined in the guidance document if they want to continue to receive Medicare coverage for their item/service.

Comment (3. Study Protocol): One of the medical specialty societies and an academic medical center recommended public reporting of all aspects of a planned study, including a prespecified evidentiary threshold for primary outcomes. Another commenter requested that CMS' requirements include a detailed statistical analysis that is publicly available; the commenter recommended that full details on the statistical analysis, along with programming code and data, be submitted with study results. One academic medical center recommended that CMS require study sponsors to report any changes to approved study protocols publicly.

> Response: CMS generally agrees with the concerns reflected in the recommendations. The proposed CED guidance document included registration of the study protocol on Clinicaltrials.gov and publication or some other form of public reporting of the results of studies as general conditions. The final document has been amended to note that any changes to approved study protocols should be explained and publicly reported to ensure adequate public notice.
>
> CMS expects that the *a priori* posted study protocol includes sufficient details of the statistical analysis plan to allow a judgment of whether the study is FFP and whether reasonable efforts will be taken to minimize the risk of bias. This issue has been clarified in the final guidance document.

Comment (5. Study Design): One academic medical center appreciated CMS's recognition that conventional randomized controlled trials (RCTs) have important limitations. One medical specialty society requested that CMS accept data from registries and other real-world data (RWD) types, such as administrative claims. However, one advocacy organization comprised of physician members urged CMS to uphold blinded RCTs as the strongest type of study design and to clarify when single-arm and open-label studies would be acceptable. One academic medical center urged more detail on the appropriate use of noncomparative studies and guidance on minimizing bias in all study designs.

> Response: CMS and AHRQ endorse the concept that CED studies under 1862(a)(1)(E) should be FFP. That is, the study design, analysis plan, and data source(s) must be sufficient to credibly answer the question(s) posed by the CED. Some questions posed in post-market evidence

generation may require an RCT, while others may be addressed through studies that make secondary use of real-world data. The final document clarifies that CMS considers RCTs as the gold standard for minimizing bias but that if previous RCTs have demonstrated efficacy and safety in the specific context of a study, well-designed observational studies may provide complementary information that may address questions that persist after market approval.

CMS' view of the relative strength of different study designs and questions that might be appropriately answered by studies other than blinded RCTs is presented in the CMS National Coverage Analysis Evidence Review guidance. Detailed guidance on observational study designs and techniques for minimizing bias will be included in a forthcoming FFP study guidance document. CMS' guidance documents can be accessed here: https://www.cms.gov/medicare-coverage-database/reports/national-coverage-medicare-coverage-documents-report.aspx?docTypeId=1#.

Comment (6. Study Population): One commenter interpreted the guidance statement "The study population reflects the demographic and clinical diversity among the Medicare beneficiaries who are the intended population of the intervention" to mean that all Medicare beneficiaries with the indication of interest must be enrolled in a clinical study. One academic medical center agreed that the participants in studies submitted for FDA approvals are not representative of the Medicare population and recommended requiring a demonstration of the reasonable and necessary standard for each relevant subgroup.

Response: When reviewing evidence to assess whether items or services are reasonable and necessary, CMS must have a basis to conclude that the available evidence is generalizable to the intended Medicare population(s). The NIH, FDA, and CMS have long stressed the importance of broadly including diverse patient groups in clinical studies. CMS already collaborates closely with FDA through our reviews of investigational device exemption (IDE) studies and encourages greater inclusion of important relevant Medicare population(s). Despite these efforts, pre-market studies frequently lack adequate inclusion of important patient subgroups that limit their generalizability to the Medicare population(s) that the item or service is intended. CMS agrees that post-market FFP studies may be important in addressing this common limitation of pre-market RCTs; the guidance document does not suggest that each distinct Medicare population must be studied.

Comment: One commenter asked how "social determinants of health" should be reflected; rural versus urban residence was suggested as a possibility.

Response: The CMS Framework for Health Equity website[6] provides information on a number of Agency initiatives, including information on social determinants of health.

Comment: One academic medical center cautioned CMS against requiring evidence specific to the Medicare population unless there were legitimate scientific or clinical reasons that outcomes might be different in the Medicare population. They asked CMS to work with FDA to encourage more diverse representation in studies offered to the two agencies.

[6] https://www.cms.gov/priorities/health-equity/minority-health/equity-programs/framework

Response: The final guidance clarifies that CED studies should include specific patient groups when there is good clinical or scientific reason to expect that the results observed in premarket studies might not be observed in older adults or subpopulations identified by other clinical or demographic factors.

Comment (8. Care Setting): One advocacy organization asked that this section acknowledge that patients with disabilities often receive care in the home. They urged making this a standard rather than qualifying it by "When feasible and appropriate for answering the CED question."

Response: CMS appreciates this comment regarding care delivery in the home but we are not adopting the suggestion. CMS will retain the qualifying phrase "When feasible and appropriate for answering the CED question" to provide flexibility to accommodate all potential technologies and health conditions.

Comment (9. Health Outcomes): A device manufacturer found the phrase *clinically meaningful* to be vague. Three commenters, including two academic medical centers, requested greater clarification of CMS' expectations regarding validating a surrogate endpoint as a predictor of clinical benefit. One nonprofit organization cautioned that observed relationships between a surrogate endpoint and health outcomes are subject to variable interpretation and called for more detailed guidance. They also urged CMS to require that the evidence demonstrate a *net* benefit, i.e., a positive balance of benefits against harms, and referred to comments submitted during the 2023 MEDCAC meeting.

Response: CMS appreciates the feedback on the desire for greater clarity on "clinically meaningful" and what evidence is needed to validate surrogate endpoints. The CED guidance does not preclude the use of surrogate endpoints but rather states that CMS generally emphasizes improved health outcomes when assessing benefits and harms within national coverage analyses. Generally, when study sponsors propose using surrogate endpoints to measure outcomes, validation studies published in peer-reviewed journals should be cited to provide a rationale for assuming these endpoints predict the health outcomes of interest. The cited validation studies should be longitudinal and demonstrate a statistical association between the surrogate endpoint and the health outcomes it is thought to predict. We have clarified this point in the final CED guidance document.

CMS appreciates the distinction between demonstration of benefit and demonstration of net benefit. However, *net benefit* refers to the actual results of studies, not the type of outcomes to be measured, which is the focus of this subsection in the guidance. In general, CMS assesses the net benefit based on a review of the totality of the publicly available evidence.

Comment: Three patient advocacy organizations urged CMS not to recognize "discriminatory" outcome measures such as quality-adjusted life-years (QALYs).

Response: We are not recognizing QALYs as an appropriate outcome measure. Section 1182(e) of the Social Security Act prohibits the Secretary from using QALYs or similar measures to determine coverage, reimbursement, or incentive programs under Medicare.

Comment: One advocacy organization suggested recognition that, in the case of slowly progressive genetic diseases, trials needed to show a statistically significant change in clinical benefit may not be feasible. This commenter stated that correcting a missing or malfunctioning protein should be

considered evidence of benefit. Representatives of drug manufacturers and an advocacy organization stated that surrogate endpoints might be meaningful to patients with serious, life-threatening diseases.

> Response: CMS' National Coverage Analysis Evidence Review Guidance notes that "each NCD has its unique methodological aspects." CMS recognizes that there may be cases where improved health outcomes may take many years to manifest, and surrogate measures may be appropriately included within clinical studies. In some cases, appropriate surrogate outcomes may consist of claims-based measures such as hospitalizations and nursing home admissions as objective complements to clinical assessments. The CED guidance document allows flexibility to consider outcomes within their specific context of use: "A validated surrogate outcome that reliably predicts these outcomes may be appropriate for some questions." All CMS Coverage Guidance Documents may be found at: https://www.cms.gov/medicare/coverage/determination-process/guidance

Comment: Some commenters questioned whether the reasonable and necessary standard implies health outcomes, especially given FDA's recognition of surrogate endpoints in its Accelerated Approval Program.

> Response: An interpretation of the reasonable and necessary standard is beyond the scope of this guidance document. CMS makes reasonable and necessary determinations under section 1862(a)(1)(A) of the Social Security Act. In making national coverage determinations, we focus on whether the treatment is clinically beneficial for Medicare patients. CMS reviews all relevant evidence and weighs the harms and benefits. In the NCA Evidence Review guidance document we note that "An intervention's benefits should generally be clinically meaningful and durable rather than marginal or short-lived. When making NCDs, CMS generally places greater emphasis on health outcomes important to patients and their caregivers, such as quality of life, functional status, duration of disability, morbidity, and mortality, and less emphasis on outcomes in which patients often have a less direct interest, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses."

Comment: One medical specialty society recommended that CMS establish additional acceptable outcomes, other than health outcomes, for new imaging technologies and products such as diagnostic radiopharmaceuticals used with imaging technologies. The commenter proposed the impact on patient management as an appropriate outcome for imaging technologies. One academic medical center stated that claims-based measures such as hospitalizations and nursing home admissions be identified as objective complements to clinical assessments.

> Response: CMS appreciates the suggestion to consider the impact on patient management as an appropriate outcome in evidence development for diagnostic technologies and products. CMS agrees that a change in patient management could be considered to demonstrate an indirect measure of change in health outcomes, however, a change in health outcomes is the best measure of the value of new technologies and products. Several structured methods exist for evaluating diagnostic tests, including diagnostic imaging studies. In past diagnostic imaging NCDs, we considered the evidence in the hierarchical framework of Fryback and Thornbury

(1991)[7] where Level 1 concerns technical quality of the images; Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan; Level 5 measures the effect of the diagnostic information on patient outcomes; and Level 6 examines societal costs and benefits of a diagnostic imaging technology. In our analyses, we generally look for sound evidence that shows a test is analytically and clinically valid (Levels 1-2) and that use of the test to guide treatment improves health outcomes (clinical utility, Levels 3-5).

Comment (10. Objective Success Criteria): The non-profit organization asked why the principle of prespecifying an evidentiary threshold agreed upon at the February 2023 MEDCAC meeting was not required.

Response: We appreciate the comment. CMS included the principle in the guidance document.

Comment (14. Reporting): Some commenters specifically endorsed the goal of publishing CED studies in peer-reviewed journals. However, three manufacturers voiced objections regarding peer-reviewed publication preceding public announcement that the CED phase has ended. One of the medical specialty societies recommended more flexibility in accepting publication outside peer-reviewed journals.

Response: CMS believes that rigorous and publicly available evidence is necessary to inform beneficiaries, the clinical community, and the public about the benefits and harms of available treatment options. Published studies are often necessary for technologies to be included in evidence-based guidelines, which feature heavily in CMS' assessment of accepted standards of medical practice. Therefore, we agree with the commenters that suggested that publication of evidence in peer-reviewed clinical literature is important. CMS applies rigorous methodologic standards in evaluating evidence when making NCDs.

CMS, however, may sometimes review pre-publication evidence to accelerate our reviews, but the National Coverage Analysis process is an open and transparent one and evidence considered is usually in the public domain. Our decisions are clearer when the public has access to the information that CMS relied on to conduct its evidence review. The guidance document encourages, when possible, that the study results be submitted for peer-review publication; however, "results may also be published in an online publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with incomplete results)." Further, CMS generally considers peer-reviewed evidence of higher quality and evidentiary value than study results that are not peer-reviewed.

Comment (15. Sharing): One device manufacturer expressed concern that the standard of sharing a de-identified dataset constitutes an administrative burden. One academic medical center endorsed the recommendation on data sharing and called for independent verification of the submitted data by a CMS-approved party. A few commenters urged that datasets be made publicly available.

[7] Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making. 1991 Apr-Jun;11(2):88-94. doi: 10.1177/0272989X9101100203. PMID: 1907710.

Response: CMS generally agrees that data used to support coverage should be available for examination, if appropriate and permitted by law. This recommendation is important to enhance public confidence in findings from studies that make secondary use of real-world data. We note that if we have concerns about false information or data being submitted to CMS, we may refer the issue to the Office of Inspector General (OIG) or the Department of Justice (DOJ). CMS disagrees that sharing a deidentified dataset with CMS or an approved third party constitutes an undue burden. The final guidance clarifies that "sharing data, methods, analytic code, and analytical output with CMS or with a CMS-approved third party" makes study data publicly available.

Comment (criteria for deciding on CED): Some commenters requested more details on when CED would be considered necessary. Commenters also noted that the general criteria outlined in the CED guidance document would be applied differently for different technologies and indications. One commenter suggested that CMS build on the AHRQ final report "The Analysis of Requirements for Coverage with Evidence Development (CED)" by providing more specific guidance on factors like patient characteristics and outcomes most critical to CMS decision-making.

Response: CMS agrees that applying the general guidance document to specific evidence development plans will vary across technologies and indications, and for this reason, welcomes early discussion with study sponsors. The new Clinical Endpoint Guidance series aims to provide greater predictability and transparency on preferred outcome measures within different clinical areas. For example, see the Clinical Endpoints Guidance for Knee Osteoarthritis. The discussion of applicability to the intended Medicare population in the CMS National Coverage Analysis Evidence Review guidance may also offer helpful context. These guidance documents can be accessed here: https://www.cms.gov/medicare-coverage-database/reports/national-coverage-medicare-coverage-documents-report.aspx?docTypeId=1#.

VII. Importance of Control Groups and Blinding in CED Studies

Comment: A device manufacturer objected to the standard of contemporaneous comparison groups and claimed that an FFP philosophy should allow for situations where a comparison group is unnecessary. The commenter additionally recommended that CMS consider accepting indirect comparison methods. In contrast to these comments, one academic medical center urged strict adherence to the justification standard for research lacking a control group. This commenter recommended adding clarification of when noncomparative studies would be considered appropriate.

Response: The proposed guidance document does not preclude consideration of studies without comparison groups but notes in section VI.5 that "If a contemporaneous comparison group is not included, this choice should be justified, and the sponsors/investigators discuss in detail how the design contributes to the evidence base that allows for valid causal inference." The CMS National Coverage Analysis Evidence Review (see https://www.cms.gov/medicare/coverage/determination-process/guidance) provides more detail on the appropriate use of noncomparative studies.

Comment: A non-profit organization emphasized that blinding represents the ideal and urged deleting the phrase 'or not used' in the sentence "In cases where blinding is not possible or not used, CMS will closely examine the study design and analysis elements that may mitigate the risk of bias."

Response: In the final CED guidance document, the phrase 'is not used' has been removed from the sentence that begins with "In cases where blinding is not possible or is not used. . ."

Comment: One non-profit organization objected to the statement that, in some cases, observational studies instead of randomized controlled trials (RCTs) are sufficient; the commenter recommended that CMS require RCTs except when RCTs are not possible.

Response: The final document clarifies that CMS considers RCTs as the gold standard for minimizing bias but that if previous RCTs have demonstrated efficacy and safety in the specific context of a study, well-designed observational studies may provide complementary information that may address questions that persist after market approval.

VIII. Ending CED

Comment (details on timeframes): Numerous commenters from different perspectives requested a more explicit CMS commitment to clarifying, for each CED NCD, the factors that would constitute the end to CED or trigger a reconsideration and agree with the sponsor on a schedule for completion of evidence development, including timelines and "stopping rules." A patient advocacy group asked CMS to protect patients by ensuring the cessation of randomized treatment assignments (i.e., assigning participants to treatment and control groups in a clinical study) if a CED shows clinical benefit before the study ends.

Response: CMS agrees that CED should not persist indefinitely. The TCET pathway illustrates a new coverage framework for emerging technologies that is more predictable and transparent and where approved CED studies are designed to address specific evidence gaps over a defined timeframe and with prespecified outcomes. As we gain experience with the TCET pathway, CMS may consider modifications to the broader CED approach. CMS regularly receives feedback on approved CED studies, including any evidence of concerning safety signals, either from the company directly or from FDA.

We note that an NCD with CED requirements remains in place until it is removed through a reconsideration. CMS may choose to reconsider a CED NCD at any time, and any member of the public may submit a complete, formal NCD reconsideration request at any time. Details of the NCD process and the requirements for submitting a complete, formal NCD request may be found at 78 FR 48164.

Comment: Commenters expressed concerns with the long duration of CED status following a CED NCD.

Response: We understand the commenters concerns that the CED research studies may take some time for the studies to be completed and for summaries of the new evidence to be prepared and analyzed. CMS endorses the concept that CED studies should be fit-for-purpose (FFP). That is, the study design, analysis plan, and data source(s) should be sufficient to credibly answer the question(s) it intends to answer. The length of CED studies depends on the question they intend to address. Particularly where the durability of treatment response is a significant concern, a longer CED duration may be unavoidable. CED studies that rely on real-world data may make important contributions to the evidence base and generally involve less burden and cost than conventional clinical studies. However, where FFP studies make secondary use of administrative and clinical data, there may be as much as an 18-month delay before the data are available for analysis. Where CED studies require a long follow-up duration, CMS recommends

that manufacturers incorporate an interim analysis to provide early feedback to the public about the use and performance of an item or service. To decrease burden, CMS agrees that CED status should be limited the shortest period necessary to address the evidentiary gaps identified in a national coverage analysis.

Comment: One commenter requested that CMS issue additional guidance documents for public comment that spells out the entire CED process with details regarding timeline and milestones from consultations between manufacturers and CMS through MAC implementation of NCDs, similar to what has been posted for TCET.

Response: We appreciate these comments. However, a detailed discussion of the process and timeframes for planning and completing CED studies is beyond the scope of this document.

Comment: A commenter proposed that CED apply for three years or until research questions are answered, whichever came sooner, with an option to extend CED for up to two additional years under certain circumstances.

Response: CMS disagrees that most post-market studies can be completed within a three-year timeframe, particularly if durability is a central concern, and we note that the burden associated with longer study follow-up may be substantially mitigated through fit-for-purpose study designs. The appropriate duration of CED is determined by the question that a CED study is designed to answer, and it should not be set arbitrarily for all CED studies. To decrease burden, CMS agrees that CED status should be limited the shortest period necessary to address the evidentiary gaps identified in a national coverage analysis.

Comment: One academic medical center believed the document should more clearly state CMS' authority to end CED when study sponsors do not report interim results according to the agreement signed by the sponsor or study site for the specific CED trial under the NCD as outlined in the guidance document or if completed studies produce negative results.

Response: An NCD with CED requirements remains in place until a reconsideration is finalized. CMS has published details of the NCD process at 78 FR 48164. We have added language to the guidance document that states that CMS retains the right to reconsider an NCD at any point in time.

Comment (assurance of continued coverage): Two device manufacturers, an associated trade association, an advocacy group, and a nonprofit research organization requested continued coverage of a product or service between the end of CED and a revised NCD.

Response: CMS agrees that coverage continuity is important between completing an approved CED study and reconsidering a CED NCD. Study sponsors are encouraged to incorporate continued access studies into their evidence development plans to ensure that coverage continues during this time.

OTHER COMMENTS

Pathway Differences

Comment: One of the device manufacturers requested a presentation of the differences in processes and timelines, comparing NCDs without CED, NCDs with CED, and TCET.

> Response: A review of the differences between NCDs with and without CED and the TCET pathway is beyond the scope of this guidance document. CMS appreciates this suggestion and will consider posting an online graphic showing the differences between these coverage pathways.

CED and Access to FDA-Authorized Products and Services

Comment: One academic medical center cited their research showing that the evidence behind FDA-approved devices was generally insufficient to support broad national coverage and creates the need for separate evaluation of FDA-authorized products by CMS. The pharmacy professional association viewed the CED pathway as encouraging evidence development and providing "vital access to promising treatments that would not otherwise be covered."

> Response: We appreciate the support for using CED to fill these evidentiary gaps. As the comments acknowledge, the standard for Medicare coverage (that is, a determination that a device is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member) is not synonymous with the standards for FDA marketing authorization of devices, which are not specific to the Medicare population. While FDA generally reviews a device to ensure it meets the applicable safety and effectiveness standard, there is often limited evidence regarding whether the device is clinically beneficial to Medicare patients. CMS may conduct its own independent review to determine whether a medical item or service can be covered nationally by Medicare, including whether an item or service is reasonable and necessary under section 1862(a)(1)(A) of the Social Security Act. We believe that consideration of the health impact on the Medicare population is a key factor in determining national coverage for Part A and Part B. When the evidence supporting FDA market authorization does not meet the reasonable and necessary standard for the Medicare population, an NCD without CED requirements would either non-cover the item or service or substantially restrict its use to the limited contexts where the evidence is sufficient to satisfy the reasonable and necessary standard.

Comment: Commenters representing both patient advocates and manufacturers generally expressed that CED restricts access and should not require duplication of evidence already deemed by FDA to demonstrate safety and effectiveness.

> Response: CMS disagrees. When the evidence supporting FDA market authorization does not meet the reasonable and necessary standard for the Medicare population, an NCD without CED requirements would likely be more restrictive than one with CED. If the item and service evidence does not meet the reasonable and necessary standard, CMS would likely either non-cover the item or service or substantially restrict its use to the limited contexts where the evidence is sufficient to satisfy the reasonable and necessary standard. Under CED, the item or service could be more broadly covered while collecting information to answer key evidentiary questions for patients, caregivers, and their providers.

Comment: Some commenters disagreed with submitting new drugs to CED since FDA holds drugs to higher evidentiary standards than it does devices. These commenters urged that CED not be applied to products that have been authorized through FDA's Accelerated Approval Program. Two drug manufacturers stated that, in some cases, FDA already requires postmarket studies to answer remaining questions and expressed concern that additional requirements imposed by CMS could be confusing and diminish public confidence in both agencies.

Response: While each NCD has unique aspects, CMS disagrees with the suggestion all FDA approved drugs should be excluded from CED. If the reviewed evidence is insufficient to meet the reasonable and necessary standard required for coverage, CED may allow a pathway to coverage that provides early beneficiary access, establishes important beneficiary protections, and ensures further evidence generation to address material evidence gaps. CMS works closely with our FDA colleagues to reduce burden on manufacturers and other interested parties during post-market evidence generation and commits to avoiding duplication of FDA requirements.

Comment: Another commenter suggested that CED might be useful for devices receiving FDA market authorization through 510(k) clearance to establish additional data for efficacy since similar alternatives to those technologies would already be in use, making patient access to the new technology a less acute problem. This commenter further notes that this is not true in the case of drugs that have a more robust FDA approval process to demonstrate safety and efficacy.

Response: We disagree with the commenter's statements. We believe it is important to promote innovation across all items and services under Medicare. Decisions regarding whether a CED NCD is most appropriate are driven by the strength and sufficiency of the available evidence for a particular item/service under review. Regardless of whether a technology is a device or drug, CMS must assess whether the reasonable and necessary standard has been met. This is true regardless of whether a new device received FDA market authorization through 510(k) clearance, the granting of a De Novo request, or Premarket Approval.

Comment: Many commenters criticized CED for creating disparities in access due to problems such as the difficulties rural patients may have traveling to academic medical centers for their care or the resistance some racial and ethnic groups have against clinical trial participation. However, the pharmacy professional society urged CMS to set very stringent standards for overcoming these disparities in CED studies.

Response: CMS encourages FFP study designs, including appropriately designed observational studies that use real-world data from patients cared for in community settings, including rural settings. CMS recommended that study sponsors proactively seek to address disparities in study participation and specifically address in the clinical protocol how to minimize disparities for coverage of the item or service. As such, FFP studies are likely to diversify clinical study participation by including data from a broader range of patients and care delivery settings than is typical for conventional clinical studies. Because many FFP observational studies make secondary use of data gathered in routine clinical practice, they are also unlikely to contribute to access disparities or require travel to academic medical centers.

Comment: Seven commenters expressed concern that CED would repeat research already completed for FDA authorization and that this would violate the ethical principle of equipoise, which requires that all

patients be offered the intervention in question unless there is genuine uncertainty about the safety or benefits that intervention; particular concern was voiced about postmarket placebo-controlled trials.

> Response: CED studies are designed to address evidence gaps that persist after FDA marketing authorization relative to the CMS reasonable and necessary standard. Such gaps might have to do with the types of outcome measures reported, the generalizability of the study participants to the Medicare population, duration of follow-up, or other criteria outlined in Section V of the CED guidance and the CMS National Coverage Analysis Evidence Review guidance documents. Study sponsors can sometimes address evidence gaps by extending the follow-up interval of studies submitted to FDA. CMS aims to avoid duplication of FDA post-market-authorization study requirements through the Evidence Development Plan process.
>
> The principle of equipoise applies to randomized controlled trials, in which the choice of treatment is not left to patients and their clinicians. Observational studies are studies in which the investigators do not determine which patients receive the treatment of interest. CMS will heavily emphasize appropriately designed observational studies and recommend randomized controlled trials in a CED evidence development plan only when they are necessary to fill an evidence gap not addressed by premarket studies.

Comment: Other commenters expressed concern that CED would fail to demonstrate effectiveness in the real world or among diverse populations because it would limit coverage to patients participating in clinical trials.

> Response: This CED guidance updates CED study criteria to allow for greater use of fit-for-purpose (FFP) study principles, including real-world data use. CMS believes that FFP study designs may reduce the burden of evidence generation and address getting items and services to a more diverse population.

Comment (public engagement): Many commenters representing different types of organizations encouraged CMS to add a statement in the guidance document regarding CMS engagement with various interested parties. Several commenters suggested that patients be able to provide input on CED decisions and evidence development plans, including patient input on identifying evidence gaps and observing patient preferences and priorities in evaluating new technologies. Among the recommended interested parties mentioned by commenters were FDA, specialty societies, and patients, particularly patients with disabilities and rare disorders.

One of the academic medical centers advocated other countries' "health technology assessment" models, which were described as involving more public input. This commenter believed that the existing opportunities for public and patient input were insufficient; notices in the Federal Register, news alerts, and community open forums were recommended. The same commenter also urged CMS to enlist individuals with clinical effectiveness and outcomes research expertise.

> Response: CMS routinely engages with interested parties about coverage requests for new technologies or reconsiderations of existing technologies. Most NCDs allow two opportunities for public comment, first when a national coverage analysis is initiated and second when an NCD is proposed. We believe the current process provides ample opportunity for the public to

provide their views and for CMS to consider them. Additional public engagement requirements would increase administrative costs and may slow the initiation and completion of NCDs.

Comment: Some commenters saw opportunities for greater collaboration between FDA and CMS so that premarket studies might satisfy more of CMS' evidence requirements. FDA's recent encouragement of decentralized trials to improve trial recruitment was cited as an example.

Response: CMS collaborates extensively with FDA and manufacturers in several areas, including CMS review and feedback on investigational device exemption (IDE) studies. The newly announced TCET pathway includes increased FDA-CMS coordination. CMS hopes that the new CMS National Coverage Analysis Evidence Review guidance and the clinical endpoints guidance series will enhance the transparency of CMS evidence expectations.

Comment: One commenter recommended that CMS consider the health burden imposed by a technology's target health condition and provided a set of criteria for evaluating technologies in light of healthcare system impact.

Response: CMS considers the health burden imposed by health conditions when evaluating the benefits and harms of technologies. When reviewing evidence, CMS primarily considers the impact of items and services on the Medicare beneficiary population. However, in some instances, healthcare system impacts may also be relevant.

Comment (practical concerns): Some commenters asked for recognition of the challenges faced in evidence development and requested that CMS require the minimum additional data necessary. One device manufacturer appreciated the CED guidance document's allowance for less burdensome study designs such as registries. One academic medical center stated that participating clinical sites should receive additional reimbursement when active data collection is required.

Response: The guidance document emphasizes the importance of early agreement with study sponsors on the specific evidence gaps to be filled. CMS appreciates these concerns and shares the goal of identifying the least burdensome evidence development plan that will satisfy evidence gaps. CMS expects the forthcoming guidance document on FFP studies to be a valuable resource for designing less burdensome but methodologically rigorous studies. A discussion of additional reimbursement for clinical sites when active data collection is required is beyond the scope of this document.

Comment: An academic medical center requested a more extensive database of CED NCDs, including those from which CED status has been removed.

Response: We appreciate this comment and will consider it as we update our webpages.

Comment (CED versus TCET): One commenter asked for clarification on how the CED requirements will apply to TCET. This commenter stated that acceptance into the TCET pathway implies acknowledging the importance of a device for Medicare beneficiaries and suggested that CMS should be more flexible in its study design requirements than it would be for other CED NCDs.

Response: We appreciate this comment; however, it is beyond the scope of this document. A discussion of how CED applies to TCET can be found in the TCET final notice.

Comment (confidentiality): Two device manufacturers requested that any information supplied to CMS beyond what is posted on Clinicaltrials.gov be kept confidential.

> Response: In general, the national coverage analysis process is an open and transparent one, yet CMS also recognizes manufacturers' interest in maintaining the confidentiality of certain proprietary data. We will maintain confidentiality of proprietary data as required by law.

Comment (flexible coverage): One device manufacturer recommended flexible coverage during CED, where FDA approves expanded indications before CED has ended for a particular technology.

> Response: We appreciate the comment but disagree. We note that CED NCDs often include specific requirements for indications not expressly addressed by the NCD. Where the initial approved indication for an item or service is subject to CED, extensions of coverage for additional indications will, in most cases, also require CED. CMS carefully considers the particular circumstances when assessing whether submitted study designs for subsequent indications are fit-for-purpose.

Comment (the need for additional CMS resources): Some commenters called for more resources to expand CMS' capacity to reach coverage decisions. One academic medical center stated that more resources are needed to address the accelerating market authorizations of novel technologies that do not yet satisfy CMS' reasonable and necessary standard for coverage. The same commenter claimed that investment in additional resources that allow expanded use of CED would be justified by the positive impact on innovation and beneficiaries' health outcomes.

> Response: CMS appreciates that as more innovative items/services come to market, more coverage reviews may be needed, and many may warrant CED. While recognizing that additional resources would help expand our coverage review capacity, we expect that TCET will increase CMS' NCD volume relative to recent years.

Comment (long-range planning): One academic medical center requested a posting of disease areas where CED might be warranted and to proactively engage relevant patient organizations to get input on patient experience in these areas.

> Response: CED decisions are not tied to specific disease areas. Instead, decisions regarding whether an NCD, including a CED NCD, is most appropriate are driven by the strength and sufficiency of the available evidence for a particular item/service under review.

Comment (transparency in funding): A medical specialty society recommended that the funding source for CED studies be publicly available.

> Response: The funding source for studies is generally documented in published, peer-reviewed articles. CMS does not diminish the value of industry funded studies but notes that funding source may influence patient inclusion/exclusion criteria, study parameters, outcomes studied, and follow-up duration. Therefore, our CMS National Coverage Analysis Evidence Review guidance (https://www.cms.gov/medicare/coverage/determination-process/guidance) acknowledges that when reviewing individual studies, CMS carefully considers the funding source and potential conflicts of interest for study investigators.

Comment: One manufacturer expressed concern that CMS may be planning to expand the CED paradigm, especially given the issuance on the same date of two other proposed guidance documents and notice of the proposed Transitional Coverage for Emerging Technologies (TCET) pathway. This commenter and several others cited the recent NCD with CED for Monoclonal Antibodies Directed Against Amyloid for the treatment of Alzheimer's Disease as a potential indication that drugs will more frequently be the subject of CED NCDs, and that the Medicare program will reduce access to new drugs.

Response: The TCET notice and the three guidance documents we released in conjunction with it are not a reflection of expanding the CED paradigm. Rather, CMS is taking these important steps to increase transparency and predictability regarding evidence development expectations to support innovation and provide more timely beneficiary access to new technologies. In addition to the updated CED criteria in the CED guidance document that provides new flexibility for FFP study designs, the NCA Evidence Review guidance document communicates the principles CMS uses when evaluating evidence to support NCDs. CMS also committed to publishing a series of guidance documents that identify important clinical outcomes for treatments addressing specific therapeutic areas. The first Clinical Endpoints Guidance document specifies the types of health outcomes and evidence CMS expects to review when making coverage determinations for knee osteoarthritis treatment. We expect that these guidance documents will encourage innovation and expedite access by improving transparency, predictability, and efficiency of evidence generation for parties seeking Medicare coverage for an item or service.