Coverage with Evidence Development

Guidance Document

August 7, 2024

Contents

I. Preamble

Section 1862(l)(1) of the Social Security Act (the Act) requires that the Secretary of Health and Human Services (the Secretary) make available to the public the factors that are considered in making national coverage determinations (NCDs) of whether an item or service is reasonable and necessary. The Centers for Medicare & Medicaid Services' (CMS) procedures for issuing guidance documents under this authority are set forth in 69 Fed. Reg. 57325 (September 24, 2004).

NCDs concerning whether a particular item or service is reasonable and necessary under section 1862(a)(1)(A) are based on information including clinical experience and medical, technical, and scientific evidence.[1] The NCD process also considers public comments. The public is afforded the opportunity to comment on a proposed determination as set forth in section 1862(l). When we make an NCD, we provide a clear statement of the basis for the NCD as well as responses to the comments received from the public. When the available evidence is insufficient to demonstrate that the items and services are reasonable and necessary under section 1862(a)(1)(A), CMS may use authority under section 1862(a)(1)(E) to provide coverage with evidence development (CED).

To encourage innovation and accelerate beneficiary access to new items and services, CMS is proactively publishing this guidance document to provide a framework for more predictable and transparent evidence development.

This guidance represents CMS' current thinking on the factors CMS considers in making NCDs using the CED paradigm. It does not create or confer any rights for or on any person and does not operate to bind CMS or the public. Where warranted by circumstances, CMS may consider an alternative approach if it satisfies the requirements of the applicable statutes and regulations. Individuals interested in discussing an alternative approach, or those with questions about this document, are encouraged to contact CAGInquiries@cms.hhs.gov and reference this guidance.

For information regarding NCDs, local coverage determinations (LCDs), or other coverage materials, including those referenced throughout this guidance document, please see the Medicare Coverage Database website[2] and Chapter 13 of the Medicare Program Integrity Manual.

[1] SSA § 1862(a) in the material following (25). ("[I]n making the [national coverage] determination, the Secretary has considered applicable information (including clinical experience and medical, technical, and scientific evidence) with respect to the subject matter of the determination[.]")
https://www.ssa.gov/OP_Home/ssact/title18/1862.htm

[2] MCD Search, https://www.cms.gov/medicare-coverage-database/search.aspx.

II. Purpose of this Guidance Document

The purpose of this guidance document is to address the factors CMS considers in making NCDs using the CED paradigm. At the outset, it is important to remind the public that beneficiary participation in a CED trial is voluntary, as is the choice for an entity to seek to sponsor an approved trial. CED provides an opportunity for beneficiaries to participate in medical research for promising treatments, but where the evidence is not yet adequate for Medicare coverage under the reasonable and necessary statute. This guidance describes the history of CED, its statutory basis, and establishes principles for CED studies that are supported by the Agency for Healthcare Research and Quality (AHRQ) under section 1142 of the Act.

Under Part A and Part B of the Medicare program, items and services that fall within a statutory benefit category may be covered if they are not statutorily excluded and meet other statutory requirements. See 42 CFR Part 411, Subpart A.

III. Background

In general, in order for an item or service to be covered under Medicare, it must meet the standard described in section 1862(a)(1)(A) of the Act – that is, it must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The statute, however, also contains express exceptions that authorize payment for other items and services that may not meet the reasonable and necessary standard.[3] Some examples are coverage for hospice care, certain vaccines to prevent illness, and specific preventive or cancer screening services. Under existing regulations at 42 CFR § 411.15(o), Medicare does not cover experimental or investigational devices, except for certain Category B devices.[4]

When the available evidence is insufficient to demonstrate that the items and services are reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member under section 1862(a)(1)(A) of the Act, CED has been used to support evidence development for certain items and services that are likely to show benefit for the Medicare population. CED relies primarily on the statutory exception in section 1862(a)(1)(E) of the Act, which effectively permits Medicare payment for items and services that are reasonable and necessary to carry out research conducted pursuant to section 1142 of the Act. Items and services that are not reasonable and necessary to carry out that research are excluded. As noted above, participation in a CED trial is voluntary, and beneficiaries are protected by separate regulations including those at 45 CFR Part 46 related to the protection of human research subjects.

[3] Section 1862(a)(1)(A) expressly acknowledged exceptions by including the phrase "except for items and services described in a succeeding subparagraph or additional preventive services (as described in section 1861(ddd)(1))[.]")

[4] Information on Investigational Device Exemption coverage is described in 42 CFR Part 405, Subpart B, which can be accessed here: https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-B/part-405/subpart-B.

CED has been a pathway whereby, after a CMS and AHRQ review, Medicare covers items and services on the condition that they are furnished in the context of approved clinical studies or with the collection of additional clinical data. CMS and AHRQ established CED based on section 1862(a)(1)(E) of the Act in 2006 and have used the NCD process to provide public notice and to obtain the public's input. The term "national coverage determination" is defined in section 1862(l)(6)(A) of the Act as a determination by the Secretary with respect to whether or not a particular item or service is covered nationally under Title XVIII of the Act. In general, NCDs are national policy statements published to identify the circumstances under which particular items and services will be considered covered by Medicare. NCDs serve as generally applicable rules to ensure that similar claims for items or services are covered in the same manner. Oftentimes, an NCD is written in terms of defined clinical characteristics that identify a population that may or may not receive Medicare coverage for a particular item or service.

Since CMS started covering items and services in the context of CED clinical studies almost two decades ago, the timing of evidence development and the stages of the technology development lifecycle have evolved. Over the past few years, innovative technologies have come on the market earlier in the technology development lifecycle and reached the market with a limited or developing evidence base for coverage purposes. CMS has received inquiries for coverage of new technologies that are early in the product lifecycle, which means the clinical evidence is just starting to accumulate. New technologies often lack sufficient clinical evidence to support broad national coverage under section 1862(a)(1)(A) of the Act.

In general, CMS relies heavily on health outcomes data before proposing an NCD. Early in the product lifecycle there is usually evidence about whether the product is safe and may produce the intended result (for example, a laboratory measurement, radiographic image, physical sign or other measure).[5] For drug trials, the FDA requires that surrogate endpoints be reasonably likely to predict clinical benefit for accelerated approval but requires validated surrogate endpoints for full approval. Surrogate outcomes are not direct measures of clinical benefit, and there is often little evidence at this point regarding health outcomes (for example, mortality, disease progression, quality of life). When premarket, pivotal clinical study data are collected to support an application to FDA for marketing authorization, they provide clinical evidence for a defined population enrolled in the study.

These pivotal clinical study data, however, may not be generalizable to the Medicare population if Medicare beneficiaries are insufficiently represented. Medicare beneficiaries have been historically underrepresented in pivotal studies due to age, access, disability status, multiple comorbidities, and concurrent treatments. When there is little or limited evidence, CMS may not have enough information to make a favorable NCD due to gaps in research about health outcomes. Thus, coverage under CED can expedite earlier beneficiary access to new items and services while ensuring that systematic patient safeguards, including assurance that items and services are provided to clinically appropriate patients, are in place to reduce the risks inherent to new technologies or to new applications of older technologies. In addition, the

[5] https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf

CED framework can support manufacturers that are interested in working with CMS to generate additional evidence that is appropriate for Medicare beneficiaries and that may demonstrate improved health outcomes in the Medicare population to support more expeditious national Medicare coverage.

CMS has issued a total of 27 NCDs requiring CEDs over the last two decades to provide Medicare beneficiary access to promising items and services that could not otherwise be covered under section 1862(a)(1)(A) of the Act. CMS has approved over 120 CED studies and five national registries to facilitate evidence development for these CED NCDs. Forty-two of these studies have generated evidence across 14 topics covered under CED. Three CED NCD topics have had the CED requirement removed following an NCD reconsideration and have received national coverage. CMS has been actively collaborating with the AHRQ to update the general criteria for CED studies described in our CED guidance document from 2014. We aim to ensure the general criteria are up to date and continue to maintain CMS' and AHRQ's rigorous evidentiary standards. In November 2022, in order to better inform the CED process, AHRQ released a final report on "The Analysis of Requirements for Coverage with Evidence Development (CED)."[6] The AHRQ report was first released in draft form in September 2022 and the public had an opportunity to provide comment on the draft report.

The AHRQ report served as the basis for discussion at the February 13-14, 2023 public meeting of the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC). CMS convened the MEDCAC to examine the general requirements for clinical studies submitted for CMS coverage under CED. Specifically, the MEDCAC evaluated the CED criteria to assure that studies informing CED are assessed using consistent, feasible, transparent and methodologically rigorous criteria. The MEDCAC advised CMS on whether the criteria are appropriate to ensure that studies approved to inform CED decisions will continue to produce informative evidence that CMS can rely on when making future reasonable and necessary determinations.[7] Following the MEDCAC meeting, AHRQ and CMS collaboratively evaluated the information and MEDCAC panel scores and made corresponding refinements to the new criteria which is included in section VII of this document.

IV. Statutory Basis

Sections 1862(a)(1)(A) and 1862(a)(1)(E) of the Act (42 U.S.C. 1395y) state:

> (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—

[6] https://effectivehealthcare.ahrq.gov/products/coverage-evidence-development/research-report

[7] Additional information on the MEDCAC can be found at https://www.cms.gov/medicare-coverage-database/view/medcac-meeting.aspx?medcacid=79&year=all&sortBy=meetingdate&bc=15.

> (1)(A) which, except for items and services described in a succeeding subparagraph or additional preventive services (as described in section 1861(ddd)(1)), 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.

Recent NCDs have relied on section 1862(a)(1)(E) and 1142 of the Act in order to support clinical research that addresses evidence gaps. In these instances, the item or service was promising but the evidence was insufficient to conclude that the item or service is reasonable and necessary under section 1862(a)(1)(A) of the Act. Clinical registries offer an important means of robust data collection for certain items and services following FDA market authorization. Submission of data to clinical registries has since been required for transcatheter aortic valve replacement (TAVR; NCD Manual §20.32), left atrial appendage closure (LAAC) (NCD Manual §20.34), and others. Nonetheless, CMS recognizes that CMS-approved registries may not be necessary to address all evidentiary deficiencies; in 2015 and 2017 we finalized CED NCDs that allowed clinical studies that rely on analysis of administrative claims (Percutaneous Image-guided Lumbar Decompression for Lumbar Spinal Stenosis, NCD Manual §150.13; Leadless Pacemakers, NCD Manual §20.8.4).

Section 1142 of the Act

Section 1142 of the Act describes the authority of AHRQ to conduct and support research on outcomes, effectiveness, and appropriateness of services and procedures to identify the most effective and appropriate means to prevent, diagnose, treat, and manage disorders and other health conditions. That section includes a requirement that the Secretary assure that AHRQ research priorities under Section 1142 appropriately reflect the needs and priorities of the Medicare program.[8]

[8] Section 1142(b)(3) states:

> Relationship with Medicare program—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 title XVIII, as set forth by the Administrator of the Centers for Medicare & Medicaid Services.

The coordination of AHRQ priorities under section 1142 with the needs and priorities of the Medicare program is accomplished through direct collaboration between AHRQ and CMS. Consistent with section 1142, AHRQ supports clinical research studies that meet specific scientific standards, reviews all CED NCDs, endorses those trials that CMS determines address the CED questions for CED studies, and recommends changes to the CED guidance document when necessary.

V. Principles governing the application of CED:

- CED NCDs will occur within the national coverage determination process, which is transparent and open to public comment.
- CED will not be used when less restrictive coverage is justified by the available evidence.
- CED will generally expand access to medical technologies[9] for beneficiaries because the technologies would not otherwise meet the reasonable and necessary coverage standard.
- CED will generate evidence that addresses specific evidentiary deficiencies identified in National Coverage Analyses.
- CED will not duplicate or replace the FDA's authority in assuring the safety and effectiveness of drugs, biological products, and devices.
- CED will not duplicate or replace the NIH's role in fostering, managing, or prioritizing clinical trials.
- CED will be consistent with federal laws, regulations, and patient protections.[10]

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

As noted previously, participation in CED studies is voluntary both for beneficiaries and trial sponsors and participating study sites. Following the recent MEDCAC meeting, CMS and AHRQ developed and refined the characteristics needed for CED clinical studies. This guidance is part of a broader CMS coverage modernization initiative that aims to provide a more transparent and predictable evidence generation framework to facilitate Medicare coverage. As part of this effort, we are updating our CED guidance to better allow for a broader range of fit-for-purpose study designs. If a sponsor or study site would like to voluntarily participate in a CED study, we expect that they will sign an agreement for the specific CED trial under the NCD. The agreement would include the following general conditions:

[9] Note: The term "technologies" is referenced to be consistent with prior guidance but CED can apply broadly to items and services.

[10] Notably, the Paperwork Reduction Act, the Privacy Act of 1974, and the HHS regulations on the protection of human subjects.

1. Sponsor/Investigator:

The study is conducted by sponsors/investigators with the resources and skills to complete it successfully.

2. Milestones:

A written plan is in place that describes a detailed schedule for completion of key study milestones, including study initiation, enrollment progress, interim results reporting, and results reporting, to ensure timely completion of the CED process.

3. Study Protocol:

The CED study is registered with ClinicalTrials.gov and a complete final protocol, including the statistical analysis plan, is delivered to CMS prior to study initiation. The published protocol includes sufficient detail to allow a judgment of whether the study is fit-for-purpose[11] and whether reasonable efforts will be taken to minimize the risk of bias. Any changes to approved study protocols should be explained and publicly reported.

4. Study Context:

The rationale for the study is supported by scientific evidence and study results are expected to fill the specified CMS-identified evidence deficiency and provide evidence sufficient to assess health outcomes.

5. Study Design:

The study design is selected to safely and efficiently generate valid evidence of health outcomes. The sponsors/investigators minimize the impact of confounding and biases on inferences through rigorous design and appropriate statistical techniques. If a contemporaneous comparison group is not included, this choice should be justified, and the sponsors/investigators discuss in detail how the design contributes useful information on issues such as durability or adverse event frequency that are not clearly answered in comparative studies.

6. Study Population:

The study population reflects the demographic and clinical diversity among the Medicare beneficiaries who are the intended population of the intervention, particularly when there is good clinical or scientific reason to expect that the results observed in premarket studies might not be observed in older adults or subpopulations identified by other clinical or demographic factors. At a minimum, this includes attention to the intended population's racial and ethnic

[11] That is, the study design, analysis plan, and data source(s) are sufficient to credibly answer the question(s) posed by the CED.

backgrounds, gender, age, disabilities, important comorbidities, and, dependent on data availability, relevant health related social needs. For instance, more than half of Medicare beneficiaries are women so study designs should, as appropriate, consider the prevalence in women of the condition being studied as well as in the clinical trial and subsequent data reporting and analyses.

7. Subgroup Analyses:

The study protocol explicitly discusses beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion requirements effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. In the protocol, the sponsors/investigators describe plans for analyzing demographic subpopulations as well as clinically-relevant subgroups as identified in existing evidence. Description of plans for exploratory analyses, as relevant subgroups emerge, are also included.

8. Care Setting:

When feasible and appropriate for answering the CED question, data for the study should come from beneficiaries in their expected sites of care.

9. Health Outcomes:

The primary health outcome(s) for the study are those important to patients and their caregivers and that are clinically meaningful. A validated surrogate outcome that reliably predicts these outcomes may be appropriate for some questions. Generally, when study sponsors propose using surrogate endpoints to measure outcomes, they should cite validation studies published in peer-reviewed journals to provide a rationale for assuming these endpoints predict the health outcomes of interest. The cited validation studies should be longitudinal and demonstrate a statistical association between the surrogate endpoint and the health outcomes it is thought to predict.

10. Objective Success Criteria:

In consultation with CMS and AHRQ, sponsors/investigators establish an evidentiary threshold for the primary health outcome(s) so as to demonstrate clinically meaningful differences with sufficient precision.

11. Data Quality:

The data are generated or selected with attention to provenance, bias, completeness, accuracy, sufficiency of duration of observation to demonstrate durability of health outcomes, and sufficiency of sample size as required by the question.

12. Construct Validity:

Sponsors/investigators provide information about the validity of drawing warranted conclusions about the study population, primary exposure(s) (intervention, control), health outcome measures, and core covariates when using either primary data collected for the study about individuals or proxies of the variables of interest, or existing (secondary) data about individuals or proxies of the variables of interest.

13. Sensitivity Analyses:

Sponsors/investigators will demonstrate robustness of results by conducting pre-specified sensitivity testing using alternative variable or model specifications as appropriate.

14. Reporting:

Final results are provided to CMS and submitted for publication or reported in a publicly accessible manner within 12 months of the study's primary completion date. Wherever possible, the study is submitted for peer review with the goal of publication using a reporting guideline appropriate for the study design and structured to enable replication. If peer-reviewed publication is not possible, results may also be published in an online publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with incomplete results).

15. Sharing:

The sponsors/investigators commit to making study data publicly available by sharing data, methods, analytic code, and analytical output with CMS or with a CMS-approved third party. The study should comply with all applicable laws regarding subject privacy, including 45 CFR § 164.514 within the regulations promulgated under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and 42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient Records.

16. Governance:

The protocol describes the information governance and data security provisions that have been established to satisfy Federal security regulations issued pursuant to HIPAA and codified at 45 CFR Parts 160 and 164 (Subparts A & C), United States Department of Health and Human Services (HHS) regulations at 42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient and HHS regulations at 45 CFR Part 46, regarding informed consent for clinical study involving human subjects. In addition to the requirements under 42 CFR and 45 CFR, studies that are subject to FDA regulation must also comply with regulations at 21 CFR Parts 50 and 56 regarding the protection of human subjects and institutional review boards, respectively.

17. Legal:

The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals, although it is acceptable for a study to test a reduction in toxicity of a product relative to standard of care or an appropriate comparator. For studies that involve researching the safety and effectiveness of new drugs and biological products aimed at treating life-threatening or severely-debilitating diseases, refer to additional requirements set forth in 21 CFR § 312.81(a).

VII. Importance of Control Groups and Blinding in CED Studies

Within randomized controlled trials, blinding of patients and their treating clinicians may reduce the chances that treatment effect estimates are biased. Participants' knowledge that they are receiving a treatment, extra attention from health care professionals, and the expectation of a treatment's effectiveness, can each affect the apparent benefit from a treatment. Blinding can be especially important when evaluating endpoints that may be vulnerable to subjective interpretation, such as changes in pain levels, depression, or patient/caregiver reported quality of life. CMS recognizes that not all studies can be single- or double-blinded. In cases where blinding is not possible, CMS will closely examine the study design and analysis elements that may mitigate the risk of bias. For example, improvement in outcomes with subjective elements may be more convincing when combined with physiologic or structural outcomes.

In the most rigorous study designs, the treatment being studied is compared to something else for purposes of assessing effectiveness and controling bias/confounding. For example, a carotid stent procedure may be compared, using the appropriate randomization, to the current best standard of medical care; in a drug trial, some subjects may be randomized to receive a placebo medication. Within clinical trials, appropriately created control groups are important to exclude the possibility that factors other than the study intervention changed health outcomes. The patient's condition may improve or worsen independent of the treatments the patient is receiving. Factors unrelated to the treatment may also impact health outcomes. For example, use of a broad range of healthcare services was substantially altered during the COVID-19 public health emergency, which complicated interpretation of findings from clinical studies performed during that time frame. Without an appropriately created (typically contemporaneous) comparison group, it is often impossible to convincingly isolate and measure the treatment effect of interest.

CMS and AHRQ endorse the concept that CED studies under 1862(a)(1)(E) should be fit-for-purpose (FFP). That is, the study design, analysis plan, and data source(s) are sufficient to credibly answer the question(s) posed by the CED. In some cases, an identified evidence deficiency may only be addressed through use of a randomized controlled clinical trial (RCT). In other cases, observational studies that employ advanced designs and analytic methods may be sufficient. In observational study designs randomization is not used, but various methods may

be employed to simulate randomization and construct an active comparator that serves to minimize the potential for bias / confounding.

VIII. Ending CED

When making NCDs, CMS conducts a careful review of the published, peer-reviewed literature. We expect that CED studies will generate evidence that addresses evidentiary deficiencies identified in the NCD. Studies with a specific design, such as randomized controlled clinical trials and studies approved by CMS as part of an Evidence Development Plan, have established start and end dates. Regardless of whether a study is completed or generates favorable evidence, publication of clinical studies is necessary to inform patients, their caregivers, and their healthcare providers about the risks and benefits of available health care options.

When the available evidence about a particular item or service is insufficient to support coverage without further evidence development within a well-designed clinical research study, CMS considers an NCD with CED. However, CMS does not believe that an NCD that requires CED as a condition of coverage should last indefinitely. If the evidence supports a favorable coverage decision under CED, coverage should be time-limited to facilitate the timely generation of sufficient evidence to inform patient and clinician decision making and to support a Medicare coverage determination under section 1862(a)(1)(A) of the Act. To minimize delays in transitioning from a CED NCD to coverage without evidence development requirements, sponsors should build interim analyses into their study design and communicate these results to CMS. If the final results support consideration of a change in the coverage status of the item or service, a revised NCD could be expedited once the study is completed and the results are published. CMS would also accept a manuscript that has been peer-reviewed and accepted for publication or studies that are otherwise published in the public domain.

A CED cycle is considered completed when CMS completes a reconsideration of the CED coverage decision and removes the requirement for study participation as a condition of coverage. As with any NCD, any member of the public may request to reopen the NCD that requires CED. CMS prospectively plans to re-examine the published evidence at a date tied to completion of a CMS-approved CED study or other available evidence. CMS retains the right to reconsider an NCD at any time. CMS will review the evidence resulting from the CED studies as well as any other available evidence. The NCD process is described in the Federal Register (78 Fed. Reg. 48164).

IX. Transparency of CED

The NCD process, in general, is a transparent one. Requesters may meet with CMS and frequent, informal contact is possible. A tracking sheet is posted on the CMS website that allows interested individuals to participate in and monitor the progress of the review. A proposed decision is generally issued for public comment within six months of opening the NCD review. The proposed decision generally includes details of CED study design, which are also open to public comment. Consistent with section 1862(l)(3)(B) of the Act, we provide 30 days

for public comment on the proposal. There may be a Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) meeting, which is open to the public. In general, CMS will issue a final decision memorandum within 60 days after the close of the 30-day public comment period.

CMS expects that results of all CED approved studies under 1862(a)(1)(E) will be analyzed and published in the public domain, preferably in peer-review journals. CMS has used and will continue to use reported CED results to inform new or revised coverage decisions. CMS intends to maintain information on ongoing CED research studies on its website along with links to the ClinicalTrials.gov website maintained by the National Library of Medicine. We also plan to include links on our website to CED study results.

All studies seeking Medicare coverage under CED should be registered with ClinicalTrials.gov. Registrants at ClinicalTrials.gov should submit a standardized set of data elements to describe the study design, eligible populations, outcome measures, and other parameters and results. Registration on this site, for most studies, serves as a way for Medicare beneficiaries to learn about, and identify studies in which they may want to participate. Reporting study results also offers an assurance of quality because, generally, public access to information incentivizes a higher level of accountability in the accurate reporting of the clinical study protocol and results, and in the conduct of the trial itself. This accountability derives both from public access to information about studies and from the potential risk of penalty for submitting false or misleading clinical trial information in some trials.[12] Registration with ClinicalTrials.gov also helps to ensure that Medicare beneficiaries and their treating healthcare professionals will have pertinent information about CED studies, and we expect this may facilitate better informed decision-making.

X. **Revision History.**

This guidance was first published in 2006. It was revised in 2014 and 2024.

[12] See e.g., Public Health Service regulation at 42 CFR 11.6.