USC Schaeffer
Leonard D. Schaeffer Center
for Health Policy & Economics

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Dr. Robert Otto Valdez, Ph.D., M.H.S.A.
Director, Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857

Re: Comments on AHRQ Analysis of Requirements for Coverage with Evidence Development

Dear Dr. Valdez:

Thank you for the opportunity to comment on Agency for Healthcare Research and Quality (AHRQ)'s analysis for the Center for Medicare and Medicaid Services (CMS)'s requirements for Coverage with Evidence Development (CED) study design. Researchers at the USC Schaeffer Center for Health Policy & Economics have been studying how evidence can be used to define value in our healthcare system since 2012; 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 the delivery of healthcare through evidence-based policy solutions, research excellence, and private and public-sector engagement.

CED is a good example of an intervention to improve health outcomes (e.g., by improving patient access to new technologies) through public policies such as coverage decisions based on evidence gathered through CED. 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. Below, we outline our critique on how AHRQ's analysis addresses these important goals.

I. CED study design recommendations not aligned with public health needs

Though no fault of AHRQ's, the assignment to provide CMS feedback on the research study criteria required when applying CED appears misaligned with the primary goals of CED. Instead, CMS would have been better served by AHRQ's research expertise and perspectives by providing the agency with specific recommendations on how improve CED to facilitate its primary goals: patient access, evidence generation and driving innovation.

CED is broken and AHRQ should have focused its recommendations on how to fix it

While the scope of AHRQ's remit may not have included a broader assessment of CED, the assignment seems to ignore an important challenge: CED does not work properly. If CED were to perform as designed, it would allow access to a promising new therapy and use real-world data to learn how patients who truly are suffering respond to treatment. The real-world evidence gathered often proves invaluable with respect to clinical trials that lack generalizability or considerations for health equity. For example, it took several years in the market before cholesterol-reducing statins were proven to show a

[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).

reduction in deaths from heart disease.[2] Scientists suspected that would happen, but it took time collect data and illustrate the association using real-world evidence, while in the meantime many lives were saved.

In April 2012, President Obama issued his National Bioeconomy Blueprint, which acknowledged the purpose of CED as being a driver of innovation. Coincidentally, the blueprint also acknowledged that CED had been used sparingly since the creation of the program in 2005.[3] This likely was not an accident or oversight on the part of CMS; rather, it is a tacit acknowledgement that technologies that could be considered for CED get stuck in a bureaucratic holding pattern, and it becomes unclear who had authority to execute CED for specific technological innovation. Unfortunately, recent CMS actions reflect its hesitancy to promote innovation on behalf of its beneficiaries, including its repeal of the Medicare Coverage of Innovative Technologies (MCIT) rule, delay in proposing the successor Transitional Coverage for Emerging Technologies (TCET) rule, and finalizing a National Coverage Determination implicating an entire class of drugs aimed at treating Alzheimer's.[4]

Unfortunately, the CED Program has stifled innovation. Since the 2005 inception of the CED program, twenty-seven therapies have been subjected to CED, however, only four of these have had their evidence development programs retired. Many therapies that did have their evidence development programs retired ultimately ended up having their coverage decided by Medicare's regional administrative contractors. The remaining twenty-three items and services continue to be subject to evidence collection requirements, and none have preset timeframes for "graduating" from the program and receiving a final coverage determination. Even amongst the four therapies for which evidence collection was retired, the time elapsed between initiation of CED, and retirement ranged between four and twelve years.[5] Multiple therapies that were amongst the first to receive CED continue to be required to generate clinical data today, almost twenty years later. As an example, Medicare issued a National Coverage Determination requiring CED for PET scans in conjunction with certain cancers in 2005. While Medicare loosened this policy in 2013 by deferring coverage decisions to its regional contractors when PET is used for oncologic services, Medicare continues to tightly constrain PET services for other conditions, including neurological disorders and dementia.[6] For these purposes, PET scans are still covered under CED today despite the fact that hospitals across the U.S. collectively perform almost two million scans per year.[7]

The slow offramp from CED creates several negative consequences, including discouraging innovation. Ironically, the substantial resources required to facilitate CED can serve as a barrier to evidence development. It is not always clear which entity should bear the costs of developing systems to collect and input data, or share the data with registries, and who should bear the cost of participation. This problem can be pronounced in circumstances where multiple commercial actors may market the

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[2] Navarese EP, Robinson JG, Kowalewski M, et al. Association Between Baseline LDL-C Level and Total and Cardiovascular Mortality After LDL-C Lowering: A Systematic Review and Meta-analysis. *JAMA.* 2018;319(15):1566–1579. doi:10.1001/jama.2018.2525

[3] The White House. "National bioeconomy blueprint, April 2012." *Industrial Biotechnology* 8.3 (2012): 97-102.

[4] Centers for Medicare & Medicaid Services. "Monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease." *Accessed May* 4, 2022: https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=305.

[5] 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.

[6] Tunis, Sean, and Danielle Whicher. "The National Oncologic PET Registry: lessons learned for coverage with evidence development." *Journal of the American College of Radiology* 6.5 (2009): 360-365.

[7] Weiner J. "Seeing More with PET Scans: Scientists Discover new Way to Label Chemical Compounds for Medical Imaging." July 27, 2019. Accessed September 28, 2022: https://newscenter.lbl.gov/2017/07/27/new-chemistry-pet-scans-medical-imaging/

technology, none with a large enough stake to take on these responsibilities alone. This occurred when CMS placed home oxygen for cluster headaches under CED in 2011; no trials were developed to facilitate data collection, and ten years later CMS revoked its NCD and deferred coverage determinations to its regional administrative contractors.[8] Additionally, data generation may prove burdensome for providers, and failure to incorporate such collection into clinical workflow may fail to generate sufficient data and discourage further adoption of the technology.

Lastly, the long or ambiguous timeframe for CED creates uncertainty that chills willingness to innovate. Without a set timeframe, providers may be unsure as to what requirements must be met to "graduate" from CED and what events may trigger failure. MCIT may serve as a guide for CMS to address many of these concerns. Unlike the current CED process, TCET would have a clear time limit during which an innovator could collaborate with CMS to address concerns surrounding medical necessity and gather the necessary data to demonstrate medical necessity. At the end of four years of TCET, the innovator would be assured that evidence generation requirements would cease and that they would graduate; either through coverage determinations made by CMS or its contractors, or through claim-by-claim decisions.[9] Temporal limits to CED such as this, and clear indications as to what data CMS is looking for to grant coverage, could all help improve innovator confidence in this process.

CMS and FDA evidence evaluation roles should be clearly delineated and respected

An additional challenge with the current CED system is the temptation it places on CMS officials to second-guess the work of the FDA. Nowhere is this more apparent than in CMS's National Coverage Decision concerning Aduhelm. A read of that decision shows that CMS is concerned with the potential harms associated with the use of Aduhelm, which may include brain bleeds and falls amongst other factors. CMS does not believe an item or service to be reasonable and necessary if the harms of the treatment outweigh the benefits.[10] Such a stance is difficult to distinguish from FDA's adjudications regarding the safety and efficacy of an item or service. Additionally, unless otherwise contraindicated for populations represented by Medicare, (e.g., seniors or patients in renal failure) 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.

II. Methods

The agency's research approach in evaluating the current and proposed requirements for CED study design requirements appears to use a version of the Delphi method to facilitate the input of experts in the field. While it is not apparent in the methods discussion of the report that the agency fully followed the most recent best practices,[11] it appears the approach was generally appropriate and useful for this research question. That said, we have concerns with the agency's methods:

- **The guiding and key questions should have been tied to the purpose of CED**. As already mentioned, it appears CMS tasks AHRQ with the wrong assignment: providing feedback on the research criteria used when applying CED. Instead, CMS would be better served by AHRQ's research expertise and perspectives by providing the agency with specific recommendations on how

[8] Where are We Now *op cit.*

[9] Centers for Medicare & Medicaid Services. Medicare Coverage of Innovative Technology (CMS-3372-F). (2021)

[10] Centers for Medicare & Medicaid Services. "Monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease." *Accessed May* 4, 2022: https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=305.

[11] Beiderbeck D, Frevel N, von der Gracht HA, Schmidt SL, Schweitzer VM. Preparing, conducting, and analyzing Delphi surveys: Cross-disciplinary practices, new directions, and advancements. MethodsX. 2021 May 28;8:101401. doi: 10.1016/j.mex.2021.101401. PMID: 34430297; PMCID: PMC8374446.

best to facilitate the primary purpose of CED: driving innovation. Even if CMS/AHRQ limited the scope of review to the research criteria, the questions could have been more focused on: "how to prioritize research criteria to meet the goals of CED?"

- **Identification of "Key Informants" (KIs) should have been revealed at this stage**. While we appreciate that the use of a version of the Delphi method encourages preserving the anonymity of the experts, and that AHRQ plans to release the identities of the "Key Informants" (KI) in the final report, we believe the KI should have been identified in the agency's draft report for public comment. This aligns with the field of public health's migration towards open peer-review, and can help AHRQ in future reports maintain public confidence in its processes and avoid potential negative feedback from public stakeholders.

- **AHRQ should have sought to expand the number and diversity of KIs**. While Delphi methods are amenable to the use of a relatively small sample of participants, in this case given the public health impact, the agency should have endeavored to ensure a wide range of diversity and inclusion of multiple KIs with different perspectives, most notably those representing underrepresented populations, patients and life sciences industries.

- **Patients, patient organizations and life sciences industry experts should have been better represented as KIs**. These are important stakeholders in the public health ecosystem, some of which whose voices are typically not heard in these kinds of discussions. While the agency sought input from "patient/consumer advocacy," patients and patient organizations have unique perspectives to the "usual suspects" (medical societies, health registries, health plans, etc.). In addition, the life sciences industry has valuable resources whose biases can be just as mitigatable as those of the other stakeholders involved in this process.

- **The options for methodological approaches for life science companies to take in order to develop new evidence that meets expectations for clinical safety and efficacy should be broadened.** The average cost of a clinical trial conducted by a pharmaceutical company today exceeds $19 million, including the combination of successes and failures that these companies take risk on.[12] Budget constraints for most health technology (e.g. medical devices and diagnostics) manufacturers limit the risk they can take to develop such technology using traditional research methods. However, alternative methods in observational research and quasi-experimental design support real-world evidence development at lower costs, and therefore more affordable investments that can still succeed in establishing the causal inference pathway of treatment effect.

- **CMS/AHRQ should leverage expertise and experience of health economics professionals and institutions to base its recommendations on methods in health technology assessment**. USC Schaeffer has published recommendations on how the US healthcare system could better assess value of new therapies.[13] In addition, more than 10,000 health economists work in the public health sector of the U.S. This bandwidth for innovation in value assessment offers us potential to redefine the methodology and ground rules for conducting value assessment – and how it is applied to

[12] Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016. JAMA Intern Med. 2018 Nov 1;178(11):1451-1457. doi: 10.1001/jamainternmed.2018.3931. PMID: 30264133; PMCID: PMC6248200.

[13] Lakdawalla D, Neumann PJ, Wilensky GR, et al. Health Technology Assessment in the U.S. – A Vision for the Future. February 9, 2021. Last Accessed September 28, 2022: https://healthpolicy.usc.edu/research/health-technology-assessment-in-the-u-s-a-vision-for-the-future/

decision-making – to meet the unique needs of US health systems. If value is to be better defined and assessed, then CMS could break the mold and start tying reimbursement to meaningful patient outcomes, as identified and prioritized with quantitative patient preference data. Once safety and function are established by FDA review, value is best established by seeing how new treatments diffuse into clinical practice. US health systems have the bandwidth and the unique perspective to perform assessments in accordance with their own values.[14]

III. Amended Requirements

If the primary goals of CED are to provide coverage, collect evidence and drive innovation, the AHRQ recommendations for amending the CED study design requirements appear in some ways to run counter to those goals. Common sense would dictate that any effort to improve patient access to new, innovative technologies would dictate a streamlining and/or reduction in study design requirements. Instead, AHRQ recommends expanding the requirements from 13 to 22. While some of this expansion was the result of an admirable effort to simplify and streamline existing "compound" requirements by splitting them, the addition of several new requirements resembles an effort to increase the scientific rigor of these studies.

We recommend AHRQ and CMS consider prioritizing the requirements in order of importance and allowing sponsors of CED studies the ability to remain flexible on the less important criteria. Below is a table with our comments on a sample prioritization, based in part on the results of the report's Table 5: Amended Requirements Based on the Recommendations of the Key Informants. We would recommend the agency re-evaluate the importance of each of these criteria using a similar method used in this report, but with a more diverse and expanded stakeholder population. Prioritizing the design requirements in this way would help AHRQ and CMS balance the goals of quality evidence generation and patient access.

Priority	Final Amended Requirements for Public Posting	Comment
High	A. The study is conducted by investigators with the resources and skills to complete it successfully.	
High	D. CMS and investigators agree on an evidentiary threshold for the study as needed to demonstrate clinically meaningful differences in key outcome(s) with adequate precision.	Evidentiary thresholds for outcomes should be set by the target patient populations, based in quantitative evidence of patient preferences and tolerance for uncertainty.
High	E. The study's protocol is publicly posted on the CMS website and describes, at a minimum, the data source(s), key outcome(s), and study design.	A description of the study should be registered on ClinicalTrials.gov. Study sponsors should not be compelled to disclose proprietary information (potentially including study protocol) until a reasonable period of time after the conclusion of the study.
High	F. The protocol describes the information governance and data protection requirements that have been established.	
High	G. The data are generated or selected with attention to completeness, accuracy, sufficiency of duration of observation, and sample size as required by the question.	
High	H. Data for the study comes from patients treated in the usual sites of care delivery for the product.	

[14] Padula WV. The US should assess the economic value of drugs rather than leave it up to other countries. STAT News, January 17, 2019. https://www.statnews.com/2019/01/17/us-assess-economic-value-drugs/

USC Schaeffer Researcher Comments
Re: AHRQ Analysis of Requirements for Coverage with Evidence Development (CED)

Priority	Final Amended Requirements for Public Posting	Comment
High	I. The key outcome(s) for the study are those that are important to patients. A surrogate outcome that reliably predicts these outcomes may be appropriate for some questions.	Outcomes should be limited to those that are of high importance to the target patient populations, based in quantitative evidence of patient preferences of risks and benefits
High	S. The research study complies with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration, it is also in compliance with 21 CFR Parts 50 and 56.	
High	P. The results and analytic code are submitted for peer review using a reporting guideline appropriate for the study design and structured to enable replication.	The results should be published; submission to peer review is not sufficient to satisfy publication. The publication of the analytic code publication should not be a requirement; consider moving separating it and moving it down to an optional design element.
High	Q. The investigators commit to sharing de-identified data, methods, and analytic code with CMS or with a trusted third party. Other sharing is to follow the rules of the funder and the institutional review board.	Taxpayer-funded data collection mandates should require that de-identified data should be made publicly available as soon as ethically or reasonably possible. CED should be discontinued if data collected under CED is not made publicly available in a reasonable timeframe.
Medium	K. When using secondary data, investigators provide information about the performance of the algorithms used for measurement of key exposures and outcomes.	
Medium	N. In the protocol, the investigators describe considerations for analyzing demographic subpopulations as well as clinically-relevant subgroups as motivated by existing evidence.	
Optional	L. The study design is selected to efficiently generate valid evidence. If a contemporaneous comparison group is not included, this choice must be justified.	
Optional	M. The investigators minimize the impact of confounding and biases on inferences with appropriate statistical techniques, in addition to rigorous design.	
Optional	O. The investigators demonstrate robustness of results by conducting alternative analyses and/or using other data sources.	
Delete as a requirement of the sponsor		
	B. A written plan describes the schedule for completion of key study milestones.	This is more of a requirement for CMS, who should be required to provide the study sponsor with specific expectations on what, if any, key study milestones would need to be reached for the study to allow CMS to end a CED with a coverage or non-coverage decision or with deferral to a MAC.

Priority	Final Amended Requirements for Public Posting	Comment
	R. The study is not designed to exclusively test toxicity unless the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.	This question should be answered as a safety outcome included in any FDA-approval related clinical trial. It appears that CMS could be inappropriately extending its jurisdiction to that of FDA's (safety and efficacy).
	C. The rationale for the study is supported by scientific evidence and study results are expected to fill the specified knowledge gap.	The burden should be on CMS to provide the rationale for the study, outlining what evidence generated would allow CMS to end a CED with a coverage or non-coverage decision or with deferral to a MAC.
	J. The study population reflects the demographic and clinical diversity among the Medicare beneficiaries who are the intended users of the intervention.	The burden should be on CMS and FDA to ensure the population studied for FDA approval is reflective of the population that will be treated.

IV. Conclusions

- **This is important**: AHRQ and CMS should consider the broad impact of its positions on the innovation of new health technologies and their corresponding opportunity to improve public health. CED could offer innovators a pathway to market access for technologies if it is clear what evidence is required to achieve meaningful use and reimbursement.
- **CMS could make a positive impact**: Most other nations already look to CMS for coverage policies, and private payers in the U.S. opt to emulate CMS decisions rather than create competing policies that could cost them beneficiaries.

- **CED doesn't work right now, and an opportunity exists to fix it**: CED as currently applied negatively impacts innovation. This need not be the case. Absent any changes, care should be taken to more clearly define when it is appropriate to apply CED, and limits should be placed on its use. Well-designed CED with concrete milestones could improve access to innovation.

- **CED study design requirements should be "fit for purpose (innovation)."** Studies should be "least burdensome." Evidentiary requirements should be limited to unanswered questions related to CMS's jurisdiction, that is, reasonable and necessary, as opposed to safety and efficacy.

Sincerely,

Dana Goldman, PhD
Dean and C. Erwin and Ione L. Piper Chair, USC Sol Price School of Public Policy
Co-Director, USC Schaeffer Center
Nonresident Senior Fellow, Brookings Institution

William Padula, PhD
Fellow, USC Schaeffer Center
Assistant Professor, Department of Pharmaceutical & Health Economics, USC School of Pharmacy

Joseph Grogan, JD
Nonresident Senior Fellow, USC Schaeffer Center
Former Assistant, U.S. President
Former Director, Domestic Policy Council (DPC)

Barry Liden, JD
Director of Public Policy, USC Schaeffer Center