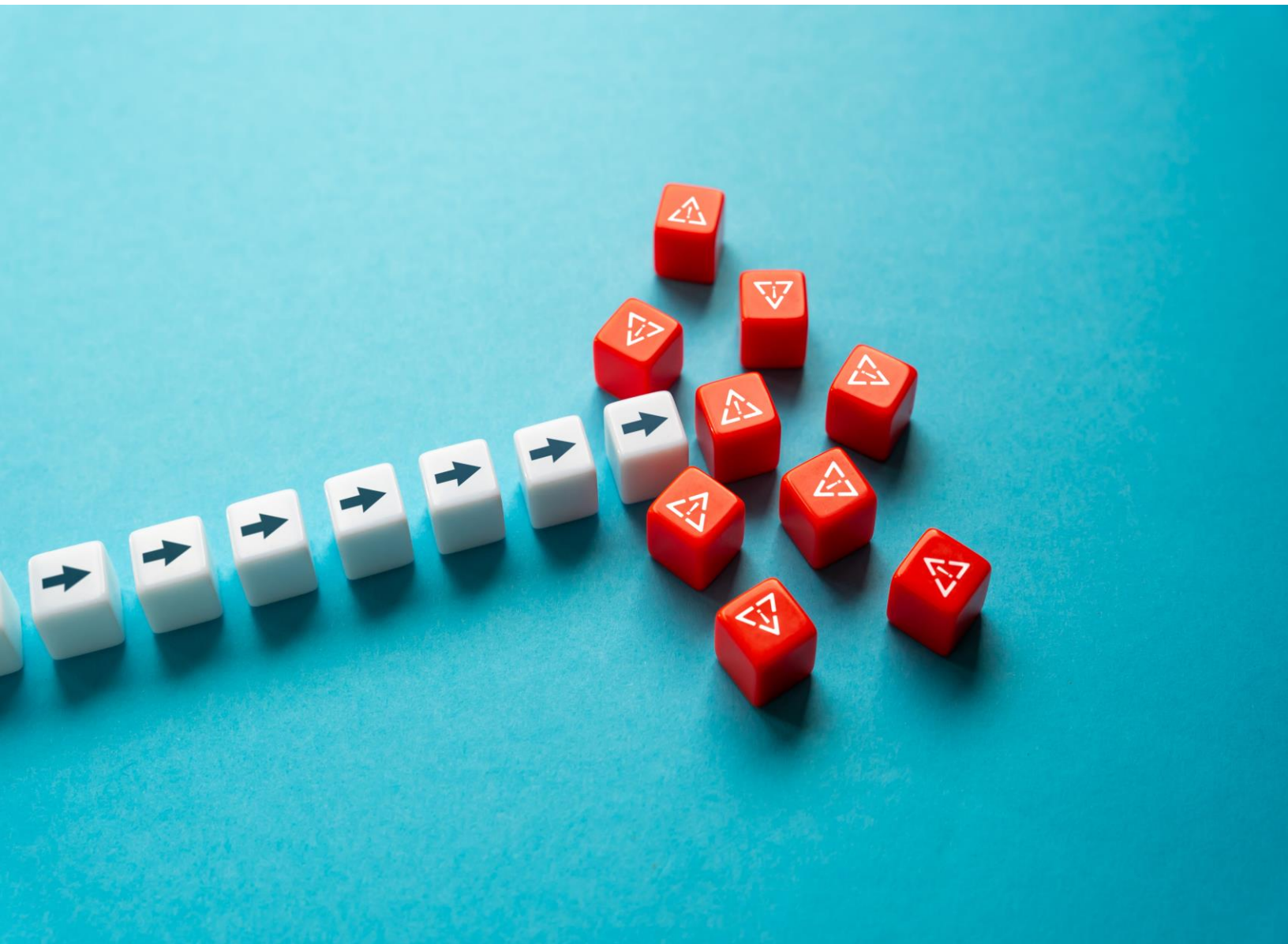


Façade of Evidence:

**How Medicare's Coverage
with Evidence
Development Paradigm
Rations Care and
Exacerbates Inequity**

February 13, 2023



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I. Executive Summary

The Medicare program is the predominant insurer for the over 65 and disabled populations and provides medical coverage for 64 million Americans. By statute, the Centers for Medicare & Medicaid Services (“CMS” or “the Agency”) provides coverage for items and services that are deemed “reasonable and necessary” under the Social Security Act (the “Act”). By comparison, the U.S. Food & Drug Administration (“FDA”) generally approves a drug or biological product based on a finding that it is “safe and effective” based on the Federal Food, Drug, and Cosmetic Act. Separately, medical devices are approved based on a “reasonable assurance” of safety and efficacy to receive FDA approval.

Given the FDA’s rigorous, evidence-based approval process, CMS has largely considered FDA-approved drugs and biologics as “reasonable and necessary.” Medicare can formally establish national coverage policy for Medicare Part B physician-administered services or therapeutics through a National Coverage Determination (“NCD”) or allow a Medicare contractor to establish regional coverage guidelines. More commonly, the need for therapeutics and services are considered on a claim-by-claim basis.

CMS has the option to issue a NCD to set a single coverage standard on how an FDA-approved product or service is covered nationally in the Medicare Part B program. Between 2012 and 2022, CMS issued 336 NCDs, primarily for medical devices and services. CMS utilizes a range of potential coverage outcomes for NCDs, from full coverage to a prohibition on coverage. Given the size of the Medicare population, NCDs represent a high-stakes decision by the Agency that can either procure coverage for a new therapeutic or result in nearly 20% of the U.S. population being unable to potentially access a treatment for a given condition. Unfortunately, it is not uncommon for the CMS coverage decision process to become highly politicized due to its economic impacts on public and private payers, industry, specialty providers, and national and regional medical systems and hospitals.

In recent years, CMS has escalated its focus on the prices of drugs, biological products, and medical devices at a time when growth in U.S. healthcare cost increases have outpaced economic growth, notwithstanding the fact that such considerations fall outside of Medicare’s legal mandate. Drug pricing and payment policies are statutorily distinct from coverage considerations. CMS has repeatedly insisted that it does not consider

the price of medical products and services when determining coverage policy; however, former HHS assistant secretary Dr. Richard Frank has characterized NCDs as “the most powerful coverage tool that Medicare has and have generally been reserved for Medicare services that are costly ...”ⁱ

Since 2005, CMS has turned to using an extralegal paradigm known as coverage with evidence development (“CED” or an “NCD requiring CED”). Initially, CED was utilized to accelerate access to medical devices, which have fewer clinical trial requirements in comparison to drugs and biologics. As time passed, CMS expanded its use of CED to other therapeutic types and diagnostics. Under CED, the Agency denies Medicare coverage for an FDA-approved item or service *except* when it is provided to beneficiaries within a population-limited clinical study, such as a CMS-approved clinical trial or data registry. Beneficiaries who are ineligible under the strict CED requirements, cannot access the clinical study sites, or are reluctant to be required to

enroll in a clinical study to receive access are left without coverage.

Once CMS places a treatment in CED, it is extraordinarily difficult for the coverage restriction to be lifted. An August 2022 systematic review of CED program history, published in *The American Journal of Managed Care* identified that, between 2005–2022, CMS issued a total of 27 NCDs requiring CED. Only four have been retired¹ by the Agency, which has taken an average of 8 years to do so.² Under its current paradigm, CMS has enabled 22 CEDs to continue in perpetuity, including several that have been ongoing for more than 15 years.ⁱⁱ

Additionally, CMS sets “conditions of coverage” (e.g., the treatment is only provided for beneficiaries in certain settings of care and overseen by designated specialists) for health facilities participating in CED studies that often prohibit access for beneficiaries in rural communities and in communities of color. In some cases, the lack of enrollment from these populations has provided the Agency justification to continue

¹ There were two CEDs, artificial hearts and home oxygen for cluster headaches, that resulted in revocation of the NCD and deferral of coverage decisions to local contractors.

² See Emily P. Zeitler et al., Coverage with Evidence Development: Where Are We Now? 28 AM. J. MANAGED CARE 382, 382 (Aug. 2022), <https://www.ajmc.com/view/coverage-with-evidence-development-where-are-we-now->. Dr. Zeitler’s et al conclusions are not new. Other studies have similarly concluded that “CED schemes . . . are often costly, complex, and challenging.” Carlo Federici et al., Coverage with evidence development schemes for medical devices in Europe: characteristics and challenges, 22 EUR. J. HEALTH ECON. 1253, 1253–73 (Nov. 2021).

a CED determination. In practice, NCDs requiring CED have been operationalized and evolved to restrict access to potentially life-saving therapies for millions of Medicare beneficiaries.

CMS's unchecked use of CED has led to harmful consequences including:

- The continuation of restrictive coverage requirements for an indefinite period of time;
- Barriers to beneficiary access for potentially clinically meaningful items and services and the deterioration of health outcomes;
- Perpetuation and exacerbation of access to care barriers for beneficiaries of color and those from rural communities;
- The regulatory repudiation of the FDA's statutorily-authorized accelerated approval program;
- The imposition of unnecessary costs and burdens on sponsors and healthcare providers; and
- The failure to advance the Congressional intent of Medicare.

As a result of these harmful outcomes, it is imperative that CMS cease its use of CED. However, CMS has indicated its intent to instead deploy additional NCDs requiring CED by commissioning a November 2022 report from the Agency for Healthcare Research and Quality (AHRQ) on recommendations to refine CED study design requirements.ⁱⁱⁱ On February 13-14, 2023, the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) will use the final AHRQ report as a basis for its discussion and provide its recommendations to CMS.^{iv} Other potential expansions of CED by CMS include a proposed rule that conditions coverage of technologies (and potentially including drugs) on the collection of additional evidence in CMS-approved studies^v; and recommendations from the Medicaid and CHIP Access Commission (MACPAC) for Congress to grant states outright authority to limit Medicaid formularies based upon Medicare NCD determinations.^{vi}

II. Overview of Medicare Coverage

Under Section 1862(a)(1)(A) of the Social Security Act, CMS provides coverage for items and services that are deemed “reasonable and necessary” for the diagnosis or treatment of an illness or injury and that fall within the scope of a

Medicare benefit category.^{vii} There is no statutory definition for “reasonable and necessary,” but CMS generally posits that an intervention is not reasonable and necessary if its risks outweigh its benefits.^{viii}

In order for a service to be considered reasonable and necessary, it must be assessed as 1) safe and effective, 2) not experimental or investigational, and 3) appropriate for Medicare beneficiaries.^{ix} By comparison, the FDA generally approves a drug, biological product, or medical device based on a finding that such product has substantial evidence that it is “safe and effective” (based on evidence from adequate and well-controlled clinical trials).^x **Given the FDA’s rigorous, evidence-based approval process, CMS has historically considered most FDA-approved items and services as “reasonable and necessary,” and therefore Medicare either covered them nationally or permitted regional contractor-based coverage decisions.**

a. National Coverage Determinations

Under Section 1862(l) of the Act, CMS may issue a “national coverage determination” (“NCD”) to set limits or conditions on national coverage for therapies (*e.g.*, patient eligibility and healthcare provider requirements).^{xi} CMS may create a NCD for

an item or service for which the Agency believes there is inadequate data to support a determination of “reasonable and necessary” under Section 1862(a)(1)(A) of the Act.^{xii} To do so, CMS undertakes an “national coverage analysis” (“NCA”) to review and determine whether it will establish a NCD for the item or service, a process the Agency generally completes within 9-12 months.^{xiii}

Between 2012 and 2022, CMS issued 336 NCDs (or an average of eight NCDs per year).^{xiv} Most of these NCDs apply to medical devices, but CMS does issue NCDs for FDA-approved drugs and almost always provides coverage in accordance with the drugs’ labels.^{xv} More commonly, provider-administered drugs are presumed to be covered under Medicare Part B and CMS defers to third-party contractors to make the vast majority of these coverage decisions on either a case-by-case basis or through establishing regional coverage policies.^{xvi} When CMS opts to promulgate a NCD, it can either establish nationwide access or cause dramatic, adverse impacts on beneficiary access to innovative and potentially life-saving treatments and services—especially when CMS mandates additional evidence development requirements.

b. Coverage with Evidence Development

Coverage with evidence development (“CED” or an “NCD requiring CED”) is a markedly restrictive coverage requirement. It is important to note that the Agency’s CED policy was *not* authorized by Congress—it was created and implemented by CMS starting in 2005 as a NCD requiring study participation. The CED “paradigm,” as coined by CMS, was first outlined in a 2006 regulatory guidance, and updated in 2014.^{xvii} A NCD requiring CED can be initiated internally by CMS or at the request of an external party, and the process includes

a brief (i.e., 30-day) period of public comment.^{xviii}

Under a NCD requiring CED, CMS denies coverage for an FDA-approved item or service *except* when it is provided to beneficiaries within a limited CMS-approved clinical study (i.e., requiring beneficiaries to enroll in a CMS-approved clinical trial or data registry).³ According to CMS, CED is intended to expedite access to an innovative new therapy while additional evidence is collected to resolve outstanding questions regarding its reasonableness and necessity—rather than the Agency denying coverage.^{xix, 4} In reality, CMS denies many

Is CED a Form of Comparative Effectiveness Research?

Contrary to popular belief, CMS-approved CED studies do not constitute comparative effectiveness research (CER). There is a perception that CMS-approved CED clinical studies compare a new treatment against the previous standard of care side-by-side in the same clinical study—referred to as comparative effectiveness research—but that is a myth. When analyses are conducted between a treatment under CED and the standard of care, data from separate clinical trials or registries may be reviewed, *which means they are not directly comparable*. In contrast, CER directly compares the benefits and harms of medical interventions for the same condition in the same study to assist stakeholder decision making on treatment paths or coverage policy.

³ At the same time, CMS disclaims that CED “will not duplicate or replace the FDA’s authority in assuring the safety, efficacy, and security of drugs, biological products, and devices.” *Id.*

⁴ Medicare covers most FDA-approved items and services, except those specified as “non-covered” in statute (e.g.,

more patients access to those items and services because they are barred by restrictive NCD or CED requirements on any number of grounds, including provider volume requirements, inclusion of practitioners in a care team that are not integral to a patients' care, or unfunded mandates for providers to join data registries that require significant additional provider effort and paid subscriptions. The effect of these types of requirements can be to limit participation only to large or more highly resourced medical facilities, which can restrict access to underserved populations. Broadly, when a Medicare beneficiary is excluded from participating in a CED program due to these external factors, they

must make a costly decision: pay out-of-pocket for the item or service themselves or forgo care.

Data collection to support CED is hampered by CMS's absence of enforcement authority to ensure that permitted modes for data collection (such as a data registry) provide regular analyses and readouts for applicable

CED for Cochlear Implants in Effect Since 2005

At least 1.2 million adults in the United States live with severe or profound hearing loss—a level of impairment that is not sufficiently corrected with hearing aids.¹ A cochlear implant is an electronic device, requiring surgical placement and hearing therapy, and several clinical trials have clearly demonstrated that cochlear implants are a safe and effective treatment for significant hearing loss in older adults.¹ Medicare has had a NCD requiring CED for cochlear implants in place since 2005 (i.e., over 17 years) that includes five, small CMS-approved clinical trial studies with 212 participants total in actual enrollment, according to clinicaltrials.gov.¹ Yet, it is estimated that greater than 150,000 of adults over 70 years likely have hearing loss of a severity that would meet cochlear implantation candidacy criteria.¹

eyeglasses, hearing aids, cosmetic surgery); services and supplies determined to be medically unreasonable and unnecessary; services and supplies denied as bundled or included in another service's basic allowance; and items and services paid by other organizations or provided without charge. Medicare outlines coverage exclusions as well as exceptions in its Medicare Benefit Policy Manual and summarizes them in an MLN booklet: <https://www.cms.gov/outreach-and-education/medicare-learning-network-mln/mlnproducts/downloads/items-and-services-not-covered-under-medicare-booklet-icn906765.pdf> (last visited Feb. 1, 2023).

therapeutics to the Agency and to Medicare beneficiaries. Because CED was created by CMS under the auspices of the NCD statutory authority, former Agency officials have concluded that “there is no specific enforcement mechanism to ensure timely research reporting compliance, which results in an ad hoc process that leaves Medicare beneficiaries in a state of uncertainty regarding their treatment.”^{xx}

Importantly, CMS has not clearly articulated what type or level of evidence is adequate to justify ending CED. In its 2014 guidance on CED, within the section “Ending CED,” CMS states that the purpose of the studies is to “produce evidence that will lead to revisions in Medicare coverage policies,” and cites two examples of completed CED processes.^{xxi} The implication of CMS’s statement is that there would be a clear beginning and end to the CED process.

However, in more than 17 years of applying CED policy, CMS has shown that once it issues a NCD requiring CED, there is no clear end in sight. An August 2022 systematic review of CED program history, published in *The American Journal of Managed Care* identified that, between 2005–2022, CMS issued a total of 27 NCDs requiring CED, but retired only four of them (14.8%).^{xxii} Notably, CMS kept the four

CEDs in effect for between four to 12 years, or an average of eight years, before retiring them.^{xxiii} CMS took an average of 16 months from the date of receiving a reconsideration request to end the CED requirements for these determinations.^{xxiv} During the prolonged time taken by the Agency during the reconsideration process, CMS continues to deny Medicare beneficiaries access to these treatments and services outside of approved clinical trials or data registries. The authors state, “Few programs have achieved retirement of data collection requirements, suggesting that barriers remain to accessing CED therapies.”^{xxv}

The analysis published in the *American Journal of Managed Care* also found “wide variability in CED requirements among therapies including how requirements have been addressed by stakeholders and over what time period; some therapies have no data collection mechanisms.” In fact, four of the NCDs requiring CED have never initiated a registry or trial.^{xxvi} Three of these four have been under CED for at least 10 years: transcutaneous electrical nerve stimulation for chronic low back pain, home oxygen for

CED By the Numbers

Between 2005-2022, CMS issued a total of 27 NCDs requiring CED
In 17 years, CMS has only retired 4 NCD/CEDs

CEDs are in 8 therapeutic areas, with the greatest number in cardiovascular

Retired to NCD without CED (i.e., evidence was adequate)-average length of time for CED was 8 years:

- 1) Carotid artery stenting;
- 2) ICD for primary prevention of sudden cardiac death;
- 3) Magnetic resonance angiography/MRI in patients with a cardiac implantable electronic device; and
- 4) Autologous blood-derived products for nonhealing wounds

The number of registries and clinical trials per therapy or service ranges from 0-34

Four CEDs have not initiated a CED trial or registry:

- 1) CPAP for obstructive sleep apnea
- 2) Home oxygen for cluster headaches
- 3) TENS for chronic back pain
- 4) Anti-amyloid monoclonal antibody (mAb) AD therapies

- There has been wide variability in CED requirements among therapies including how requirements have been addressed by stakeholders and over what time period; some therapies have no data collection mechanisms
- Few programs have achieved retirement of data collection requirements, suggesting that barriers remain to accessing CED therapies.

Source: Emily P. Zeitler et al., "Coverage With Evidence Development: Where Are We Now?", 28 AM. J. MANAGED CARE 382, 382 (Aug. 2022).

cluster headache,⁵ and continuous positive airway pressure for obstructive sleep apnea. The fourth CED is the April 2022 determination on FDA-approved anti-amyloid monoclonal antibody (mAb) Alzheimer's therapies, however, but there is no currently planned CED clinical trial announced since the release of the determination.^{xxvii} CED therapies without any mechanisms for evidence development are essentially unavailable to Medicare beneficiaries despite a determination by the FDA that a therapeutic is safe and effective and a determination from CMS that it may be

appropriate for Medicare beneficiaries pending additional data.

The variability among CEDs extends to the number of CMS-approved clinical studies (either clinical trials, registries, both, or neither), which ranged from 0 to 34 per therapy.^{xxviii} There were seven NCDs requiring CED with one approved data registry each, and of these, four had a registry administered by the American College of Cardiology's National Cardiovascular Device Registry (NCDR) suite.^{xxix} Twenty-one of the 27 CED

⁵ Effective September 27, 2021, the Centers for Medicare & Medicaid Services removed the national coverage determination (NCD) for home oxygen use to treat cluster headaches.

therapies had at least one CMS-approved clinical trial and five therapies had both approved data registries and trials.^{xxx}

Data collection is, as the authors stated, also uneven. Of the 23 CEDs for which registries and/or trials existed, there were 20 (87%) with some publicly available results, including seven in which results were posted on ClinicalTrials.gov.^{xxxi}

i. CED for Drugs and Biologics

Until 2022, CMS had reserved finalized CEDs primarily for innovative medical devices and services, including imaging. The Agency has pointed to limited clinical evidence at the time of product launch and limited, long-term effectiveness and/or durability data of these technologies (such data depends on how the medical devices are adopted) as cause for CED requirements.^{xxxii}

By comparison, CMS has finalized only two CED NCDs for prescription drugs. First, in 2005, CMS established a CED NCD for the off-label use of FDA-approved, anticancer chemotherapeutic agents for the treatment of colorectal cancer when administered in National Cancer Institute-sponsored clinical trials.^{xxxiii} CMS explained that FDA's drug compendia supported the off-label use of one medication for the treatment of non-

small cell lung cancer and medical literature supported off-label indications to varying degrees. CMS concluded it could draw "a sufficient inference of benefit" to warrant coverage of these drugs in settings with patient safeguards.^{xxxiv}

Second, in 2022, CMS finalized a NCD requiring CED for monoclonal antibody therapies ("mAbs") targeting amyloid for the treatment of Alzheimer's disease ("AD").^{xxxv} CMS applied its restrictive CED policy to the entire class of mAbs, which impacts the initial FDA-approved therapies available at the time of the CED's release *and* those that were yet-to-be approved at the time of the CED's issuance.^{xxxvi} CMS's decision prospectively applied to future approved therapeutics, despite CMS's assessment of the need for additional data and effectiveness being based on a single therapeutic. The problems presented by this approach have been underlined by the release of comprehensive data with a stronger efficacy signal from a second mAb approved by the FDA less than a year after the issuance of the CED.^{xxxvii} Rather than acknowledging the challenges and access issues for subsequent therapies created by the initial determination, the Agency is thus far upholding the original coverage determination.^{xxxviii} Meanwhile, each day

1,000-2,000 people advance to moderate Alzheimer's, beyond the reach of FDA-approved disease-modifying treatments.⁶

Before the mAb CED coverage decision, CMS had never 1) declined to cover a drug for its FDA-approved, medically accepted

use; or 2) denied coverage for an entire class of drugs based on clinical trial data for a single drug before any data on other drugs in the class were available. However, the mAb CED experience was not the first time CMS tried to apply NCD requiring CED to a

Curative Therapy for Blood and Bone Marrow Disorders Still Under CED, Despite Positive Clinical Recommendation for Older Adults

Myelodysplastic syndromes (“MDS”) are cancerous blood and bone marrow disorders. Allogeneic hematopoietic stem cell transplant (“HCT”) is the only curative therapy available for MDS, but access has continued to be limited by CMS under its 2010 CED.¹ Approximately 10,000 people in the United States are diagnosed with MDS each year,¹ and it is most common among people in their 70s. However, data from the Center for International Blood and Marrow Transplant Research registry reveal a total of only 1,250 HCT transplants were performed in 2020 (of these, 582 were in those aged 65 and older).¹ This is despite a published *JAMA Oncology* 2020 study on the CED that concluded, “Availability of insurance coverage affects access to HCT. Outcomes in patients older than 65 years are only marginally different from those in younger patients. Based on current data, we would recommend coverage of HCT for MDS by CMS.”¹ The result is that patients in need of access to stem cell transplant are being denied the only curative treatment because twelve years after the start of the CED process, and two years after its completion with a positive recommendation, the CED remains open.

⁶ *Id.*; U.S. Food & Drug Admin., *Press Release, FDA Grants Accelerated Approval for Alzheimer's Drug (June 7, 2021)*, <https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug>. Even though FDA approved aducanumab through the accelerated approval pathway, accelerated approval does not affect FDA's gold standard of approval based on substantial safety and effectiveness. It simply allows FDA to accept a different type of data. See 57 Fed. Reg. 58942, 58944 (Dec. 11, 1992).

drug or biologic. In 2019 the Medicare NCA process for the cancer therapies known as chimeric antigen receptor T-cell therapy, or “CAR-T,” resulted in a draft NCD requiring CED. The draft NCD for CAR-T outlined conditions of coverage for healthcare facilities and restricted beneficiary coverage to those who participated in a CMS-approved registry or clinical study, in which patients would be monitored for at least two years post-treatment. Following opposition from community cancer centers, patient and provider advocacy groups, and industry, CMS ultimately removed the CED requirement in its final NCD decision for CAR-T.

Under the NCD for mAbs, the Agency created two pathways of CED requirements, depending on how an Alzheimer's treatment is approved by the FDA. If the FDA approves a therapy under "accelerated approval"—a pathway designed to give patients diagnosed with a serious condition where there are few therapeutic options earlier access to medicines that are likely, though not yet fully proven, to be clinically beneficial based on a secondary clinical endpoint—Medicare requires beneficiaries to enroll in randomized control clinical trials to receive access. Such studies would be limited to a small population, will take

years to complete, and patients will have to risk receiving and paying cost-sharing for a placebo rather than receiving an FDA-approved treatment.

For drugs approved under the FDA's traditional pathway—in other words, drugs that have been proven to provide clinical benefits, such as slowing the decline in patients' cognition and function in beneficiaries with Alzheimer's disease—Medicare will still require beneficiaries to enroll in a data registry clinical study. The idea of a patient registry sounds good on paper, as more evidence on a treatment's efficacy advances the body of evidence that can inform decision making for beneficiaries in the future. But when utilized as a condition of coverage, registry requirements ration treatment access and exacerbate health disparities.

ii. *CED-mandated Data Registries are Restricted Clinical Studies*

It is critical to recognize that ***data registries mandated by CMS under CED as a condition of coverage are clinical studies, just like clinical trials.*** Similar to CED clinical trials, CED data registry studies must 1) adhere to the same list of standards for clinical research studies, 2) be pre-approved by CMS for

coverage and reimbursement, 3) include an intervention study group and comparator group (e.g., patients who receive standard of care), 4) answer the same outstanding questions posed by CMS related to the therapy, and 4) adhere to all “conditions of coverage” set by CMS for the CED (e.g., the treatment is only provided for beneficiaries at specific stages of disease, in certain settings of care, and overseen by designated specialists).^{xxxix} Additionally:

- Cumbersome registry data collection requirements create workflow burden and limit patient participation;
- Care settings generally must pay fees to participate;
- Additional, often strict conditions of coverage shut smaller, less-resourced settings, providers, and communities out of participation; and
- CMS currently has no direct access to the registry data and no enforcement authority over whether the agency’s registry-related evidence questions are answered, let alone answered within a designated period.

In addition, CED-mandated data registries may take a year or more to initiate. Providers that would like to participate in a

CED registry face significant administrative and financial barriers such as assembling committed volunteer physician leaders and securing funding for dedicated staff, software, data warehouses, and analytical centers.^{xl} Providers must navigate operational challenges including a complex array of database functions (e.g., data element specifications, data security, privacy, data harvests, data quality checks and audit, feedback reports to participants, and data manager support).^{xli}

Once CED Determination is Finalized by CMS, Significant Effort is Required to Set Up Registry or Confirmatory Trial During Which Time Patients Have No Access

Significant efforts are required once CMS has finalized a CED requirement of a confirmatory trial or patient registry just to get to the start line of additional data development. It is important to note that most prominent therapeutic CEDs to date have been centralized, meaning that they are led by a convener such as a professional advocacy organization. In some cases, there is more than one convening organization. This is an important timeline consideration because the time to align across all stakeholders extends the timeline for many of the steps outlined below.

Generally, the following steps that must occur between finalization of a NCD requiring CED and the point in time when the first patient is able to enroll in a centralized CED registry and receive Medicare coverage for the item or service in question:^{xiii}

1. CMS announces a NCD with CED
2. Informal selection of a convening organization³
3. Select primary investigators³
4. Establish study governance (i.e., Steering Committee)*
5. Conceptualize a CED study protocol*
6. Write a protocol³
7. Review and revise protocol with stakeholders*
8. Study governance approval of initial protocol³
9. Submit the protocol to CMS³
10. CMS reviews and redlines (link to guidance document below which contains info on CMS response timelines)³
11. Study stakeholders and/or study governance reviews and responds to CMS redlines*
12. Repeat until aligned (this could be multiple rounds)*
13. Establishment of a clinicaltrial.gov identification number³
14. CMS approval³
15. Build a study database and other operational elements³

- | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> 16. Develop data collection forms (electronic and/or paper)³ 17. Establish an IRB process (central or local)³ 18. Select an IRB vendor (if centralized)³ 19. Conceptualize a funding model* 20. Align on a funding operational structure* 21. Establish funding contracts with all necessary stakeholders* | <ul style="list-style-type: none"> 22. Develop educational materials for providers and/or patients* 23. Launch CED study³ 24. Site IRB approval¹ 25. HCP registration¹ 26. Site and/or HCP training² 27. Patient identification¹ 28. Patient consent¹ 29. Enrollment confirmation³ 30. Drug administration¹ |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

<i>Whose involvement is required at each step?</i>	¹ Study participants
	² Study sponsors (trainer) and study participants (trainee)
	³ Study sponsors
	* Steps that require multi-stakeholder input

iii. Implications for CED Application to Drugs and Biologics in Other Clinical Areas

The impact of the final mAb NCD requiring CED will be felt far beyond Alzheimer's patients and their family caregivers. Federal officials will be able to point to the coverage determination as a precedent and path to introduce additional CED determinations for future drugs for other serious and life-threatening conditions, such as cancer, ALS, and rare diseases. CMS has finalized its 2014 declaration in *Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development*, which states,

“We believe that CED can be applied to coverage of drugs and biologics.”^{xliii} Further, an October 2022 article from the presiding chair and co-chair of the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) entitled “Medicare’s National Coverage Determination for Aducanumab — A One-Off or a Pragmatic Path Forward?”^{xliv} further illustrated that influential policy advisors are advocating that the agency expand its use of CED.

That sentiment was further advanced at the January 8, 2023, "Innovations in Regulatory Science Summit" hosted by the UCSF-Stanford Center of Excellence in

Regulatory Science and Innovation (CERSI), a collaborative effort among the University of California, San Francisco, Stanford University, and the FDA. At a panel featuring Dr. Lee Fleisher, CMS's Chief Medical Officer; Dr. Rena Conti, an economist at Boston University and now-advisor for CMS's drug pricing negotiation

implementation efforts; Dr. Jeff Shuren, director of the FDA's Center for Devices and Radiological Health, and moderated by Dr. Mark McClellan, former FDA Commissioner and CMS Administrator—the conversation focused on future application of CED to other clinical areas:

- Dr. McClellan: Are drugs just different? Does this [CED] framework potentially for coordination apply there too?
- Dr. Conti: Thank you so much. Yes, I do think the framework applies but the context is slightly different. As you mentioned in your opening remarks, fundamentally CMS faces a trade-off. It must provide access to products that are safe and effective to patients, especially those products that are available right now, and for which many patients may not have access currently because of inequities and frictions in our healthcare system. And at the same time, they must balance a budget, and that balancing of the budget entails public accountability from taxpayers, which include myself, and all the people on the panel, and everybody else in this room and listening right now. So fundamentally, for the vast majority of drugs the difference between what is proven in the trial and what is to be expected in the general population using the drug is a practically the same and therefore there's no real uncertainty. ***The difference between the FDA standard meeting the coverage standard for CMS--it's the same, it just moves forward. But there are a handful of drugs, and frankly some of the most innovative drugs that are coming to market—whether it be the monoclonal antibodies such as the ones mentioned for Alzheimer's, or immunotherapy drugs such as the ones that are coming to market for infectious disease and for cancer, and that also includes gene and stem cell therapy—for which there is***

fundamental uncertainty that is being generated, even when the companies are meeting the evidentiary standard for FDA approval.⁷

Calls for the Agency to widen the use of CED to reduce spending, combined with the lack of enforcement authority to compel timely data reporting and criteria to end CED, portend long-term harmful impacts on beneficiary access if the use of CED expands. Currently, CMS has 22 active NCDs requiring CED in effect, many for a decade or more. For example, CMS has not converted or revoked the NCD requiring CED for off-label use of colorectal cancer drugs, which CMS announced in 2005 and some sponsors have

yet to complete or publish results.^{xlv} This highlights the reality that there is currently a lack of accountability or oversight of CMS to enforce Agency action on lingering NCDs requiring CED, or any enforcement mechanism to ensure the timely completion of studies required by CED, as discussed in Part III, below.

There are currently 22 active NCDs requiring CED

*In these three CEDs, there are no associated CED clinical trials or data registries.

- Allogeneic Hematopoietic Stem Cell Transplant for MDS
- Allogeneic Hematopoietic Stem Cell Transplant for Multiple Myeloma
- Allogeneic Hematopoietic Stem Cell Transplant for Myelofibrosis
- Allogeneic Hematopoietic Stem Cell Transplant for Sickle Cell Disease
- Amyloid PET
- Autologous Platelet-rich Plasma
- Cochlear Implantation
- CPAP For Obstructive Sleep Apnea*
- Extracorporeal Photopheresis for Bronchiolitis Obliterans Syndrome Following Lung Transplant
- FDG PET and Other Neuroimaging Devices for Dementia
- Home Oxygen for COPD
- Leadless Pacemakers
- Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease*
- NaF-18 PET for Bone Metastasis
- Off-label use of Colorectal Cancer Drugs
- Percutaneous Image-guided Lumbar Decompression for Lumbar Spinal Stenosis
- Percutaneous Left Atrial Appendage Closure (LAAC)
- Pharmacogenomic Testing for Warfarin Response
- TENS for chronic low back pain*
- Transcatheter Aortic Valve Replacement
- Transcatheter Edge-to-Edge Repair (TEER)
- Vagus Nerve Stimulation (VNS) for Treatment Resistant Depression (TRD)

⁷ 2023 CERSI Summit - Panel 2: Cross-Agency Synergy to Accelerate Access to Medical Products: <https://www.youtube.com/watch?v=2acW0KMYCII>. [Note that CMS’s Dr. Fleischer does not dispute these points.]

III. CED Deficiencies and Disastrous Consequences

If CMS had statutory authority to issue NCDs requiring CED—which it does not—the CED process would still be inherently flawed and lead to adverse consequences for millions of Medicare beneficiaries. Instead of facilitating access to medically necessary care, the CED process contributes to an ongoing denial of access to treatment, especially for underrepresented minority populations.

a. Failure to Timely Retire or Revoke CED Requirements

Absent a statutory basis for CED, CMS lacks any specific enforcement mechanism to ensure that sponsors timely complete and report CED-ordered research. As a result, CMS cannot (and does not) fulfill its mission to remove the evidence collection requirements or revoke NCDs requiring CED in a timely manner once they are in place. Rather, under the current paradigm, CMS has enabled 22 CEDs to continue in perpetuity, including several that have been ongoing for more than 15 years.^{xlvi}

CMS lacks external accountability that could ensure the Agency reassesses in a timely manner NCDs requiring CED that

publicly report or publish clinical results. As previously discussed, out of the four retired NCDs requiring CED, CMS reconsidered three of them only at the request of manufacturers and took an average of 16 months to remove the CED requirements for these determinations. Further, there is no clear standard for what would merit the end of CED restrictions because CMS has never articulated what it will accept as adequate evidence to justify Medicare coverage.

b. Failure to Facilitate Beneficiary Access to Innovative, Life-Saving Treatments and Services

Once CMS initiates a NCD, a period of ambiguity begins where beneficiaries do not typically have access to therapeutics subject to the NCD. Though CMS regional contractors have the authority to extend coverage during this time, practically, they point to a pending determination as cause to avoid creating local coverage policy. As a result, any coverage that is provided is on a beneficiary-by-beneficiary basis. CMS has acknowledged that “there may be coverage uncertainty between the period of FDA market authorization and CMS finalization of a NCD”^{xlvii} In other words, CMS compels those who cannot secure local

coverage or pay out-of-pocket to forgo treatment unless and until the Agency finalizes and approves a NCD, including additional time for set-up and approval of CED clinical studies.

Upon finalizing a NCD requiring CED, CMS restricts beneficiary access with eligibility requirements such as enrollment in an approved clinical trial or a patient registry. CMS prohibits coverage for all beneficiaries who cannot meet CMS's patient eligibility criteria at time of enrollment in the clinical trial or who are precluded from participating in studies due to their geographic locations (e.g., proximity to academic medical centers or large hospitals that meet criteria for CED study participation).

Even in the best-case scenario where beneficiaries qualify for and participate in CED-required studies or registries, CMS does not extend coverage to those beneficiaries immediately. Sponsors need time to design and implement CED-required trials before enrolling the first patient. For example, beneficiaries with Alzheimer's disease have been waiting since April 2022 for the Agency to approve a clinical trial study that would confer even

very limited access to FDA-approved therapeutics.^{xlviii}

However, the best-case scenario is an elusive one. For some technologies placed under CED, CED-required studies or patient registries have not been created, even a decade after the determination. There remains no approved clinical trial or registry for the continuous positive airway pressure for obstructive sleep apnea CED NCD; and transcutaneous electrical nerve stimulation for low back pain CED NCD, which were introduced in 2008 and 2012, respectively.^{xlix} In these instances, CMS effectively delivers a *de facto* non-coverage decision: Medicare beneficiaries are not able to access the treatment if CED-required clinical trials or registries simply do not exist. The Agency bears responsibility for patient health outcomes impacted by each day it forces beneficiaries to wait for access to treatment.

c. Failure to Protect and Promote Health Equity

Notwithstanding CMS's numerous statements emphasizing the importance of diverse, representative study populations, CMS has issued NCDs requiring CED that disproportionately harm diverse and underrepresented communities of color,

particularly women of color. As evidenced in CMS’s prior CED trial experience, participating eligible hospitals are principally found in large, urban areas and connected to academic research centers. Rural and private clinics, along with smaller hospitals, are effectively shut out from participating in the CED trials. This has significant implications for underserved populations, who more often receive healthcare services from essential providers.

Neither can CMS achieve the diversity benchmarks it sets for CED trials. In its NCD requiring CED for mAbs targeting amyloid for the treatment of AD, for example, CMS requires approved studies to include a diversity of patients that are representative of the national population diagnosed with AD.^l While laudable in principle, the treatment of underrepresented populations “is window-dressing and unrealistic as currently proposed,” as noted by one of the notable leaders in Alzheimer’s disease research.^{li} CMS must learn from the equity and inclusion failures of past CED trials that such trials are a wholly inappropriate vehicle to address equity and inclusion.

CMS has historically failed to enroll a diversity of participants in CED trials in part because U.S. health systems are not designed to provide equitable care,^{lii} and partially due to the agency’s own limiting criteria, as discussed previously. Indeed, CED trials underscore this reality:

- The Amyloid PET Alzheimer’s Prevention Through Exercise (APEX) CED trial enrolled 117 participants, 112 of whom were White and five of whom were Black.^{liii}
- The Cognitive Training and Practice Effects in Mild Cognitive Impairment CED trial enrolled 197 participants. Of those that completed the trial, 111 participants were white, only two were Asian, and zero were Black or Latino.^{liv}
- The Cochlear Implantation in Adults with Asymmetric Hearing Loss Clinical Trial studied 40 participants, comprising 33 White, four Not Reported, two Asian, and one Black.^{lv}
- The Safety and Efficacy Study of Lotus Valve for Transcatheter Aortic Valve Replacement (REPRISE III) study had 1,425 participants: 1,172 White, 45 Black, 43 Not Reported, 30 Hispanic,

underserved populations, the study has only enrolled approximately one-third of the total number of Black and Hispanic individuals needed to fill the study cohort, while the “all other races and ethnicities” cohort enrollment has been paused due to that trial arm nearly reaching capacity.^{lviii} Restrictive site requirements and reimbursement structures that pay providers less than the cost of providing the service have also impeded provider enrollment in the second confirmatory study.

It is important to note that CMS’s current NCD requiring CED for amyloid PET includes a coverage limit of *one-scan per lifetime* and *only within the context of the clinical study*. The lifetime limit and strict conditions of coverage of this CED have additional negative implications for access to FDA-approved monoclonal antibodies targeting amyloid for the treatment of early Alzheimer’s. Timely and equitable access to amyloid PET scans for treatment monitoring will be critical for Medicare beneficiaries to realize the benefit of these therapies, which are also subject to CED. The financial limitations are further intensified by geographic inequities. Currently, there are 18 states that do not have an active PET scan study site.^{lix, lx}

CED for Transcatheter Aortic Valve Replacement

When the FDA approved TAVR in 2011, it was an important advance for older adults with severe aortic stenosis who needed an aortic valve replaced but were too ill or frail to withstand open-chest surgery. A group of specialty societies asked Medicare to initiate a TAVR NCD requiring CED, and the American College of Cardiology and Society for Thoracic Surgeons co-led the introduction of the CMS-approved, TVT registry clinical study in 2012.^{lxi}

The TVT registry results have demonstrated issues with inequitable participation since its start. An analysis of TVT registry data from 2012-2018 published in the November 2021 *JAMA Cardiology* found that zip codes with higher proportions of socioeconomically disadvantaged, Black, and Hispanic populations had significantly lower rates of TAVR compared with zip codes with more affluent and White populations.^{lxii} This has occurred despite CMS’s original rationale for CED—and stated need for why the coverage restrictions must continue when the CED was reconsidered—hinging upon the need for additional data on outcomes for individuals of color. In 2019, CMS

Only One-Third of Patients Eligible for Minimally-Invasive Valve Repair Eligible a Decade after Start of CED

The American Heart Association estimates that more than 20% of older Americans have aortic stenosis, one of the most common and serious heart valve disease problems. Survival rates for severe aortic stenosis, if left untreated, are low at 50% at two years after symptom onset, and 20% at five years. In 2019 the TVT Registry reported that 72,991 patients received TAVR.¹ That sounds like a high level of access, but a 2017 article in the American Heart Association Journal, *Circulation: Cardiovascular Quality and Outcomes*, suggests otherwise. The analysis estimates that the number of U.S. patients with severe symptomatic aortic stenosis eligible for TAVR at high-risk is 111,205; intermediate risk is 34,991; and low risk 89,736—a total of 235,932 eligible patients.¹ Using those estimates, only 31% of those potentially eligible for TAVR have been treated with the procedure in the U.S.

reconfirmed the TAVR CED, with certain adjustments to the conditions of coverage.^{lxiii} In the 2019 reconsideration of the TAVR CED, CMS acknowledged:

“Evidence [that] is insufficient for minority populations. We also await reports on longer-term outcomes for benefits and harms, including quality of life, for our beneficiaries. We continue to believe that the current coverage under CED offers the appropriate balance of quality and access, while simultaneously stimulating innovation of devices, procedural techniques, and indications for use (for subpopulations

and patients with various comorbidities), and so we are continuing coverage with evidence development.”^{lxiv}

An April 2019 letter^{lxv} to then-CMS Administrator Seema Verma, signed by 14 advocacy national organizations—including the Association of Black Cardiologists, National Black Nurses Association, National Hispanic Medical Association, National Medical Association, and the National Minority Quality Forum—pointed out the inconsistency of using lack of minority data to continue inequitable coverage policy as: “Citing lack of evidence

on minority populations as part of the rationale to continue a policy that restricts access to those same populations is circular reasoning and we ask that it be removed from this section.”

A November 2020 “State-of-the-Art Review” article published in the *Journal of the American College of Cardiology* on TAVR registry data reports that in 2019—which is the most recent year of data publicly reported—significant disparities persist in TAVR access based on race, ethnicity, income, and where people live: 92% of patients that received TAVR were white; only 4% were Black; 1.4% were Asian; and 5% were of Hispanic or Latino ethnicity.^{lxvi} Additionally, the same report acknowledges that it took until 2020 (eight years under the introduction of CED) before TAVR became available to Medicare beneficiaries in all 50 states.⁸ In 2019, a *Morning Consult* survey found that one in three rural adults and 36% of rural adults age 65+ find it difficult to access large urban-based hospitals.^{lxvii} These individuals reported that appointment availability, insurance coverage, distance of travel, wait times, and cost of travel are the top barriers

to accessing large urban-based hospitals for treatment.

CED for Allogeneic Hematopoietic Stem Cell Transplant (HCT) for Sickle Cell Disease

Another example of how CMS’ use of NCD requiring CED harms communities of color is the CED for Allogeneic Hematopoietic Stem Cell Transplant (HCT) for sickle cell disease (SCD). SCD is the most common inherited blood disorder in the United States, affecting approximately 100,000 Americans.^{lxviii} The disease causes red blood cells to lose their normal disc shape and become sickle shaped and rigid. These sickle-shaped cells adhere to vascular walls, impede blood flow and oxygenation, and cause episodes of intense pain and other complications that affect multiple organ systems. Children with SCD may start to have signs of the disease during the first year of life, usually around 5 months of age.

SCD can cause substantial, long-term, and costly health problems including infections, stroke, and kidney failure, many of which can reduce life expectancy by an average of 20 years even in high-resource settings.^{lxix} Although approximately 90% of persons

⁸ The last state where TAVR became available was Wyoming, in 2020.

with a diagnosis of SCD in the United States are Black, the disease also occurs among Hispanic persons and persons of Mediterranean, Middle Eastern, and Indian descent.

Allogeneic (donor) hematopoietic stem cell transplantations (HCTs or bone marrow transplants) are the only recognized cure for sickle cell disease. This type of bone marrow transplant, unfortunately, can lead to complications and sometimes death, so it is only for patients with severe sickle cell disease who have experience complications including stroke, acute chest syndrome, recurrent pain and frequent transfusions, kidney disease, and other defined criteria. In recent years, half-matched donors have been studied to help expand transplant eligibility for a larger patient population, including young adults.^{lxx} In a recent study, overall survival and disease-free survival following HCT in young adult SCD patients were 93% and 85%, respectively.^{lxxi}

In January 2015, the American Society for Blood and Marrow Transplantation (ASBMT) and the National Marrow Donor Program (NMDP) sent a letter of request for CMS to broaden Medicare coverage of HCTs for SCD as well as other conditions.^{lxxii} A year later, CMS finalized its

NCD requiring CED for HCT to treat severe, symptomatic sickle cell disease in Medicare beneficiaries. Prior to 2016, CMS was "silent" on the use of HCT for the treatment of SCD, which meant coverage decisions were up to local contractors where patients and transplant centers were put in a position of potentially taking on the full financial burden of the procedure if coverage was denied.

However, in its 2015 comment to CMS^{lxxiii} on the proposed CED, American Society of Hematology (ASH) President David A. Williams, MD, wrote in support of Medicare coverage, but outlined access concerns related to CMS' non-transplant control group requirement:

ASH believes that the requirement for concurrent non-transplant control groups may limit access to the service despite the coverage expansion.... Comparative clinical studies typically limit accrual to a highly selected cohort of patients at a limited number of transplant centers. *This could have the unintentional negative consequence of restricting access to transplant for patients with these diseases, rather than improving it. More importantly, it will yield small numbers of patients and*

insufficient power to address meaningful clinical questions about prognostic factors for patients, policy makers and physicians. [emphasis added]

Young adults with severe SCD below the age 65 would need to be on Social Security Disability Insurance (SSDI) to potentially be eligible for coverage of HCT under Medicare.⁹ There are two CED studies for HCT in SCD that are currently listed as CMS-approved. One is a prospective trial that started in 2016 and is scheduled to be completed in 2023.^{lxxiv} It has an estimated enrollment of only 200 patients with severe symptomatic SCD and includes those who would receive the HCT as well as those assigned to the non-transplant control group. The second study supports data collection from the clinical trial to allow for Medicare reimbursement.^{lxxv}

d. Failure to Respect Medical Ethics in Trials

In NCDs requiring CED where CMS demands that clinical studies be conducted as randomized controlled trials (“RCT”), CMS imposes medically unethical requirements. For example, in the CED NCD for the use of mAbs in the treatment of Alzheimer’s disease, CMS states that it will cover such drugs in a CMS-approved RCT (*i.e.*, an RCT that includes a control or placebo arm).^{lxxvi} CMS would contravene medical ethics by requiring patients to take the chance of receiving a placebo when the drug has already been approved by the FDA based on its safety and efficacy profiles.¹⁰

CMS further defies medical ethics as it leaves open the door for the Agency to charge a co-payment for patients who receive placebo (*i.e.*, payment for non-treatment when patients are seeking to halt

⁹ The CED does not apply to those with Medicaid, who make up about half of all people with SCD.

¹⁰ When CMS was confronted with this glaring issue upon the release of the proposed NCD for mAbs, CMS offered conflicting guidance on the need for an RCT with a placebo arm. For example, during a stakeholder teleconference on January 13, 2022, CMS suggested that RCTs may not need to be randomized or placebo controlled after all. Cathy Kelly, *Medicare’s Final Coverage Decision on Alzheimer’s Drugs: Thoughts from a Former CMS Chief*, PINK SHEET (Jan. 21, 2022), <https://pink.pharmaintelligence.informa.com/PS145562/Medicare-Final-Coverage-Decision-On-Alzheimers-Drugs-Thoughts-From-A-Former-CMS-Chief> (quoting Mark McClellan, former CMS Administrator). But this is directly at odds with the plain meaning of the proposed NCD decision memorandum. If CMS wants to arrogate FDA’s accelerated approval of aducanumab, it will only be able to determine whether the “benefits outweigh the risks” if the CED trial(s) has a control group against which it can measure treatment outcomes (both adverse events and efficacy). If the CED trial(s) is to be conducted and ever finish, there must be clinical endpoints and a control group to be measured. For CMS to suggest after publishing its proposed NCD for mAbs that no placebo group may be required—particularly when the draft CED was so explicit on the point—is uninformed and exacerbates confusion across the stakeholder community.

the progression of a debilitating, fatal disease like Alzheimer’s disease).

e. [Failure to Honor Congressional Intent for Access in Areas of Clinical Need](#)

The FDA has utilized the accelerated approval (AA) program as an important regulatory mechanism to allow for earlier approval of drugs that treat serious and life-threatening illnesses than would occur through the traditional approval pathway. Created in 1992, the AA program was conceived as a direct response to patient therapy during the HIV/AIDS epidemic and in recognition of the urgency of access to new therapy needs faced by patients with life-threatening illnesses. As opposed to traditional approval, which is based upon a direct measure of clinical benefit or a validated surrogate, the AA program is intended to allow for the initial approval of a drug based on a demonstration of an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict a clinical benefit.^{lxxvii}

This regulatory pathway is used frequently in oncology and has been used for other life-threatening conditions such as multiple sclerosis and rare diseases, where patients and physicians have run out of (or lack entirely) options to treat a fatal illness.

Under FDA regulations, sponsors must conduct post-marketing studies that verify and describe the expected clinical benefit of the drug with a clinical trial design greenlit by FDA at the time of accelerated approval.^{lxxviii} The statute also establishes provisions for withdrawal of an AA program drug where confirmatory trials fail to verify clinical benefit or when safety concerns arise.^{lxxix}

FDA has approved hundreds of new drugs and biologics to treat serious or life-threatening illnesses through the AA program.^{lxxx} CMS currently covers all physician-administered drugs approved through the AA program and covered by Medicare Part B (with the exception of mAb treatments for Alzheimer’s disease) because they meet the same FDA “safe and effective” statutory requirements and are approved through the same statutory provisions as non-accelerated approval drugs.^{lxxxi}

However, CMS appears to be joining the Institute for Clinical and Economic Review’s (“ICER”) efforts to undermine the FDA’s AA program.^{lxxxii} While ICER has recommended to Congress and the Medicare and Medicaid program’s advisory committees that they restructure payment for therapies approved through the AA

program, CMS has taken the ICER argument one step further by creating novel, differentiated coverage requirements for AA products (as in the case of mAbs for Alzheimer’s disease) and those provided a traditional approval.¹¹ In doing so, CMS calls into question FDA’s approval of drugs that treat serious and life-threatening illnesses pursuant to the congressionally authorized—unlike CED—AA program. Congress recently reinforced their statutory commitment to the importance of the AA pathway by passing changes to strengthen the FDA’s programmatic authority in the *Consolidated Appropriations Act of 2022*.^{lxxxiii}

Accelerated approval and explicit outcomes in the AA process should not be a factor in CMS’s coverage decision-making, as it would have a significant negative impact on the development of future Alzheimer’s, cancer, HIV, and other novel therapies for life threatening diseases. In 2018, then-FDA Center for Drug Evaluation and Research Director (and former FDA Acting Commissioner) Janet Woodcock stated,

“Individuals with serious, life-threatening diseases (and their families, and the physicians who care for them) have repeatedly stated their desire and willingness to tolerate more uncertainty, including about effectiveness, in a trade-off for faster access. They point out that their lives may be the cost of waiting for definitive clinical outcome trials to be completed.”^{lxxxiv} By applying differing criteria for therapeutics approved through the AA program, CMS has missed the point that the AA program is predicated on the fact that people living with deadly diseases have no existing meaningful treatment options.

f. Failure to Advance Medicare’s Intent

The CED policy fails to advance Medicare’s intent to meaningfully advance the availability of clinical data. Accepting for argument’s sake the notion that the CED process is designed to generate additional efficacy data across Medicare populations, with particular focus on minority populations, the results to date are

¹¹ Partnership to Fight Chronic Disease, *New Analysis of Medicaid Spending Reinforces Value and Patient Impact of FDA Accelerated Approval Pathway* (Mar. 30, 2021), <https://www.fightchronicdisease.org/latest-news/new-analysis-medicaid-spending-reinforces-value-and-patient-impact-fda-accelerated>; see, e.g., *Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (CAG-00460N) Decision Memo*, *supra* note viii, (demanding “evidence sufficient to conclude that the use of monoclonal antibodies directed against amyloid for the treatment of Alzheimer’s disease improves health outcomes for Medicare beneficiaries,” when the statute authorizing accelerated approval explicitly does not require evidence of improved outcomes).

disheartening at best. Rather than stimulate development of additional data, CED and the uncertain and vague way CMS has implemented the process have suppressed further research and clinical trial analysis. For example, CMS without explanation has routinely rejected numerous proposed studies of drugs subject to the amyloid PET scan NCD, strictly limited overall participation, and restricted the current coverage policy to one scan per patient per lifetime.^{lxxxv} And to further demonstrate the capricious nature of the CED process, even when a sponsor completes a CMS-approved CED study the Agency can reverse course by deciding that the study criteria are insufficient and that a second CED study is required.¹²

IV. Dangerous Precedent for Future Medicare Coverage

Particularly worrisome are the signs from CMS toward wider application of NCDs requiring CED. CMS, through its NCD requiring CED for mAbs for the treatment of AD, made a sweeping change in Medicare Part B coverage policy that inexplicably denies coverage for an entire class of

treatments that have yet to receive FDA approval and present different safety and efficacy profiles from one another.^{lxxxvi} CMS has consequently stoked uncertainty about whether Medicare would eventually cover two other Alzheimer's drugs: (1) Eisai and Biogen's Leqembi (lecanemab), which FDA granted accelerated approval on January 6, 2023; and (2) Eli Lilly's treatment candidate (donanemab), which FDA is expected to make a decision on in 2023.^{lxxxvii}

The Agency may seek to apply the same class approach to limit beneficiaries' access to new, FDA-approved drug and biologic treatments for *any disease* in the future. After all, in its 2014 CED Guidance, CMS expressly affirmed its belief that it can apply CED to coverage of FDA-approved drugs and biologics that fall within the scope of Medicare.^{lxxxviii} CMS has indicated its intent to deploy additional NCDs requiring CED by commissioning a report from the Agency for Healthcare Research and Quality (AHRQ) that analyzes and provides recommendations on updating CED study

¹² See, e.g., *NEW IDEAS Study Protocol*, <https://www.ideas-study.org/Getting-Started/Protocol> (accessed Jan. 4, 2023) (a subsequent CED study designed to build upon the original IDEAS CED study but with a smaller sample size, an increased focus on recruiting underrepresented minority populations, the inclusion of early-onset and typical clinical representations of Alzheimer's disease, ApoE genotyping via saliva collection, and optional blood collection to establish a biorepository).

design requirements.^{lxxxix, 13} AHRQ recommended CMS update the CED study design requirements with a particular focus toward the efficient completion of CED studies, but that falls short of curing the deficiencies and consequences of the CED paradigm, discussed in Part III.^{xc} In February 2023, the Medicare Evidence Development and Coverage Advisory Committee (“MEDCAC”) is slated to review AHRQ’s report and make recommendations to CMS on updates to the CED study design requirements.^{xci}

CMS has also indicated its intent to imminently introduce a proposed rule that conditions coverage of technologies (and potentially including drugs) on the collection of additional evidence in CMS-approved studies.^{xcii} CMS explained that this proposed rule would replace the rescinded final rule, “The Medicare Coverage of Innovative Technology and Definition of Reasonable and Necessary,” that would have granted “expedited Medicare coverage” for up to four years for

any FDA-designated breakthrough device upon marketing authorization or clearance and established a regulatory standard to make “reasonable and necessary” determinations for purposes of Medicare coverage.^{xciii}

The Medicaid and CHIP Access Commission (“MACPAC”) also supports CMS’s movement toward tighter restrictions on care. In 2021, MACPAC recommended that Congress increase the rebates under the Medicaid Drug Rebate Program on accelerated approval drugs until these drugs have verified clinical benefit through the FDA’s traditional approval process.^{xciv} In January 2023, MACPAC voted in favor of a recommendation to Congress to grant states outright authority to limit Medicaid formularies based upon Medicare NCDs, including those requiring CED.^{xcv} In addition to the central challenges discussed in this paper, basing Medicaid decisions on CED is grossly inappropriate because CMS states they are making decisions based on

¹³ During the public comment period, 20 national organizations including the Alliance for Aging Research submitted a letter to AHRQ’s Director expressing serious concerns that “the draft report proposes to add even more ill-defined study ‘options’ to the list of CED study programs that CMS may already employ. The AHRQ report will thus not contribute to the improvement of the CED process, but rather further cloud the already muddy CED waters.” Alliance for Aging Res., *Twenty Organizations Submit Comments on Proposed Requirements for Medicare Coverage with Evidence Development Parameters* (Sept. 29, 2022), <https://www.agingresearch.org/news/twenty-organizations-submit-comments-on-proposed-requirements-for-medicare-coverage-with-evidence-development-parameters/>; Letter from Alliance for Aging Res. et al. to Dr. Robert Otto Valdez, Dir., AHRQ (Sept. 28, 2022), available at <https://www.agingresearch.org/wp-content/uploads/2022/09/AAR-Draft-AHRQ-CED-Comments-FINAL-9.23-FINAL.pdf>.

whether a treatment is reasonable and necessary in the Medicare program, which has a different composition than the Medicaid population.

To curtail CMS from broadening its application of NCDs requiring CED in the absence of statutory checks, there must be proscribed limitations around CMS and its use of CED. As it stands, CMS wields unilateral discretion to issue *de facto* non-coverage determinations and demand that sponsors meet additional requirements while Medicare beneficiaries are left without coverage. Inaction or the failure to make meaningful changes to the CED paradigm will result in future CEDs that exacerbate these disastrous consequences.

V. Illegality of Coverage with Evidence Development

CMS's use of CED has revealed inherent flaws with the paradigm and raised adverse implications for beneficiary access, health equity, medical ethics, and fellow agencies' expertise. As a threshold matter, CMS lacks statutory authority to justify its use of CED and has overreached its authority.

CMS traces the origins of the CED pathway to a 1995 regulation issued under the agency's previous name, the Healthcare Financing Administration ("HCFA"). The

HCFA established a process for covering certain investigational devices and services related to those devices when furnished in an FDA-approved investigational device exemption trial.^{xcvi} In 2005, CMS began to implement NCDs that required study participation.^{xcvii} Then in 2006, CMS issued a 2006 guidance document, "National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development," that set forth two separate pathways for CED (*i.e.*, Clinical Study Participation and Coverage with Appropriateness Determination).^{xcviii} CMS later merged these two arms in a 2014 guidance update and no longer uses the terminology to distinguish them.^{xcix}

In its 2014 "Coverage with Evidence Development" guidance for the public, industry, and CMS staff, CMS erroneously asserted that it has statutory authority to utilize CED from Sections 1862(a)(1)(A), 1862(a)(1)(E), and 1142 of the Social Security Act. CMS cites Section 1862(a)(1)(A), which states:

(a) Notwithstanding any other provision of this title, no payment may be made under

part A or part B for any expenses incurred for items or services—

(1)(A) which, except for items and services described in a succeeding subparagraph or additional preventive services (as described in section 1395x(ddd)(1) of this title), are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member,

(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section.^c

CMS also references Section 1142(b)(3) of the Act, which reads:

In establishing priorities under paragraph (1) for research and evaluation, . . . the Secretary shall assure that such priorities appropriately reflect the needs and priorities of the program under subchapter XVIII, as set forth by the Administrator of the

Centers for Medicare & Medicaid Services.^{ci}

None of these provisions, however, authorize or describe a CED trial. Section 1862(a)(1)(A) requires that an item be reasonable and necessary to diagnose or treat illness or injury; not to conduct a clinical trial. Section 1862(a)(1)(E) only addresses research by AHRQ and Section 1142 of the Act simply describes the authority of AHRQ to carry out research in line with the needs and priorities of the Medicare program. CMS cannot explain how a proposed CED clinical trial could ever qualify as “research conducted pursuant to section 1320b-12.” Moreover, Robert Charrow, former HHS General Counsel, previously issued an HHS Office of General Counsel Advisory Opinion explaining that CMS’s interpretation of its statutory authority to use CED as the basis for coverage of items and services is “*unlawful* under Section 1862 [of the Social Security Act]” because CMS’s “broad reading of the term [support] is fundamentally inconsistent with the

regulatory definition of ‘support’ at 42 C.F.R. § 93.221.”¹⁴

Recently, CMS again discarded its prior lines of reasoning and asserted anew that its CED decision-making “follow[s] a long-standing process established by Congress in making a NCD under section 1862(l) of the [SSA].”^{cii} CMS was correct insofar as that statutory provision describes making a NCD.¹⁵ However, CMS pointed to a statutory authority that is silent and does not contemplate coverage with evidence development.^{ciii} CMS cannot justify the legal grounds for CED simply by citing its historical use of CED. CMS’s justifications are laid bare by the inconvenient truth that CMS lacks flexibility and enforcement powers over post-market treatments and services and attempts to deploy CED as a mechanism to surveil them.¹⁶

Just as Congress never ratified CMS’s CED powers, Congress never authorized CMS to conduct research studies into the effectiveness of medications or medical

devices. Congress explicitly authorized such research through the creation of the Patient-Centered Outcomes Research Institute (“PCORI”).^{civ} When Congress formed this clinical outcomes research body, it explicitly defined how the Secretary of HHS could use PCORI research findings for Medicare coverage and reimbursement purposes.^{cv} It would be duplicative and a poor use of government resources for Congress to vest PCORI with the authority to research clinical outcomes if Congress ever believed that CMS already had the authority to mandate that the very same clinical outcomes research be conducted through the CED process.

The CED paradigm is fundamentally illegal and *ultra vires*. CMS lacks any statutory basis to justify the use of CED and falls flat in its attempts to justify its actions on novel interpretations of the Act.

At the same time, CMS perpetuates an *ad hoc* process with minimal gain. There is no data to support the value of NCDs requiring

¹⁴ Robert Charrow, *Advisory Opinion 21-03 on Medicare Coverage with Evidence Development*, U.S. Dep’t of Health & Human Servs. at 2 (Jan. 14, 2021) (emphasis added) (rescinded). While this advisory opinion has since been withdrawn, Charrow’s legal interpretation remains valid.

¹⁵ 42 U.S.C. § 1395y(l) (describing the relevant factors used in making an NCD, the timeframe for making NCDs, a public comment period for NCDs, and the need to consult with external experts on the review of certain NCDs).

¹⁶ In the Transcatheter Edge-to-Edge Repair NCD requiring CED, it was noted that the associated registry had not released timely data on outcomes preceding the reconsideration of TEER, with the Agency instead noting they would only be able to review more recent data when such updates would be published in an academic journal – after the completion of the redetermination process.

CED for purposes of ascertaining whether an item or service is reasonable and necessary. According to a team from the Urban Institute and its Center for Medical Technology Policy, “Without a clear legal mandate to pursue CED, [CMS’s] efforts have by necessity been ad hoc, with no formal process for selecting appropriate topics; little learning from one initiative to the next; and limited resources and lack of dedicated staff skilled in navigating the political and operational issues raised by CED, including CMS’s ability to require provider and supplier compliance with CED reporting requirements.”^{evi} The authors conclude that, “The current authority is sufficiently ambiguous to prevent CMS from fully developing and implementing coverage with evidence development consistently and systematically.”^{cvi}

VI. Conclusion

Coverage with evidence development sounds compelling, and the terminology hints at its original intent – to permit coverage when additional evidence is needed to establish clinical benefit. However, the threshold that offered the promise to make FDA-approved treatments more accessible has shifted to instead limit

coverage despite the presence of clinical benefit.

Recent agency-wide efforts by CMS to incorporate equity considerations into strategic planning and care initiatives are laudable. However, the agency would do well to examine the track record of CED in failing to enable additional data on the impacts of therapeutics on beneficiaries of color, and in many cases perpetuating gaps in access and care. CMS should not inadvertently exacerbate the massive racial and ethnic inequalities in access to healthcare with increased use of CEDs that will layer on additional clinical studies, with strict coverage requirements for sites of care and types of specialists, and/or mandate the collection of health outcomes through burdensome patient registries that may either duplicate planned sponsor studies or take longer to complete. If nothing else, CMS should not use “lack of evidence on minority populations” as part of the rationale to establish a coverage policy that will likely restrict access to those very same populations who have the highest need.

While the Medicare program contends that coverage decisions do not include cost considerations, there is a reason that NCDs

are issued when a new therapeutic has a differential cost in comparison to the prior standard of care. When CED is utilized, it is framed by CMS as enabling access; however, given the shortcomings of the

CED paradigm, the result is the prolonged elimination of coverage to beneficiaries that would otherwise be eligible to receive a therapeutic service preferred by the patient and their care provider.

ⁱ Sean Dickson et al., *Limiting Coverage Based On Efficacy And Safety: A Path Forward For Medicare Regarding The Alzheimer's Treatment Aducanumab*, Health Affairs (June 7, 2021), <https://www.healthaffairs.org/doi/10.1377/forefront.20210604.489197>.

ⁱⁱ See Zeitler, *supra* note xii, at 385–87.

ⁱⁱⁱ Agency for Healthcare Res. & Quality, *Analysis of Requirements for Coverage With Evidence Development (CED) – Topic Refinement* (Nov. 2022), <https://effectivehealthcare.ahrq.gov/products/coverage-evidence-development/research-report>.

^{iv} MEDCAC Meeting: Analysis of Coverage with Evidence Development (CED) Criteria: <https://www.cms.gov/medicare-coverage-database/view/medcac-meeting.aspx?medcacid=79>.

^v Fleisher LA, Blum JD. A Vision of Medicare Coverage for New and Emerging Technologies—A Consistent Process to Foster Innovation and Promote Value. *JAMA Intern Med.* 2022;182(12):1241–1242.

^{vi} Medicaid Coverage based on Medicare National Coverage Determination: Review of Draft Chapter and Recommendations for March Report, MACPAC, January 26, 2023, https://www.macpac.gov/wp-content/uploads/2023/01/04_Medicaid-coverage-based-on-Medicare-national-coverage-determination-NCD_-_Review-of-recommendations-and-draft-chapter-for-March-report.pdf.

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^{viii} Ctrs. for Medicare & Medicaid Servs., *Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N) Decision Memo*, at Appx. A (Apr. 2022), <https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncid=305&fromTracking=Y&>.

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^x See, e.g., 21 U.S.C. § 355(d) (new drugs); *id.* § 360e(d) (class III medical devices); 21 C.F.R. § 601.2(a) (biological products).

^{xi} See 42 U.S.C. § 1395y(l).

^{xii} Zeitler, *supra* note 2, at 382.

^{xiii} See 85 Fed. Reg. 54,327, 54,329 (Sept. 2020); Ctrs. for Medicare & Medicaid Servs., Press Release, *CMS Opens National Coverage Determination Analysis on Treatment for Alzheimer's Disease* (July 12, 2021), <https://www.cms.gov/newsroom/press-releases/cms-opens-national-coverage-determination-analysis-treatment-alzheimers-disease>.

^{xiv} See Ctrs. for Medicare & Medicaid Servs., *National Coverage Annual Report Results*, <https://www.cms.gov/medicare-coverage-database/reports/national-coverage-annual-report.aspx?docType=NCD&year=2022&sortBy=title> (last visited Jan. 4, 2023); William Newton, *Medicare's National Coverage Determination could boost chances of limited Aduhelm coverage despite backlash* (updated Aug. 11, 2021), CLINICAL TRIALS ARENA, <https://www.clinicaltrialsarena.com/analysis/aduhelm-medicare-coverage/>.

^{xv} Newton, *supra* note xiv.

^{xvi} Ctrs. for Medicare & Medicaid Servs., *What's a MAC* (updated Jan. 12, 2022), <https://www.cms.gov/Medicare/Medicare-Contracting/Medicare-Administrative-Contractors/What-is-a-MAC>.

^{xvii} Ctrs. for Medicare & Medicaid Servs., *Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development* (“CED Guidance”) (Nov. 20, 2014), <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27>.

^{xviii} Zeitler, *supra* note 2, at 382.

^{xix} *Id.*; Zeitler, *supra* note 2, at 382–83.

^{xx} See Sean R. Tunis, et al. *Improving the Quality and Efficiency of the Medicare Program Through Coverage Policy, Timely Analysis of Immediate Health Policy Issues*, (August 2011). <https://www.urban.org/sites/default/files/publication/27516/412392-Improving-the-Quality-and-Efficiency-of-the-Medicare-Program-Through-Coverage-Policy.PDF>.

^{xxi} Ctrs. for Medicare & Medicaid Servs., *Guidance for the*

Public, Industry, and CMS Staff: Coverage with Evidence Development (“CED Guidance”) (Nov. 20, 2014), <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27>.

^{xxii} Zeitler, *supra* note 2, at 385.

^{xxiii} *Id.* at 383–84 tbl. 1.

^{xxiv} *Carotid Artery Stenting (CAG-00085R) NCA, supra* note <https://www.cms.gov/medicare-coverage-database/view/nca.aspx?NCAId=157&DocID=CAG-00085R&id=157> (issuing a decision memorandum 14 months after receipt of a reconsideration request); *Implantable Defibrillators (CAG-00157R3) NCA, supra* note <https://www.cms.gov/medicare-coverage-database/view/nca.aspx?ncaid=148&bc=0> (issuing a decision memorandum 10 months after receipt of a reconsideration request); *Magnetic Resonance Imaging (MRI) (CAG-00399R4) NCA, supra* note <https://www.cms.gov/medicare-coverage-database/view/nca.aspx?ncaid=289&keyword=MRI%20in%20patients%20with&keywordType=starts&areaid=all&doctype=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1> (issuing a decision memorandum nine months after receipt of a reconsideration request).; *Autologous Blood-Derived Products for Chronic Non-Healing Wounds (CAG-00190R4) NCA, supra* note <https://www.cms.gov/medicare-coverage-database/view/nca.aspx?ncaid=300&keyword=Autologous%20Blood-Derived%20Products%20for%20Chronic%20Non-Healing%20Wounds&keywordType=starts&areaid=all&doctype=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1> (issuing a decision memorandum 23 months after receipt of a reconsideration request).

^{xxv} See Zeitler, *supra* note 2, at 383.

^{xxvi} See Zeitler, *supra* note 2, at 386.

^{xxvii} <https://www.cms.gov/medicare-coverage-database/view/nca.aspx?ncaid=375&ncdver=1&keywordType=starts&keyword=alzheimers&bc=0>.

^{xxviii} See Zeitler, *supra* note xii, at 385.

^{xxix} <https://cvquality.acc.org/NCDR-Home/registries>.

^{xxx} See Zeitler, *supra* note xii, at 383–384.

^{xxxi} See Zeitler, *supra* note xii, at 386.

^{xxxii} Caregiver Action Network, *Medicare Coverage is Critical to Caregivers*, <https://www.caregiveraction.org/medicare-coverage-critical-caregivers> (last visited Jan. 4, 2023).

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^{xlvi} See Zeitler, *supra* note xii, at 385–87.

^{xlvii} *Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease* (CAG-00460N) Decision Memo, *supra* note viii.

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^{civ} *See* 42 U.S.C. § 1320e.

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^{cvi} Sean R. Tunis et al., *Improving the Quality and Efficiency of the Medicare Program Through Coverage Policy*, TIMELY ANALYSIS OF IMMEDIATE HEALTH POLICY ISSUES 9 (Aug. 2011); *see also* Zeitler, *supra* note xii, at 388.

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