Analysis of Requirements for Coverage with Evidence Development (CED)

Johns Hopkins University
Evidence-based Practice Center

This report is based on research conducted by the Johns Hopkins University Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 75Q80120D00003). No statement in this report should be construed as an official position of AHRQ or CMS.

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Agenda

Agenda

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  - Key Informant Stakeholder Input
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  - Resulting Final Proposed Requirement
  - Methodologic Suggestions for Future Evaluation of CED Requirements

CED Background

Background – Definition of CED

Coverage with Evidence Decision (CED):

- CMS may issue a CED If insufficient evidence exists to conclude definitively that an item or service is “reasonable and necessary.”
- A CED is a National Coverage Determination (NCD) that allows patients to access these select medical items and services, with coverage, on the condition that there is prospective collection of agreed upon clinical data.

Background – CED History

CED History:

- 2005: CED process was designed.
- 2012: New CMS guidance clarified: 1) CED should be carried out via prospective studies and 2) a CED cycle is completed when CMS has sufficient evidence to reconsider the coverage decision.
- 2014: New CMS guidance: 1) reiterated **CED goal** is to expedite beneficiary access to innovative items and services while assuring that the technology is provided to clinically appropriate patients. 2) included **13 criteria/requirements** that should be met when data collection is underway.

Original 13 Requirements (1)

a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.

b. The rationale for the study is well supported by available scientific and medical evidence.

c. The study results are not anticipated to unjustifiably duplicate existing knowledge.

d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.

e. The study is sponsored by an organization or individual capable of completing it successfully.

f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.

Original 13 Requirements (2)

g. All aspects of the study are conducted according to appropriate standards of scientific integrity.

h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.

i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.

j. The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).

Original 13 Requirements (3)

k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line 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 negative or incomplete results).

k. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

Original 13 Requirements (4)

m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

AHRQ Report Scoping & Award

AHRQ Report Initiated

AHRQ Report Initiated in May 2022:

- Report scope*:
  - Question 1: What revisions to the CED criteria (“requirements”) may best address the limitations while preserving the strengths?
  - Question 2: How might the revised criteria (“requirements”) be evaluated in the future?

  *The CED process or other aspects of CED not included in the questions above were not included in the scope.

- AHRQ awarded report to Johns Hopkins University Evidence-based Practice Center (EPC)

AHRQ Report: Objective

Objective:

We aimed to refine the study design requirements so that investigators are efficient in completing studies that contribute to an evidence base, with the goal of ending the CED process when there is:

1) sufficient evidence for a coverage NCD;
2) sufficient evidence for a non-coverage NCD; or
3) a decision to defer the coverage decision to a Medicare Administrative Contractor (MAC).

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EVIDENCE-BASED PRACTICE CENTERS

AHRQ Report Literature Search

Methods: Literature Search (1)

PubMed Literature Search:

- Targeted search (English-language restriction)
  - "coverage with evidence development"[All Fields]
  - "access with evidence development"[All Fields]
  - "managed entry schemes"[All Fields]
  - "conditional licensing"[All Fields]
  - "approval with research" [All Fields]
  - 1 OR 2 OR 3 OR 4 OR 5

- Expanded search: Searched for guidance documents about the production of real-world evidence in the literature

Methods: Literature Search (2)

Grey Literature Search

- Searched the CED polices of other countries:
  - Identified candidate countries from three international review articles of CED schemes.
  - Resulting countries included Australia, Belgium, Canada, England, France, Germany, the Netherlands, Spain, Sweden, and Switzerland.
- Searched English-language government websites for health technology assessment (HTA) bodies located in these countries to identify documentation of CED policies.
- Asked international experts in the HTA field in Canada, England, the Netherlands, Sweden, and Switzerland about the existence and documentation of CED policies in their countries.

Methods: Development of 1st Draft

Development of 1st Suggested Requirements Revisions:

- Reviewed the 13 requirements in the existing CED guidance and assigned labels;
- Extracted recommendations that are intended to lead to the production of a strong body of evidence;
- 27 articles, which included 172 recommendations, were relevant to the update
- Labeled the extracted recommendations and added new thematic labels as needed;
- Aggregated recommendations and sorted by labels;
- Where appropriate, drafted one or more requirements to correspond to each of the labels based on the language of the recommendations and the perceived intent in the source documents.

Revised Requirements: Post Literature Review (1)

Revised Proposed Requirements Presented to Key Informants	Changes after Literature Review
A. The study is sponsored by investigators with the resources and skills to complete it successfully.	Perceived need to add "resources and skills," as both will contribute to success. Removed "organization".
B. A written plan describes scheduled communication by the investigators with CMS throughout the evidence generation period for review of study milestones.	Perceived need to add a requirement for a written plan for milestones to increase likelihood of timely completion.
C. The information governance and data protection requirements are established in writing and included in the study protocol.	Perceived need to add explicit data governance and protections, as these are best practices.
D. The rationale for the study is supported by scientific and medical evidence and its results are expected to fill a knowledge gap.	Perceived efficiency to combine Requirements b and c, as they are both about context and could be combined without loss of clarity

Revised Requirements: Post Literature Review (2)

Revised Proposed Requirements Presented to Key Informants	Changes after Literature Review
E. CMS and investigators agree upon the evidentiary threshold for the stated question. This reflects the clinically relevant difference in the key outcome(s) relative to the chosen comparator and the targeted precision.	Perceived need to clarify that an evidentiary threshold should be set so that the meaningful difference that is the target of the study is stated at the outset. Separated out the recommendation regarding representativeness.
F. The key outcome(s) for study are those that are clinically important to patients and durable. A surrogate outcome that reliably predicts key clinical outcomes might be appropriate for some questions.	Perceived need that the outcomes should be patient-relevant, and that, if a surrogate is used, this should be explicitly recognized.

Revised Requirements : Post Literature Review (3)

Revised Proposed Requirements Presented to Key Informants	Changes after Literature Review
G. A protocol describing the data source(s), key outcome(s), and key elements of design, at a minimum, is publicly posted on the CMS website.	Perceived need to remove requirement to register in RoPR, as RoPR is no longer available. We retained the protocol, listing key components, and adding a public posting for transparency. Perceived efficiency to combine Requirements h and j, as they are both about steps in preparation for the study.
H. The studied population reflects the intended users of the product and also the racial, gender, and socio-economic diversity of the Medicare beneficiary population including older adults, individuals on dialysis, and disabled younger persons when relevant to the questions.	Perceived need to add a requirement that the population studied reflects the Medicare beneficiaries who will use the product or service and that attention is given to the inclusion of diverse users of the product.

Revised Requirements : Post Literature Review (4)

Revised Proposed Requirements Presented to Key Informants	Changes after Literature Review
I. The investigators obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data, unless an institutional review board deems it to not be human subjects research or eligible for waiver or alteration of consent.	Perceived need for an explicit statement about informed consent.
J. When feasible and appropriate for answering the CED question, data for the study should come from the real-world practice of medicine including from practitioners diverse in experience and diverse sites of care delivery.	Perceived need for beneficiaries to be studied in their usual sites of care to better reflect the effectiveness of the product or service.

Revised Requirements: Post Literature Review (5)

Revised Proposed Requirements Presented to Key Informants	Changes after Literature Review
K. The data are of sufficient size, completeness, continuity, and accuracy to assess participant eligibility, key prognostic and predictive factors, exposure to therapy (including a unique device identifier, if relevant), and key outcomes.	Perceived need to ensure that the data are sufficient to expediently generate the needed evidence.
L. The investigators validate algorithms for the measurement of key exposures and outcomes. When infeasible, the investigators assess the performance of the operational definition of the variable or cite relevant validation exercises.	Perceived need for a data validity requirement to improve scientific integrity with the goal of high strength evidence.
M. The study design is selected to efficiently generate the needed evidence. Expected designs include pragmatic trials with randomization and blinding when feasible, single arm intervention studies with contemporaneous comparator groups, prospective cohort studies with contemporaneous comparison groups, self-controlled designs where appropriate, or retrospective cohort studies with contemporaneous comparators nested within registries.	Perceived need to clarify about study design selection for the generation of high strength evidence.

Revised Requirements : Post Literature Review (6)

Revised Proposed Requirements Presented to Key Informants	Changes after Literature Review
N. The investigators minimize the impact of confounding and biases on inferences by using rigorous design and statistical techniques.	Perceived need to clarify important threats to valid inferences so that the results have integrity, and to minimize these threats by adding: "minimize the impact of confounding and biases on inferences by using rigorous design and statistical techniques."
O. The investigators pre-specify subpopulations for study if they expect that key outcomes in response to treatment will be meaningfully different in those subgroups compared with the majority population. Otherwise, investigators will explore for heterogeneity of treatment effect if there are not a priori hypotheses.	Perceived need to reflect best practices for understanding heterogeneity in treatment effect led to revised recommendations about evaluating subpopulations.

Revised Requirements : Post Literature Review (7)

Revised Proposed Requirements Presented to Key Informants	Changes after Literature Review
P. When relevant, investigators follow best practices for establishing and maintaining a registry.	Perceived need to add explicit attention to registries given expectation that CED studies may involve registries.
Q. The investigators demonstrate reproducibility of results from the study by conducting alternative and sensitivity analyses, and/or using other data sources.	Perceived need to demonstrate reproducibility of results as a best research practice
R. The results and analytic code are submitted for peer review using a reporting guideline appropriate for the design.	Perceived need to split this existing requirement due to its lengthiness. We removed the date requirement (expecting that this would be established when setting milestones at the study outset) and retained attention to sharing results and analytic code to improve transparency.

Revised Requirements : Post Literature Review (8)

Revised Proposed Requirements Presented to Key Informants	Changes after Literature Review
S. The reporting is structured to enable replication by a regulator, payor, or another research team.	Perceived need for reporting sufficiency with the goal of replication.
T. The investigators commit to sharing data, methods, and analytic code with CMS. Other sharing is to follow the rules of the funder and the institutional review boards.	Perceived need for requirement about sharing with CMS to allow replication and verification of results.
U. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.	No change made.
V. The research study complies with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56.	Perceived continued need to specify requirement for compliance with applicable Federal regulations, although text about consent was moved to a unique requirement.

AHRQ Report Key Informant Stakeholder Input

Methods: Key Informant Stakeholder Input (1)

Sought "Key Informant" stakeholder input on 1st Draft.

Expertise included:

- patient/consumer advocacy,
- real-world data and evidence,
- medical specialty societies,
- health technology assessment,
- commercial health plans, and
- health policy

Key Informants

Naomi Aronson, PhD	Executive Director, Clinical Evaluation and Innovation, Office of Clinical Affairs, Blue Cross Blue Shield Association
Peter Bach, MD, MAPP	Past Chair of MEDCAC and Chief Medical Officer at Delfi Diagnostics
Helen Burstin, MD, MPH	CEO of Council of Medical Specialty Societies
Daniel Arthur Caños, PhD, MPH	Director, Office of Clinical Evidence and Analysis, Office of Product Evaluation and Quality, CDRH, Food and Drug Administration
John Concato, MD, MS, MPH	Associate Director for Real-World Evidence Analytics in the Office of Medical Policy (OMP), CDER, Food and Drug Administration (FDA)
Eric Gascho, BA	National Health Council, Senior Vice President Policy and Government Affairs
Richard Hodes, MD	Director, National Institute on Aging (NIA)
Ashley Jaksa, MPH	Scientific Partnerships Lead, Aetion
Kathryn Phillips, PhD	Professor of Health Economics and Health Services Research, Department of Clinical Pharmacy, UCSF
Nancy Dreyer, MPH, PhD	Principal, Dreyer Strategies LLC, Chief Scientific Officer Emerita at IQVIA
Michael Drummond, BSc, MCom, DPhil	Professor of Health Economics and former Director of the Centre for Health Economics at the University of York.
Eliseo Perez-Stable, MD	Director, National Institute of Minority Health and Health Disparities (NIMHD)

Methods: Key Informant Stakeholder Input (2)

Key Informant (KI) stakeholder involvement process:

- Pre-Meeting Activities:
  - KIs reviewed 1st draft and provided comments
  - KIs assessed each of the 22 revised requirements:
    - 0=not needed; 1=important; and 2=essential (mean: 1.3 to 2.0)
    - whether in need of textual revision (suggested by 2+ KIs for 17 of 22 requirements)
- 2 KI meetings (each with half of the KIs)
  - KIs received summary of their collective grading before the discussion
  - PI focused discussion on areas requiring resolution.
- EPC revised report/criteria based on input, and shared revised criteria with KIs for 2nd assessment

Revised Proposed Requirements: Post KI Input (1)

Revised Proposed Requirements	Revisions
A. The study is conducted by investigators with the resources and skills to complete it successfully.	The KI Panel suggested that the focus be prioritized on those who conducted the research. We responded by changing “sponsored” to “conducted.”
B. A written plan describes the schedule for completion of key study milestones.	The KI Panel suggested clarification that the priority was on communicating milestones, rather than general communication. We added “schedule for completion of key study milestones.”
C. The rationale for the study is supported by scientific evidence and study results are expected to fill the specified knowledge gap.	The KI Panel noted that there are many potential sources of uncertainty, and the importance of specifying which uncertainty the study is trying to address. Added the word “specified.” Also, simply to be concise, removed “and medical.”

Revised Proposed Requirements: Post KI Input (2)

Revised Proposed Requirements	Revisions
D. CMS and investigators agree on an evidentiary threshold for the study as needed to demonstrate clinically meaningful differences in key outcome(s) with adequate precision.	The KI Panel requested additional clarity; we responded by re- writing as a single sentence and prioritizing "precision" (which refers to sufficient sample size for statistically significant comparisons) and removing attention to comparators.
E. The study's protocol is publicly posted on the CMS website and describes, at a minimum, the data source(s), key outcome(s), and study design.	The KI Panel requested that the sentence be reordered for clarity.
F. The protocol describes the information governance and data protection requirements that have been established.	The KI Panel suggested reordering of the sentence to improve clarity.

Revised Proposed Requirements: Post KI Input (3)

Revised Proposed Requirements	Revisions
G. The data are generated or selected with attention to completeness, accuracy, sufficiency of duration of observation, and sample size as required by the question.	The KI Panel commented that the investigator needs to choose data with attention to completeness, accuracy, duration, and sample size. It is expected that this information will be included in the protocol.
H. Data for the study comes from patients treated in the usual sites of care delivery for the product.	The KI Panel commented that the evaluation of devices differs from evaluation of drugs, and that evaluation may be optimal in diverse settings; however, the "usual site of care delivery" may be a specialized clinical facility (e.g., "center of excellence") when the product is newly in use and may include more diverse sites of care as usage expands. This terminology replaced the term "real-world practice."

Revised Proposed Requirements: Post KI Input (4)

Revised Proposed Requirements	Revisions
I. The key outcome(s) for the study are those that are important to patients. A surrogate outcome that reliably predicts these outcomes may be appropriate for some questions.	The KI Panel agreed with the importance of patient relevance and that surrogate outcomes are sometimes appropriate. We changed "clinically important" to "important," as there is often existing information about what is important to patients. If there is not, this information may need to be generated. As item E states that outcomes are described in the protocol, it is expected that this will be described in the protocol.
J. The study population reflects the demographic and clinical complexity among the Medicare beneficiaries who are the intended users of the product.	The KI Panel noted that the requirement needed revisions for clarity and conciseness, while maintaining the intended purpose.
Deleted requirement. [consent]	After discussion with the KI Panel, this requirement was deemed unnecessary, as Institutional Review Board includes informed consent requirements.

Revised Proposed Requirements: Post KI Input (5)

Revised Proposed Requirements	Revisions
K. When using secondary data, investigators provide information about the performance of the algorithms used for measurement of key exposures and outcomes.	Due to KI Panel input, we revised wording for clarity; we added the phrase "secondary data" to indicate data from electronic health records, claims, etc.
L. The study design is selected to efficiently generate valid evidence. If a contemporaneous comparison group is not included, this choice must be justified.	KI Panel comments suggested that the detailed list of possible study designs was unnecessary and restrictive; thus, we removed it. The KI Panel also provided agreement with the importance of the word "efficient." Our revision ("to efficiently generate valid evidence") reflects that efficiency is NOT being prioritized over validity. They also suggested a focus on the need for a design that generates valid evidence. Regarding comparators, they noted that a comparator is not always necessary in these settings. We added: "If a contemporaneous comparison group is not included, this choice must be justified."

Revised Proposed Requirements: Post KI Input (6)

Revised Proposed Requirements	Revisions
M. The investigators minimize the impact of confounding and biases on inferences with appropriate statistical techniques, in addition to rigorous design.	The KI Panel noted overlap with the requirement about choosing a study design that generates valid evidence; therefore, since the previous element addresses study design, we changed the language to: "appropriate statistical techniques, in addition to rigorous design."
N. In the protocol, the investigators describe considerations for analyzing demographic subpopulations as well as clinically relevant subgroups as motivated by existing evidence.	The KI Panel urged avoidance of suggestion that investigators need only evaluate social class and race/ethnicity when the data indicate a difference. In addition, they noted that a set of fundamental factors should always be measured in a standardized way and considered as affecting outcomes until proven otherwise. In response, the requirement was modified to reflect that existing evidence (such as from phase II/III studies, related products, or class effects) should inform the pre- specification of clinically relevant subgroups, while all studies should include analysis of demographic subpopulations.

Revised Proposed Requirements: Post KI Input (7)

Revised Proposed Requirements	Revisions
Deleted [design registry]	The KI Panel noted that there could be confusion about whether the requirement refers to establishing a registry to meet a CED requirement or conducting a "registry study." Moreover, since establishing a registry does not generate evidence without an accompanying study design, and since other requirements cover study design, this requirement was deleted.
O. The investigators demonstrate robustness of results by conducting alternative analyses, and/or using other data sources.	The KI Panel noted that the "reproducibility" is a narrow concept and that "robustness" may be the preferred word choice.
P. The results and analytic code are submitted for peer review using a reporting guideline appropriate for the study design and structured to enable replication.	The KI Panel suggested that there could be a requirement for public posting on a website. We favored peer review for vetting rather than public posting, although both might be appropriate. This now reflects a merging of two requirements.

Revised Proposed Requirements: Post KI Input (8)

Revised Proposed Requirements	Revisions
Merged with R [Replication]	The KI Panel suggested this could be merged with R, which we did.
Q. The investigators commit to sharing de-identified data, methods, and analytic code with CMS or with a trusted third party. Other sharing is to follow the rules of the funder and the institutional review boards.	The KI Panel noted that patients may be reluctant to enroll if their personal data will be shared with the government; therefore, we clarified that the data would be de-identified. We inserted "or with a trusted third party" to allow the investigators to share data elsewhere if they learn that sharing with CMS impacts study enrollment. Rationale for sharing is so that CMS has an opportunity to verify results and possibly do additional learning.
R. The study is not designed to exclusively test toxicity unless the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.	The KI Panel commented that a study evaluating disease pathophysiology is unlikely to be brought forward for CED, so this aspect (i.e.: "disease pathophysiology in healthy individuals") was removed. Since a study of toxicity of a product seems potentially appropriate if used in an individual with few options, testing toxicity was retained.

Revised Proposed Requirements: Post KI Input (9)

Revised Proposed Requirements	Revisions
S. The research study complies with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the FDA, it is also in compliance with 21 CFR Parts 50 and 56.	No comments received or changes made.

AHRQ Report Public Comment Input

Methods: Public Comment Period

Public Comments:

- AHRQ posted the revised report and amended requirements for public comment on September 7th – September 28th, 2022
- EPC topically summarized the comments
  - Comments outside of the scope of this project were summarized in an appendix
  - Comments about the requirements were closely reviewed and informed revisions

Public Comments Summary

- **Received 27 public comments:**
  - 17 comments included specific recommendations regarding the requirements
  - Other comments:
    - Overarching comments about the set of requirements
    - Comments about the report methodology (e.g., Key Informant selection, literature review process)
    - Recommendations for revisions to the CED program (out of scope)
    - Comments about cost, cost-effectiveness, and value evaluation (out of scope)

Final Proposed Requirements
(and responses to public comments)

Revised Requirements: Post Public Comment (1)

Final Proposed Requirement	Revisions
A. The study is conducted by sponsors/investigators with the resources and skills to complete it successfully.	Inserted reference to sponsors.
B. A written plan describes the schedule for completion of key study milestones to ensure timely completion of the CED process.	Added a phrase to emphasize the goal of ensuring timely completion of the CED process.
C. The rationale for the study is supported by scientific evidence and study results are expected to fill the specified knowledge gap and provide evidence of net benefit.	Added phrase to specify that the goal includes providing evidence of net benefit.

Revised Requirements: Post Public Comment (2)

Final Proposed Requirement	Revisions
D. Sponsors/investigators establish an evidentiary threshold for the primary outcome(s) so as to demonstrate clinically meaningful differences with sufficient precision.	Inserted reference to sponsors and added wording to emphasize the importance of obtaining input from patients about their preferences regarding outcomes and their tolerance of uncertainty when deciding on the evidentiary threshold.
E. The CED study is registered with ClinicalTrials.gov and a complete protocol is delivered to CMS.	Industry representatives strongly urged against public posting of the complete protocols. They indicated that clinicaltrials.gov is sufficient for transparency and that additional protocol information could be given to CMS without public posting.

Revised Requirements: Post Public Comment (3)

Final Proposed Requirement	Revisions
F. The protocol describes the information governance and data security provisions that have been established.	We changed the wording to clarify that we mean for this to be about data security.
G. The data are generated or selected with attention to completeness, accuracy, sufficiency of duration of observation to demonstrate durability of results, and sufficiency of sample size as required by the question.	We inserted a phrase about durability of results. We do not think that the CED requirements conflict with FDA requirements regarding post-approval studies.
H. When feasible and appropriate for answering the CED question, data for the study should come from beneficiaries in their usual sites of care, although randomization to receive the product may be in place.	We revised the wording in response to requests for clarification and acknowledgment of the situation in which a product is only available through participation in a randomized trial. Public comments generally supported the requirement for data coming from patients in usual care settings.

Revised Requirements: Post Public Comment (4)

Final Proposed Requirement	Revisions
I. The primary outcome(s) for the study are those that are important to patients. A surrogate outcome that reliably predicts these outcomes may be appropriate for some questions.	We revised to refer to "primary" outcomes(s) that are important to patients. Patient-important outcomes may or may not be patient reported (e.g., death).
J. The study population reflects the demographic and clinical diversity among the Medicare beneficiaries who are the intended users of the intervention. This includes attention to the intended users' racial and ethnic backgrounds, gender, and socio-economic status, at a minimum.	We added a sentence in response to requests for more specificity.
K. Sponsors/investigators provide information about the validity of the primary exposure and outcome measures, including when using primary data that is collected for the study and when using existing (secondary) data.	We revised the wording to be inclusive of primary and secondary data. We have also clarified that secondary data are "existing data." We again insert reference to sponsors.

Revised Requirements: Post Public Comment (5)

Final Proposed Requirement	Revisions
L. The study design is selected to safely and efficiently generate valid evidence for decision making by CMS. If a contemporaneous comparison group is not included, this choice must be justified.	We revised the wording to emphasize the importance of safely and efficiently generating evidence for decision making by CMS. “Efficient” is meant to encompass both timeliness and inclusion of the minimum number of participants required to generate valid evidence.
M. The sponsors/investigators minimize the impact of confounding and biases on inferences with rigorous design and appropriate statistical techniques.	We inserted reference to sponsors and reordered the wording to mention rigorous design before statistical techniques.

Revised Requirements: Post Public Comment (6)

Final Proposed Requirement	Revisions
N. In the protocol, the sponsors/investigators describe plans for analyzing demographic subpopulations, defined by gender and age, as well as clinically-relevant subgroups as motivated by existing evidence. Description of plans for exploratory analyses, as relevant subgroups emerge, is also appropriate to include but is not required.	We added wording in response to requests for more specificity, and to define minimum requirements of analyzing gender and age subgroups for heterogeneity of treatment effects. We added a sentence to encourage exploratory analyses as appropriate.
O. Sponsors/investigators using secondary data will demonstrate robustness of results by conducting alternative analyses and/or using supplementary data.	We revised the wording to clarify that this requirement is applicable when using secondary data and doing observational studies (and not so relevant for trials).
P. 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.	We revised the wording because commenters expressed strong opposition to supplying analytic code, believing that it may include proprietary information.

Revised Requirements: Post Public Comment (7)

Final Proposed Requirement	Revisions
Q. The sponsors/investigators commit to sharing analytical output, methods, and analytic code with CMS or with a trusted third party in accordance with the rules of additional funders, institutional review boards, and data vendors as applicable. The schedule for sharing is included among the study milestones. The study should comply with all applicable laws regarding subject privacy, including section 165.514 of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).	We removed the requirement to share individual level data. We have combined the existing two sentences into one and added that there may be limitations imposed by the data vendor. We also have added wording about timing of sharing and about HIPPAA compliance.

Revised Requirements: Post Public Comment (8)

Final Proposed Requirement	Revisions
R. The study is not designed to exclusively test toxicity, 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).	We removed the requirement that the patient must have a life-threatening condition. We added a sentence to better characterize the intent of such studies.
S. The research study complies with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration, it is also in compliance with 21 CFR Parts 50 and 56.	No change

Reflections

- The proposed requirements have more explicit expectations for the studies that are designed to generate the needed evidence for CMS and *should* be easier to act upon by sponsors.
- An explanatory guide may need to accompany these requirements.
- We have encouraged use of real-world data when feasible (requirement H) which describes the inclusion of patients in their usual clinical settings.
- There will continue to be the need for more traditional trials: the therapies recommended for CED are often devices or diagnostics, rather than drugs or biologics, or are therapies being used for novel indications. Thus, there may not be the extensive clinical trial record that is generated during regulatory approval of pharmaceuticals.

Suggestions for Future Evaluation of CED Final Proposed Requirements

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- The amended requirements might be evaluated with attention to both process and outcome metrics. If protocols are described with sufficient detail in ClinicalTrials.gov, this will facilitate external evaluation.
- The impact of the requirements on outcomes can be evaluated by an assessment of the *value of the evidence* that is produced. (e.g., Does the evidence generated in a study or series of studies allow CMS to efficiently end a CED with a coverage or non-coverage decision or with deferral to a MAC?)
- The quality and strength of the evidence generated is the ultimate test of the effectiveness of the set of requirements as this will allow for a timely decision by CMS.