USC Schaeffer
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August 21, 2023

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Re: Proposed CMS Guidance for Coverage with Evidence Development (CED)

Dear Dr. Chin:

Thank you for the opportunity to comment on the Centers for Medicare and Medicaid Services (CMS)'s proposed Guidance for Coverage with Evidence Development (CED). Researchers at the University of Southern California (USC) Schaeffer Center for Health Policy & Economics have been studying how evidence can be used to define value in our healthcare system since 2009; our comments draw on our experiences and perspectives developed in that research.[1] As part of the USC Schaeffer Center, we share a mission to measurably improve value in health through evidence-based policy solutions, research excellence, and private and public sector engagement.

CED is an important policy that CMS has implemented in various forms since its inception in 2006. The policy was designed to provide Medicare beneficiaries access to new technologies while facilitating ongoing data collection to prove reasonableness and necessity.

Since CED's implementation, the healthcare community has learned more about its utility, and questions have been raised about its goals and whether those goals are being met.[2] Unfortunately, CED is an example of a policy that may not have lived up to its promise, has diverged from its original purpose, and now presents real barriers to patient access. Below, we outline our perspectives on how CMS could improve its proposed guidance. We are grateful that CMS is seeking comment because CED is important for several reasons:

- **CMS serves as a model for other healthcare payers**: CMS should consider the broad impact of its policies on the innovation of health technologies and their corresponding opportunity to improve public health. Private payers in the U.S. have frequently emulated CMS decisions,[3] and CMS policy has been shown to affect provider behavior and patient treatment well outside of the traditional Medicare system.[4] Improving CMS policy indirectly improves policy adopted by other payers,[5] providing the opportunity to strengthen incentives for patient-focused innovation.

[1] The views expressed in this letter are those of the authors and do not necessarily reflect the views of the USC Schaeffer Center or the University of Southern California (USC).
[2] Zeitler EP, Gilstrap LG, Coylewright M, Slotwiner DJ, Colla CH, Al-Khatib SM. Coverage with Evidence Development: Where Are We Now? Am J Manag Care. 2022 Aug;28(8):382-389. doi: 10.37765/ajmc.2022.88870. PMID: 35981123.
[3] Chambers JD, Chenoweth M, Thorat T, Neumann PJ. Private Payers Disagree with Medicare Over Medical Device Coverage About Half the Time. Health Affairs. 2015 Aug;34(8):1376–82.
[4] Chen AJ, Richards MR, Whaley CM, Zhao X. The Extent of Externalities from Medicare Payment Policy. American Journal of Health Economics. 2022 Mar;8(2):181–215.
[5] Clemens J, Gottlieb JD. In the Shadow of a Giant: Medicare's Influence on Private Physician Payments. J Polit Econ. 2017 Feb;125(1):1–39.

- **CED offers unrealized potential to drive meaningful[6] innovation, but improvements need to be made**: In their current form, the criteria for invoking CED are vague and, as a result, could negatively impact innovation.[7] Analysis of recent CMS National Coverage Decisions (NCDs) shows that CMS is increasingly implementing CED policies, which limit access to new therapies and add uncertainty, risk and data collection costs for drug and medical device developers – all of which impact incentives to innovate.[8] This need not be the case. By setting forth objective criteria governing the use of CED, including concrete milestones that guide developers towards completing its requirements, CED could not just improve patient access to innovation but also promote and encourage more meaningful innovation.

Below are specific responses to points raised in CMS's proposed guidance, with comments and suggestions for improvement, following the general flow of the proposed Guidance document:

1. Goals of Coverage with Evidence Development

CMS should be commended for outlining the specific goals of CED, against which all future policies and the Guidance document itself, should be measured. From a thorough review of the literature, CED policies throughout the world[9] share at least two important goals proposed by CMS:

- ". . . ***expedite earlier beneficiary access*** to new items and services . . ."[10]

- ". . . ***generate additional evidence*** that is appropriate for Medicare beneficiaries and that may demonstrate improved health outcomes . . ."[11] In addition, generating more evidence is a laudable goal for several other reasons. CED-generated evidence can:
    - Inform and justify future coverage decisions (expanded or non-coverage)
    - Facilitate ongoing value assessments
    - Drive shared decision-making between providers and patients[12]
    - Support safety surveillance or other safety-signal detection that may supplement the U.S. Food and Drug Administration (FDA) pre- or post-market requirements
    - Provide clinically meaningful evaluation that could not otherwise be collected in a clinical trial (e.g., long-term safety)
    - Assess whether clinical data generated for regulatory approval is generalizable to:
        - Real-world settings (i.e., outside the controlled environment of a clinical study)

[6] CMS may wish to consider that "meaningful" innovations could be defined as those that combine the creation of value at four levels: "users, organizations, ecosystems, and society." den Ouden, E. Meaningful Innovation. Innovation Design. 2011. Springer, London. https://doi.org/10.1007/978-1-4471-2268-5_4
[7] Fleming JJ. The Decline of Venture Capital Investment In Early-Stage Life Sciences Poses A Challenge To Continued Innovation. Health Affairs. 2015 Feb;34(2):271–6.
[8] Chambers JD, Chenoweth M, Cangelosi MJ, Pyo J, Cohen JT, Neumann PJ. Medicare is Scrutinizing Evidence More Tightly for National Coverage Determinations. Health Affairs. 2015;34(2):253-260.
[9] Drummond M, Federici C, Reckers-Droog V, Torbica A, Blankart CR, Ciani O, et al. Coverage with Evidence Development for Medical Devices in Europe: Can Practice Meet Theory? Health Economics. 2022;31(S1):179–94.
[10] Guidance page 5
[11] Guidance page 5
[12] Tunis SR, Stryer DB, Clancy CM. Practical Clinical Trials Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy. JAMA. 2003 Sep 24;290(12):1624–32.

        - The Medicare population, in cases where there is evidence an item or service may function differently in people 65-years-of-age or older[13]
    - Identify differences in outcomes among subgroups/payer populations, including under-represented and underserved communities, that may not have been discoverable in a traditional clinical trial

However, we caution CMS against its potential focus on the evidence being "appropriate for Medicare beneficiaries." CMS should be careful that its demand for sufficient representation of older Americans in clinical studies is based on legitimate scientific or clinical reasons as to why treatment effects might vary by age. Broadening the requirement risks denying Medicare patients access to effective therapies, without improving the evidence base for treating disease in this population group. There are practical and scientifically-sound reasons for excluding individuals with comorbidities from clinical studies, and there is a higher incidence of comorbidities in older people.[14]

CMS should include ***promote meaningful innovation*** as a clear, primary goal. We are surprised that this was not called out as a specific goal in the proposed Guidance, as CED being the "driver of innovation" was explicitly mentioned in President Obama's 2012 National Bioeconomy Blueprint[15] and is one of the agency's six strategic pillars in its 2023 strategic plan.[16] In addition, CMS's proposed Guidance for National Coverage Analysis Evidence Review refers to "encourage[ing] innovation" as a rationale for that Guidance.[17] By providing patients access to items or services that meet certain criteria, the U.S. sends a clear signal to innovators about where to pursue treatment solutions for America's seniors. CMS's coverage policies should prioritize predictability for innovators which will reduce some of the risks inherent in drug and device development. The current uncertainty around CED policies is increasing the expected costs associated with innovation and reducing the number of projects that receive investment.

CMS ***should <u>clarify</u> its proposed goals of:***

- ". . . [assuring] that items and services are ***provided to clinically appropriate patients*** . . ."[18] While CMS has a legitimate interest in evaluating real-world evidence on medical necessity, there has been criticism that the Agency may have waded into FDA's jurisdiction when determining what is clinically appropriate. There could also be concern that CMS could end up interfering with the practice of medicine by directing how and when clinicians should use a therapy.[19] CMS should clarify how it would determine clinical appropriateness to avoid confusion and conflict with its stated principle of "not duplicating FDA authority."

[13] Zazzara MB, Palmer K, Vetrano DL, Carfì A, Onder G. Adverse drug reactions in older adults: a narrative review of the literature. Eur Geriatr Med. 2021;12(3):463–73.
[14] Forman DE, Maurer MS, Boyd C, Brindis R, Salive ME, Horne FM, et al. Multimorbidity in Older Adults with Cardiovascular Disease. J Am Coll Cardiol. 2018 May 15;71(19):2149–61.
[15] The White House. "National bioeconomy blueprint, April 2012." *Industrial Biotechnology* 8.3 (2012): 97-102.
[16] CMS Strategic Plan [Internet]. 2023 [cited 2023 Aug 15]. Available from: https://www.cms.gov/cms-strategic-plan
[17] (PROPOSED) CMS National Coverage Analysis Evidence Review [Internet]. Centers for Medicare and Medicaid Services; 2023 [cited 2023 Aug 15]. Available from: https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?mcdid=34
[18] Guidance page 5
[19] 42 U.S. Code § 1395 - Prohibition against any Federal interference. Available from: https://www.law.cornell.edu/uscode/text/42/1395

- ***". . . ensuring that systematic patient safeguards*** . . . are in place to reduce the risks inherent to new technologies . . ."[20] As stated above, CMS has a legitimate role in managing appropriate utilization of new technologies, particularly as their risk/benefit profile may be less understood in the early days of its introduction. With appropriate evidence generation, CED can help address uncertainty in the risk/benefit profile. That said, CMS should clarify how this goal does not conflict with its stated principle of "not duplicating FDA authority." FDA has been uniquely empowered, qualified and resourced by the Congress to facilitate the benefit/risk trade-off decisions of safety and efficacy. A goal designed to "reduce the risks inherent in new technologies" could undermine FDA's authority, create confusion and unpredictability in the market, and introduce significant market inefficiencies if this is not clarified.

One goal that was not mentioned, but which may have motivated recent applications of CED, is the ***desire by CMS to manage its budget***. Recent attempts to use CED for high-cost drugs, such as the proposal to apply CED to CAR-T cell therapy[21] and its NCD on Aduhelm[22] may indicate a trend in this direction. We believe managing net program costs may be a legitimate public policy goal,[23,24] but not appropriate as a motivator for use of CED at this time because:

- **It isn't legal** – the statute precludes CMS from making coverage decisions based on cost.[25] Use of CED as a cost containment measure should be discontinued to the extent that it is occurring absent explicit Congressional authorization. Furthermore, without engaging in an appropriate public policymaking process (e.g., legislation or rulemaking), applying CED because CMS is concerned about budget implications undermines CMS's credibility and public trust.

- **Cost-cutting may be counterproductive to other CED goals** – Imposing CED on items or services that are expected to impose significant costs on the program may undermine an important CED goal: collecting evidence to address CMS's concerns. In addition, addressing the costs of one item or service could have broader health implications for other Medicare costs (e.g., the opportunity costs of not treating the disease).

- **CMS isn't equipped to conduct value assessment** – Health technology assessment (HTA) is an important process that evaluates health technologies and guides coverage and pricing decisions. CMS has not established transparent, rigorous, and predictable rules to conduct a proper value assessment of new items or services. A report recently published by the USC Schaeffer Center

[20] Guidance page 5
[21] CMS National Coverage Analysis - Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N) - Tracking Sheet [Internet]. [cited 2023 Aug 9]. Available from: https://www.cms.gov/medicare-coverage-database/view/ncacal-tracking-sheet.aspx?NCAId=291
[22] National Coverage Determination for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease; CMS CAG-00460N (April 7, 2022)
[23] Jacqueline Fox, The Hidden Role of Cost: Medicare Decisions, Transparency and Public Trust, 79 U. Cin. L. Rev. (2011) Available at: https://scholarship.law.uc.edu/uclr/vol79/iss1/1
[24] "Operationally, coverage determinations are reserved for those services that are likely to have a *major impact on cost* or quality of care or when safety concerns arise." [emphasis added] Tunis S., Berenson R. Improving the Quality and Efficiency of the Medicare Program Through Coverage Policy. The Urban Institute. August 2011
[25] Daval CJR, Kesselheim AS. Authority of Medicare to Limit Coverage of FDA-Approved Products: Legal and Policy Considerations. JAMA Intern Med. Published online July 28, 2023. doi:10.1001/jamainternmed.2023.3961

and Aspen Institute introduced an approach to creating an HTA advisory board within HHS that could benefit CMS and CED.[26]

2. Principles governing application of CED

We agree with many of CMS's proposed principles, and we offer some additional suggestions for consideration:

- Transparent and open to public comment (under an NCD process) – this is an important principle, but the guidance as written appears to undermine that principle, particularly since it ensures the CED requesting party can have continual, *private* dialogue with CMS. We agree open communication should be maintained, but with ALL stakeholders, not just the first individual or organization to request CMS's opening of a CED-NCD. CMS should consider reforming its Medicare Evidence Development & Coverage Advisory Committee process to allow for greater public participation and flexibility. CMS could benefit from the experiences of Health Technology Assessment organizations around the world that have public mandates to involve the public and the impacted communities.[27] In addition, CMS should consider a more formal process to notify the public, including publication in the Federal Register, media and news alerts, and community open forums for the public to ask questions. And CMS should provide Congress an annual report, reviewing the status of outstanding NCDs involving CED.

- Limit evidence generation to that which addresses specific evidentiary deficiencies identified in the National Coverage Analysis process – this is an important principle which, unfortunately, has not been followed in past NCD/CED decisions. For example, the STS/ACC TVT Registry[28] that was established by the American College of Cardiologists and Society for Thoracic Surgeons collects more 276 fields for each patient.[29] Such requirements can be costly and burdensome on an already taxed healthcare system.[30] Required data collection should be limited to information that can help answer the original research question(s) posed by CED.

- Don't duplicate or replace FDA authority in assuring safety and effectiveness – we wholeheartedly agree with this principle. CMS and FDA evidence evaluation roles should be clearly delineated and respected. The current CED system could be construed as justification to second-guess the work of the FDA. Nowhere is this more apparent than in CMS's National Coverage Decision concerning Aduhelm and all future monoclonal antibodies directed against

[26] Lakdawalla DN, Neumann PJ… Wilensky GR. Health Technology Assessment for the US–A Vision for the Future. USC Schaeffer Center and Aspen Institute Advisory Panel on Health Technology Assessment in the US February 9, 2021.
[27] Abelson, J., Wagner, F., Dejean, D., Boesveld, S., Gauvin, F.-P., Bean, S., Axler, R., Petersen, S., Baidoobonso, S., Pron, G., Giacomini, M., Lavis, J., 2016. Public and Patient Involvement in Health Technology Assessment: A Framework for Action. International Journal of Technology Assessment in Health Care 32, 256–264.. https://doi.org/10.1017/s0266462316000362
[28] STS/ACC TVT Registry [Internet]. 2023 [cited 2023 Aug 15]. Available from: https://www.sts.org/registries/stsacc-tvt-registry
[29] Simonato M, Vemulapalli S, Ben-Yehuda O, Wu C, Wood L, Popma J, et al. Minimum Core Data Elements for Evaluation of TAVR: A Scientific Statement by PASSION CV, HVC, and TVT Registry. The Annals of Thoracic Surgery. 2022 May 1;113(5):1730–42.
[30] Clinical Registries: Getting Necessary & Costly [Internet]. 2012 [accessed 2023 Aug 11]. Available from: https://cardiovascularbusiness.com/topics/patient-care/clinical-registries-getting-necessary-costly

amyloid that are approved by the FDA. That decision shows that CMS is concerned with the potential harms associated with this class of Alzheimer's Disease drugs, which may include brain bleeds, falls, and other outcomes. In the decision, CMS indicated that the Agency "does not believe an item or service to be reasonable and necessary if the harms of the treatment outweigh the benefits." Such a stance is difficult to distinguish from FDA's adjudications regarding the safety and efficacy of an item or service. As previously stated, this undermines FDA's authority, creates confusion and uncertainty in the market, increases costs, and impedes innovation. CMS should accept FDA's determination that an item is safe and effective, limiting its review to whether the process is reasonable and necessary to treat or diagnose an injury or illness.

Principles that we urge CMS to add to its proposed list include:

- A patient-centered approach to decision-making that includes the patient voice and perspective
- Minimally burdensome requirements on patients/beneficiaries (e.g., extensive travel to centers of excellence) and providers (e.g., costs, time) to facilitate data collection
- Coverage constraints that are fit for the purpose of data collection (e.g., if a goal of CED is to collect real-world evidence, coverage should not be limited to "centers of excellence")
- Evidence generation grounded in good research principles (e.g., the evidence gaps cited are realistic and achievable)
- Greater predictability and reduced uncertainty for providers through clear and objective application of timelines, standards and expectations

3. Factors to use when CMS considers implementation of CED

As previously stated, we recommend CMS add the important goal of promoting meaningful innovation. A principle to support that goal would be to reduce uncertainty for stakeholders through the development of clear expectations. CMS should adopt clear and predictable criteria for when CED should be considered, enabling patient groups, physicians, hospitals, and innovators to know when to expect the implementation of CED and plan accordingly.

The proposed draft indicates that there are two main criteria: 1) the "technology is likely to show benefit to the Medicare population," but 2) the "available evidence is insufficient to demonstrate Reasonable and Necessary." However, as written, the Guidance is unclear or even contradictory. For example:

- Who determines whether the evidence is "insufficient?" What objective measure is used? The arbiters would seem to be CMS, the Agency for Healthcare Research and Quality (AHRQ) and sponsors/investigators,[31] and it appears that CMS is indicating that the outcomes used should be those that matter most to patients.[32] But it is not clear how the perspectives of these competing interests are balanced, and complaints of CMS's unresponsiveness to patient organizations[33] suggest a lack of transparency on this point. Beyond the ability to comment through the public comment process, patients and patient advocacy organizations, which are most likely to

[31] "In consultation with CMS and AHRQ, sponsors/investigators establish an evidentiary threshold for the primary health outcome(s)" [Guidance page 9]
[32] "The primary health outcome(s) for the study are those important to patients and their caregivers and that are clinically meaningful." [Guidance page 9]
[33] Analysis of Coverage with Evidence Development (CED) Criteria [Transcript]. Baltimore, MD: CMS; [cited 2023 Aug 15]. Available from: https://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/downloads/id79b.pdf

understand the patient's perspective, currently have no role in this decision.

- What kind of outcomes does CMS consider "evidence" when evaluating the evidence's sufficiency? CMS relies heavily on "health outcomes data,"[34] which don't include surrogate endpoints because they are not direct measures of clinical benefit.[35] However, when a validated surrogate endpoint is available,[36] CMS should make use of data from this endpoint to support evidence generation.[37]

- Whose outcome is CMS considering? CMS appears to be concerned about the generalizability (e.g., "will this work for people treated outside the extremely controlled environment of a clinical trial?") and representativeness of the data, both in terms of demographic diversity[38] and the Medicare population (people over 65 years of age).[39] Clearly articulating this goal is critical for generating clear and consistent decisions.

- What is the measure of "insufficiency?" It appears from the proposed Guidance that CMS considers "insufficiency" to mean: any new technology,[40] cases where the evidence lacks the sample size (typically a large enough clinical trial) to power sufficient statistical certainty,[41] or when there is not enough data demonstrating long-term durability of the outcomes.[42] Interestingly, the words "certainty/uncertainty" and "effect size"[43] are not mentioned, which are common concerns in CED policies globally.[44] It again begs the question: is CMS considering whose standards will be used when setting these thresholds?

- Who determines what is considered a benefit and its likelihood? Without more clarification on these points, stakeholders may be left to guess what CMS believes is a "benefit" and its "likelihood," further weakening the Agency's ability to influence better innovation investments.

[34] "In general, CMS relies heavily on health outcomes data before proposing an NCD." Guidance page 4
[35] "Surrogate endpoints are not direct measures of clinical benefit." Guidance page 4
[36] "A validated surrogate outcome that reliably predicts these outcomes may be appropriate for some questions." Guidance page 9
[37] FDA-NIH Biomarker Working Group. Validated Surrogate Endpoint, in "BEST (Biomarkers, EndpointS, and other Tools)". Food and Drug Administration (US); 2020 [cited 2023 Aug 9]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK453484/
[38] "traditionally underrepresented groups in clinical studies, how the inclusion and exclusion requirements effect enrollment of these populations." Guidance page 9]
[39] ". . . generalizable to the Medicare population . . ." Guidance page 5
[40] "For new technologies, it is rare that there is sufficient clinical evidence to support broad national coverage under section 1862(a)(1)(A)." Guidance page 4
[41] "sufficiency of sample size as required by the question" Guidance page 9
[42] "sufficiency of duration of observation to demonstrate durability of health outcomes" Guidance page 9
[43] Sullivan GM, Feinn R. Using Effect Size—or Why the P Value Is Not Enough. Journal of Graduate Medical Education. 2012 Sep 1;4(3):279–82.
[44] Drummond M, Federici C, Reckers-Droog V, Torbica A, Blankart CR, Ciani O, et al. Coverage with Evidence Development for Medical Devices in Europe: Can Practice Meet Theory? Health Economics. 2022;31(S1):179–94.

All these questions can be answered. The statistical and economic sciences can help us create models to set objective measures for evaluation. More work will be needed to develop a specific methodological approach, but in the meantime, we recommend CMS adopt an alternative set of criteria to use when evaluating whether to apply CED. The following criteria illustrate one possible path forward:

A) An item or service promises (evidence published in a peer-review publication indicates more likely than not) to provide benefits that matter most to patients (as measured with scientifically rigorous methods for eliciting and quantifying patient preferences[45]) or the healthcare system, including four[46] or more of the following criteria:[47] The item or service:
- Shows significant promise to improve healthcare or reduce costs
- Is innovative or novel
- Poses acceptable risk to patients intended to receive treatment
- Is more closely aligned with patients' preferences
- Is a potential replacement for more complex methods/technologies
- Alleviates high disease burden
- Has no or few available alternatives
- Reduces healthcare system resource utilization (e.g., hospital capacity, demands on labor)
- Addresses unique challenges for underserved patient populations or patient subgroups that otherwise lack access to a covered treatment

AND

B) Significant (patient prioritized) questions (risks or uncertainties) exist about the value of items or services
- Significant = high risk/likelihood of a negative outcome; or low risk/likelihood of a negative, but serious, outcome, as evaluated and measured through quantitative patient preference data
- Uncertainty about relative risks/benefits remain, including any of the following:
  - Level of uncertainty for any of the risks of the item or service is outside of patient populations' tolerance levels
  - Insufficient data to power confidence levels (as defined by the patient population) in any of the risk/benefit outcomes
  - High potential for confounding factors to influence predictability of outcomes (e.g., operator performance, context of delivery environment)
  - Unavailable data/information about outcomes that matter most to patients (e.g., long-term outcomes may be more important to younger patients, but less important to older patients)

[45] Patient Preference Information (PPI) in Medical Device Decision Making [Internet]. U.S. FDA CDRH; 2023 [cited 2023 Aug 15]. Available from: https://www.fda.gov/about-fda/cdrh-patient-science-and-engagement-program/patient-preference-information-ppi-medical-device-decision-making

[46] This could be more or less than four, but should be more than one and not all.

[47] Federici C, Reckers-Droog V, Ciani O, Dams F, Grigore B, Kaló Z, Kovács S, Shatrov K, Brouwer W, Drummond M. Coverage with Evidence Development Schemes for Medical Devices in Europe: Characteristics and Challenges. Eur J Health Econ. 2021 Nov;22(8):1253-1273. doi: 10.1007/s10198-021-01334-9. Epub 2021 Jun 12. PMID: 34117987; PMCID: PMC8526454.

4. Clinical research/study design standards

It is important that CMS be consistent in supporting its stated principle of only requiring ". . . the generation of evidence that addresses ***specific evidentiary deficiencies*** identified in National Coverage Analyses." We recommend CMS also remain consistent with the additional principles we recommend, including:

- Minimally burdensome requirements on patient/beneficiaries (e.g., travel to centers of excellence) and providers (e.g., costs, time) to facilitate data collection
- Data collection grounded in good research principles (e.g., clear, achievable research questions)
- Greater predictability and reduced uncertainty for providers through clear and objective application of timelines, standards and expectations.

Clinical Study Standards - We believe ***more work needs to be done with regard to CMS's proposed clinical research/study standards*** to remain consistent with the goals and principles of CED. As some of us commented in our September 28, 2022 comments to AHRQ,[48] we respectfully disagree with many of the study standards proposed. The AHRQ recommendations that CMS adopted as its CED study design requirements expanded rather than reduced the original thirteen requirements. CMS should consider prioritizing the requirements in order of importance, thus allowing sponsors of CED studies the ability to remain flexible on the less important criteria.

Study Design - We agree with CMS that "the study design, analysis plan, and data source(s) must be sufficient to credibly answer the question(s) posed by the CED."[49] This "fit for purpose" study design is consistent with the goals and principles of CED, as adopted. But there are many questions that are raised when making this determination, the most important of which is: ***who determines if the study design is "fit for purpose?"*** CMS indicates a randomized control trial (RCT) may be appropriate where observational studies may not, but what are the objective criteria to ascertain "appropriateness?" It is difficult to imagine scenarios where an RCT would be appropriate in the context of a coverage decision. Typically, it would be inappropriate and unethical to randomize a beneficiary to a control arm. Why should one beneficiary have a 50% chance of receiving a potentially life-saving, FDA-approved treatment while another enjoys the benefits for which they both contributed to the Medicare Trust Fund through taxes? Other ethical questions remain, including: should a Medicare beneficiary be compelled to enroll in a science experiment not knowing if they will receive the benefit to which they've earned a right as a beneficiary? Or is it appropriate to conduct a "sham procedure" for a medical device implantation?

Other study designs may beg additional questions. If it is decided that a single-arm observational study (e.g., a registry) be utilized, what is a reasonable comparator? Should the comparator procedure or treatment option be included in registry data collection? Finally, there are legitimate cases where real-world studies improve external validity – e.g., interventions to improve medication adherence or influence patient behavior might produce artificial results in a controlled trial setting. In light of these questions and issues, we believe ***a consultative process with stakeholders, particularly patients and patient organizations, is the best approach to decision-making in this situation.*** At some point, researchers may propose a decision-making framework to help CMS and other payers make these kinds of determinations more consistently and objectively.

In addition, the research questions that CMS determines must be answered need to be designed to ensure that they *can* be answered with available data under realistic conditions (e.g., specific, measurable, achievable, realistic and time-specific).

[48] Comments on AHRQ Analysis of Requirements for Coverage with Evidence Development [Internet]. 2022. Available from: https://healthpolicy.usc.edu/wp-content/uploads/2022/10/USC-Schaeffer-re-AHRQ-Requirement-for-CED.pdf

[49] Guidance page 11

Data Collection Methods - to maintain consistency with CED goals and principles, the least burdensome methods of data collection should be used to answer the questions posed by CED. Ideally, data could be gathered through "passive collection" techniques, such as administrative claims data or electronic health records. Additional considerations:

- If CMS is to condition provider payment upon additional "active data collection" requirements, providers and/or data collection organizations should be compensated through increased payments to offset incremental expenses[50]
- If data collection is to be conducted or managed by a third party, the data collected as a condition of coverage should be the property of CMS and made publicly available as discussed herein
- Registries, if used, should follow best practices as outlined in "Recommendations for Advancing Safety and Public Health" - Medical Device Registry principles (by The Pew Charitable Trusts, Blue Cross Blue Shield Association, and the Medical Device Epidemiology Network)[51]
- Patient consent to their data being collected and used for research should comply with the Common Rule[52]

Data analysis - CMS rightly proposes that information gathered under CED should be published[53] and publicly accessible to inform patients, caregivers and healthcare providers about the items or services under CED[54] so they can make good decisions.[55] However, CMS's internal capabilities to analyze data and evidence collected under CED is limited.[56] To facilitate fair and balanced analysis of the data, we urge CMS to enlist the expert resources and capabilities of researchers with expertise in clinical effectiveness and outcomes research. We recommend early and real-time access to data in a phased approach, starting with expert resources providing reports to CMS, then opening the data to academic researchers, and ultimately to the public in an easily understandable format to facilitate patient decision making.

5. Ending CED

CMS has represented CED as a temporary condition, after which the Agency would make a National Coverage Determination to cover, not cover, or conditionally cover the item or service. However, many CEDs appear to never end, some lasting almost 20 years.[57] These long or ambiguous timeframes create uncertainty that could chill innovation. It also results in less accountability; the science can be advanced when all stakeholders – including manufacturers of new therapies – have "skin in the game," so they are motivated to help CMS design studies that provide the information needed to move the therapy to

[50] ". . . [D]ata are often manually collected by human abstractors, which contributes to this time lag, can result in transcription errors, and adds significant expense to the collection process." Maddox TM, Albert NM, Borden WB, Curtis LH, Ferguson TB, Kao DP, et al. The Learning Healthcare System and Cardiovascular Care: A Scientific Statement From the American Heart Association. Circulation. 2017 Apr 4;135(14):e826–57.
[51] Recommendations for Advancing Safety and Public Health" - Medical Device Registry Principles [Internet]. The Pew Charitable Trusts; 2014 [cited 2023 Aug 17]. Available from: https://www.pewtrusts.org/-/media/assets/2014/09/device-registry-conference-report.pdf
[52] https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html
[53] "results of all CED approved studies under 1862(a)(1)(E) will be analyzed and published in the public domain, preferably in peer-review journals." [Guidance page 12]
[54] "publication of clinical studies is necessary to inform patients, their caregivers, and their healthcare providers about the risks and benefits of available health care options" [Guidance page 12]
[55] "sufficient evidence to inform patient and clinician decision making" [Guidance page 12]
[56] cite inability to publish anything from Zeitler.
[57] Zeitler EP, Gilstrap LG, Coylewright M, Slotwiner DJ, Colla CH, Al-Khatib SM. Coverage with Evidence Development: Where Are We Now? Am J Manag Care. 2022 Aug;28(8):382-389. doi: 10.37765/ajmc.2022.88870. PMID: 35981123.

standard coverage. Without a predictable timeframe, providers face uncertainty about what requirements must be met to "graduate" from CED and what events may trigger failure. In the proposed Guidance, CMS continues to assert that CED should not last indefinitely,[58] and coverage should be time-limited to allow for "sufficient evidence generation,"[59] but the Agency stops short of specific recommendations. CMS does recommend a stopping rule when sufficient evidence is gathered[60] or the study is completed and published.[61]

Consistent with our proposed goals and principles of promoting innovation and the principles of transparency, predictability and minimally burdensome regulation, we would propose stopping rules similar to those proposed in CMS's TCET Guidance:

A) Any announcement of CED should carry a presumption of coverage, meaning that at the expiration of the CED time limit, CMS is expected to announce an NCD granting the product coverage, unless generated evidence patently demonstrates that the item or service is not reasonable or necessary to diagnose or treat the indicated illness or injury and warrants non-coverage or coverage with conditions.
B) Before a CED decision is finalized, CMS works with stakeholders to develop objective, *ex ante* criteria for success or failure of the research questions, based on reasonable priorities and outcomes that matter most to patients
C) CED would apply for up to 3 years, or when the research questions are answered through sufficient data collection and objective analysis, whichever comes first, subject to the following conditions
    - "Sufficiency" of data type and amounts would be determined through processes and standards as outlined above in "Factors to use when CMS considers implementation of CED" and "Clinical research/study design standards"
    - An option to remove CED requirements earlier if significant new evidence arises
    - An option to extend CED longer than 3 years, not to exceed another 2 years, if significant new evidence arises that would have warranted the triggering of CED or a non-coverage decision. CED should not last more than five years under any circumstances.
D) After CED ends, CMS must finalize an NCD granting coverage, unless the evidence supports a non-coverage or limited/conditional coverage decision

6. Process

Broader and more sustained patient and public input are needed; CMS misses an opportunity to establish a more open and transparent approach to its coverage process in this proposed Guidance. The Agency indicates that "the public is afforded the opportunity to comment,"[62] which may have been the approach of federal agencies in the late 20th Century, but public engagement practices have advanced considerably in the last two decades. The Agency should learn from the experience of global Health

[58] "CMS does not believe that an NCD that requires CED as a condition of coverage should last indefinitely" Guidance page 12
[59] "coverage should be time-limited to facilitate the timely generation of sufficient evidence" [Guidance page 12]
[60] "sufficiency of sample size as required by the question" [Guidance page 9]
[61] "a revised NCD could be expedited once the study is completed and the results are published. CMS would also accept a manuscript that has been peer-reviewed and accepted for publication or studies that are otherwise published in the public domain" [Guidance page 12]
[62] Guidance page 2

Technology Assessment organizations, which over the years have developed processes to maximize opportunities for patient and public input in the assessment phase of new technologies.[63] For example:

- Long-range planning – Publish for public comment and input a forecast of potential disease areas of concern where CED may be warranted[64]
- Near-range planning – Reach out proactively to patient organizations that represent the potential disease areas of concern to gather input and feedback on the patient experience to better inform CMS's approach
- Patient representatives – enlist the involvement of patients and carers with relevant disease experience at all stages of the process[65]
- Qualitative and quantitative data analysis – identify or generate qualitative and quantitative data specifying patient perspectives and priorities

While the development of a CED policy itself may not be an "assessment" in the sense that CMS's National Coverage Assessment is, the principle remains: a public payer has a responsibility to ensure it is representing the interests of the public it serves. Instead, the Agency has an opportunity for a "requestor" (". . . any member of the public may request to reopen the NCD that requires CED"[66]) to meet with CMS and frequent, informal contact is possible."[67] This creates an aura of secrecy and "back room dealing" between the Agency and self-interested stakeholders.

7. Coverage – the "C" of CED

While evidence development is a worthwhile goal, perhaps the more controversial aspect of CED is the use of seemingly arbitrary coverage constraints to limit patient access during this "temporary phase" until sufficient evidence is developed to justify an NCD. While CMS technically can constrain access to new technologies under any circumstance, we believe a coverage decision that is invoked for the primary purpose of generating evidence should be fit to that purpose. Coverage restrictions should be guided by specific evidence that a technology or service is not suitable for a category of patients. Broadly limiting patient access to new items or services under CED is counter to the goal of evidence development, particularly if better understanding of the generalizability of the results of clinical studies is a goal. How can we learn if an item or service has similar results in the "real world" (outside of the controlled environment of a clinical trial) if coverage is limited to sites or individuals like those in a clinical trial?

We recognize there may be other goals or principles CMS may be trying to achieve with this policy, including reducing utilization. If evidence generation tools are working properly, CMS and other stakeholders will gain a better understanding about appropriate utilization as data is reported on a regular, real-time basis. If an item or service is being inappropriately used, properly designed data-collection strategies will demonstrate this fact and enable CMS to take corrective action.

We recommend CMS consider the development of a clear, transparent, and predictable decision-making framework to guide it through the use of coverage constraints to ensure they are fit for purpose.

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[63] Abelson, J., Wagner, F., Dejean, D., Boesveld, S., Gauvin, F.-P., Bean, S., Axler, R., Petersen, S., Baidoobonso, S., Pron, G., Giacomini, M., Lavis, J., 2016. Public and Patient Involvement in Health Technology Assessment: A
[64] Framework for Action. International Journal of Technology Assessment in Health Care 32, 256–264.. https://doi.org/10.1017/s0266462316000362

[65] Nabarette H, Chastenay MH, Dupont JCK, Ganache I, Single ANV. Patient and Citizen Participation at the Organizational Level in Health Technology Assessment: An Exploratory Study in Five Jurisdictions. International Journal of Technology Assessment in Health Care. 2023 Jan;39(1):e51.

[66] Guidance page 12

[67] Guidance page 12

Conclusion

CMS's CED policy could be a valuable tool to promote and support innovation, expedite earlier beneficiary access to new items and services, generate additional evidence to evaluate these items and services, and ensure appropriate resource utilization. CMS has an opportunity, through its proposed Guidance, to improve the process, increase transparency, reduce uncertainty, stimulate meaningful innovation and build public support and confidence in the Agency's decision-making. As we outlined in this comment, there are several improvements that need to be made in order for that to happen, including:

- Limiting use of CED to those scenarios where real-world evidence is needed and will be informative rather than using it to effectively revaluate an approval decision
- Limiting constraints on coverage to the purpose of generating evidence; real-world evidence depends on real-world utilization
- Building clear and predictable decision-making tools to guide stakeholders (including CMS) on how and when to use CED, including specific guidance about when CED will be triggered (when there are significant research questions)
- Right-sizing CED to narrowly address the questions or concerns identified, and removing it as soon as those questions are answered or after a set period of time
- Involving patients and the patient community as primary stakeholders in the decision-making throughout the process

We look forward to working with CMS as it pursues continued improvement in its coverage process. Please let us know what we can do to further support CMS's goals.

Sincerely,

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