Topic Refinement

Analysis of Requirements for Coverage with Evidence Development (CED) - Topic Refinement

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States.

The Centers for Medicare and Medicaid Services requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the following EPC: (Johns Hopkins University) Evidence-based Practice Center (Contract Number: (75Q80120D00003).

The report will be presented at the public meeting – Medicare Evidence Development & Coverage Advisory Committee Meeting on December 7th, 2022.

If you have comments on this report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted a panel of Key Informants who represent subject experts and end-users of research. Key Informant input can inform key issues related to the topic of the technical brief. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Background

The Centers for Medicare & Medicaid Services (CMS) covers medical items and services when evidence supports that they are reasonable and necessary for the health of its beneficiaries.These products are demonstrated to be safe and effective, not experimental, and appropriate for Medicare beneficiaries.[1] Thus, CMS makes decisions about providing insurance coverage for use of these drugs, devices, diagnostics, procedures or technologies. In contrast, the U.S. Food and Drug Administration (FDA) makes decisions about the approval for marketing of products based on demonstrations of their safety and efficacy, often relative to placebos; the goals of the two agencies are different. When CMS decides that there is insufficient evidence to conclude definitively that an item or service is "reasonable and necessary," including FDA-approved products, it may issue a Coverage with Evidence Development (CED) decision.[2] A CED decision 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. When there is insufficient evidence to allow CMS to make a National Coverage Determination for coverage of an item or service, a CED decision enables the Medicare program to cover 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.

In brief, the CED process was designed in 2005. The stated goals were to generate data so that CMS could verify the appropriateness of the use of an item or service, consider future changes in coverage for an item or service, and generate clinical information to improve the evidence base for or against the use of an item or service.[3] With its update in 2006, CMS outlined two subtypes of CED. The first was coverage with appropriateness determination, or CAD. Here, CMS agrees that an item or service is reasonable and necessary but requests clinical data that are not generally available in claims to ensure appropriate use. The second is coverage with study participation, or CSP. In this case, CMS would ask that additional data be generated in the context of research.[4, 5] CMS no longer differentiates between these two activities, as described in the most recent guidance document.[6]

In April 2012, the Obama Administration stated that CMS should better define "the parameters and guidance for [CED] so it can be used more widely and effectively as a driver of innovation."[7] Soon thereafter, in November 2012, CMS released revised guidance clarifying that CED should be carried out via prospective studies and that a CED cycle is completed when CMS has sufficient evidence to reconsider the coverage decision. The updated guidance document of 2014 describes the updates to the program that came about following input from the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) and describes related, but distinct, programs like the coverage that is part of the Investigational Device Exemption (IDE) program.[6]

The 2014 guidance acknowledges that CMS is increasingly challenged by requests for coverage of items and services when the expectations of interested parties are not adequately supported by the existing evidence base. With the CED program, CMS can provide support for items and services that are likely to benefit the Medicare population, but where the available evidence base is insufficient to support coverage. The goal of

every CED is to provide coverage of promising technologies while evidence is collected to determine if the technology is reasonable and necessary for the stated indications/outcomes. This process is intended to expedite beneficiary access to innovative items and services while assuring that the technology is provided to clinically appropriate patients, meaning those who are likely to benefit. The process includes protections to reduce the risks inherent to new technologies, or to new applications of existing technologies. A recent review described 27 CED determinations from 2005 to 2022 in 8 therapeutic areas.[8] The duration of these CED activities ranged from 1 to 16 years. Only 4 of these CEDs led to a NCD for continued coverage, and 2 CEDs led to coverage revocation and deferral to local coverage decisions.

When a CED NCD is issued, CMS publicly posts the Decision Summary that describes the type of evidence CMS will accept during the CED process and what questions, at a minimum, must be addressed for coverage of the technology or drug within the context of a trial or other prospective data collection. For example, the recent CED NCD on monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease indicates that, for coverage, the investigators must answer the questions: Does the antiamyloid monoclonal antibody meaningfully improve health outcomes for patients in broad community practice? Do benefits, and harms such as brain hemorrhage and edema, associated with use of the antiamyloid monoclonal antibody, depend on characteristics of patients, treating clinicians, and settings? How do the benefits and harms change over time?[9] This specific Decision Summary specifies that the product may be covered in a randomized controlled trial conducted under an investigational new drug (IND) application when a surrogate endpoint is used, or may be covered in CMS-approved prospective comparative studies, with data collected in a registry, when the outcomes are selected to generate evidence of efficacy from a direct measure of clinical benefit.

Each Decision Summary also includes the list of specific study design requirements that should be met to assure study integrity.[2] The current 13 requirements are listed in item VI, Requirements for CED under Section 1862(a)(1)(E).[2] This report describes our response to the request from CMS for recommendations about updates to the CED study design requirements.

Purpose

The objective of this report is to describe our process and resulting recommendations to CMS for an update to the CED study design requirements. 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). Our goal for the set of requirements is that they will guide investigators to collect and use data generated in the care of patients to produce strong evidence about the health outcomes from use of products by Medicare beneficiaries, with integrity in the scientific process and transparency at all stages.

Questions

Guiding Questions

- Guiding Question 1: What are the strengths and limitations of the current CED criteria (that we now refer to as “requirements”)?
- Guiding Question 2: What criteria (“requirements”) are used by similar decision-making bodies?

Key Questions (KQ)

- KQ1: What revisions to the CED criteria (“requirements”) may best address the limitations while preserving the strengths?
- KQ2*:* How might the revised criteria (“requirements”) be evaluated in the future?

Methods

We generated revised requirements using the following process: searching for and reviewing relevant literature, drafting revised requirements based on the literature review, gathering input from Key Informants (KIs), revising the requirements, and delivering the revised requirements to CMS for presentation to the MEDCAC. The details of the process follow:

Literature Search

1. We started by conducting a targeted search of the English-language literature using PubMed and search terms for CED. The search included literature from 1978 through July 1, 2022. We reviewed the reference lists to include any articles that were relevant to our questions about CED. We also performed an expanded search adding terms as shown in Appendix 1.
2. The expanded search added many citations; therefore, we reviewed the abstracts of a random sample of 100 citations to estimate the incremental yield for identifying additional reports about study design recommendations (for a CED) or describing CED policies outside of the U.S. We excluded abstracts if they focused on aspects of the CED process unrelated to study design and conduct, and if they were evaluations of costs of therapies, analyses of cost-effectiveness, or were about economic or econometric valuation methods, as these are less relevant to the CMS process.
3. We looked for guidance documents about the production of real-world evidence, which we thought to be highly relevant because the data used to answer CED questions will often, although not always, be generated in the usual care of patients. Most of these documents were cited in the articles found in the initial literature search described above, and others were recommended by team members and our team’s advisors, including those from key professional

societies and national and international organizations who were part of the Key Informant Panel described below.

4. We identified and reviewed grey literature describing the CED polices of other countries, limited to documents published in English. We first identified candidate countries from three international review articles of CED schemes.[10-12] The countries were Australia, Belgium, Canada, England, France, Germany, the Netherlands, Spain, Sweden, and Switzerland. We then searched English-language government websites for health technology assessment bodies located in these countries to identify documentation of CED policies. We supplemented this government website search by asking colleagues in the health technology assessment (HTA) field (based in Canada, England, the Netherlands, Sweden, and Switzerland) to direct us to any documentation of CED policies in their respective countries. Two of these experts were part of the Key Informant Panel described below.

Generating Candidate Requirements

1. We reviewed the 13 requirements in the existing CED guidance (listed as a.– m.) and assigned labels to these requirements (e.g., data, protocol) to indicate the goals of each, expecting that each requirement contributes to assuring that the submitted study has scientific integrity.
2. The team members divided the identified literature based upon each person's expertise. Each then extracted recommendations that are intended to lead to the production of a strong body of evidence, as well as recommendations for evidence generation that are used in international settings in the context of coverage decisions. As described above, we focused on extracting recommendations for generating rigorous real-world evidence. Where needed, we used the following definitions for real-world data and real-world evidence as defined by the Food and Drug Administration (FDA).

    - "Real-world data are the data relating to patient health status and/or the delivery of health care that are routinely collected."[13]
    - "Real-world evidence is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data."[13]

    We did not extract recommendations for the conduct of traditional randomized controlled trials, such as those that are conducted for regulatory marketing approval, as we expect that these requirements are well-known to sponsors. We also did not extract recommendations that were specific to determining the costs or cost-effectiveness of medical products because CMS is not authorized to consider costs or cost-effectiveness in coverage decisions.
3. We then labelled the extracted recommendations, adding additional labels as needed.
4. The recommendations were aggregated and sorted by their labels. We then crafted 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.

5. The co-investigators and advisors reviewed the draft requirements and made suggestions that were iteratively discussed and incorporated to assure that there was not duplication of the requirements.
6. We mapped the new CED requirements onto the existing requirements and noted the rationale for changes.

Key Informant (KI) Process

Within the AHRQ Evidence-based Practice Center (EPC) Program, the Key Informant (KI) role is to provide stakeholder perspectives and input. The EPC solicits input from KIs when developing questions for systematic review or when identifying high priority research gaps and needed new research. KIs are not involved in analyzing the evidence or writing the report.

1. The team members, advisors, CMS, and AHRQ generated a list of stakeholders with varied interests whose collective knowledge would be valuable to the process. The group generated candidate names of experts who could represent these stakeholders. Federal content experts were drawn from the FDA, the National Institute on Aging, and the National Institute on Minority Health and Health Disparities within the Department of Health and Human Services. We included representatives of non-federal stakeholders who had complementary perspectives (e.g., patient/consumer advocacy organization, medical specialty societies, or commercial health plan) and areas of expertise (e.g., health care registries, use of real-world data, health technology assessment, and health policy). We included a representative of a healthcare technology company that delivers evidence to biopharma companies, payers, and regulatory agencies, but we did not include other representatives from the life sciences industry because we expected to receive extensive input from many members of the life sciences industry during the public review period. The list of Key Informants who participated in this project will be listed in the final report.
2. In preparation for virtual KI Panel meetings, we sent the KIs a feedback form via Qualtrics to introduce them to the proposed new requirements and seek their feedback. The introduction to the task indicated that we sought feedback as to whether each of the proposed new requirements should be required for a study done for the purpose of CED. The Qualtrics tool asked the KIs to assess each of the new requirements on a scale of 0 to 2 where 0 is not needed, 1 is important but non-essential and 2 is essential. The KIs were also asked if each requirement was: 1 –clear as written, or 2- in need of textual revision. They were given space to comment on each item. KIs were also given a text box to convey comments on the body of requirements and their sufficiency for meeting the goal of CMS, which is to receive studies that contribute to the evidence for a decision.
3. For each KI meeting, we gave the KIs a summary of their collective feedback.

4. The principal investigator moderated the KI call and highlighted the comments from the KIs that required further discussion. The call was recorded and automatically transcribed as a reference for the revision of the requirements.
5. The discussion points from the KI meeting were used to further revise the requirements and a second feedback form, using Qualtrics, was sent to the KIs to confirm that the revisions were consistent with their recommendations.
6. The results of this second feedback were used to determine the degree of consensus about the importance of the proposed requirements and identify points of disagreement that might be appropriate for discussion with the MEDCAC.

Public Comment Process

AHRQ posted the report with the proposed requirements on the Effective Health Care website from September 7th through September 28th, 2022. We extracted all comments specific to the proposed requirements and looked for similarities among comments submitted by different reviewers. We then revised the requirements, accordingly, giving the highest priority to similar comments submitted by multiple reviewers. We also prepared a summary of the comments (see Appendix 2).

Results

Results of Literature Search and Recommendations Extraction

From our initial literature search and the review of reference lists in relevant articles, we found 27 articles that were appropriate for data extraction. We also identified 8014 articles with our expanded search strategy. The abstract review of the random subset did not identify any additional articles for inclusion. Most articles were excluded because they did not have sufficiently granular recommendations about the process of conducting studies within a CED. Other articles were excluded because they primarily addressed the evaluation of costs of therapies, cost-effectiveness, or other economic or econometric valuation methods.

The identified literature included the existing guidance documents from CMS.[2] We also included the framework and guidance documents from the National Evaluation System for health Technology Coordinating Center (NESTcc), which was a collaboration between FDA and medical device manufacturers.[14, 15] We extracted recommendations from three reports about generation of real-world evidence that were joint publications from the International Society of Pharmacoepidemiology (ISPE) and the International Society of Pharmaceutical Outcomes Research (ISPOR).[16-18] We also extracted guidance statements from three publications from the National Academies of Medicine[19-22] and multiple guidance documents from the FDA.[13, 23-29] We reviewed the Grace principles 5.1 document about registry design recommendations,[30, 31] as well as a framework for use of evidence for coverage decisions by Pearson and colleagues in 2018[32] and a framework about regulatory use of evidence from the Margolis Center for Health Policy Research at Duke University.[33] Other key documents were the 21st

Century Cures Act[34] and the transcript of the MEDCAC meeting in 2012 when the CED process was last discussed.[35]

Informative international publications were the work by Drummond and colleagues, which was part of an initiative by EU Horizon 2020 COMED (Pushing the Boundaries of Cost and Outcome Analysis of MEDical Technologies);[36] and the guidelines describing the United Kingdom's (UK) National Institute for Health and Care Excellence (NICE) Cancer Drugs Fund[37] and the Innovative Medicines Fund.[38] The EU Horizon 2020 COMED project included development of theory regarding CED, a systematic review, and 25 semi-structured interviews with decision makers and economists, and thus provided an alternative context for this present work.[12, 39] In reviewing those international publications, we concentrated on identifying recommendations that could be applied to CED decisions, without consideration of costs or cost-effectiveness as those are not relevant to the CMS process.

We found little literature describing CED policies in countries outside of the US that were accessible in English. Indeed, two review articles relied on expert interviews to identify CED policies given the absence of written policies.[10, 12]

The recommendations ranged from 8 to more than 50 discrete recommendations within a given publication.(Appendix 3) We found that the recommendations addressed the following topics, which we used as labels: context, data, data registry, data source, data sufficiency, data validation, design, bias, blinding, censoring, controls, definitions, exposures, outcomes, monitoring, population, precision, randomization, sensitivity analyses, dissemination, experts, generalizability, governance, interpretation, investigators, protocol, reporting, reproducibility, and transparency. The team had 172 recommendations to distill into a parsimonious set of proposed CED requirements.

The proposed requirements (Table 1) were contextualized as being requirements for a study that is designed to address one or more of the question(s) stated in a CED NCD. The order of the requirements is consistent with the order in which an investigator would approach the problem of framing the questions and generating evidence. The proposed requirements reflect best practices for both experimental and observational designs to efficiently generate evidence that contributes to the key decision as to whether CMS should: 1) end the CED due to sufficient evidence for a coverage NCD; 2) end the CED due to sufficient evidence for a non-coverage NCD, or 3) defer the coverage decision to a MAC. These are framed as requirements although CMS has the discretion to adjust or delete any requirement in a specific situation.

Table 1. Proposed Requirements for CED Studies that were Presented to the Key Informants (KIs)

	Tag	Requirement Version 2a, For Key Informants
A	Team	The study is sponsored by investigators with the resources and skills to complete it successfully.
B	Communication	A written plan describes scheduled communication by the investigators with CMS throughout the evidence generation period for review of study milestones.
C	Governance	The information governance and data protection requirements are established in writing and included in the study protocol.
D	Context	The rationale for the study is supported by scientific and medical evidence and its results are expected to fill a knowledge gap.
E	Context	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.
F	Outcome(s)	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.
G	Protocol	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.
H	Population	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.
I	Consent	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.
J	Data source	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.

	Tag	Requirement Version 2a, For Key Informants
K	Data quality	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.
L	Data use	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.
M	Design	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.
N	Analysis	The investigators minimize the impact of confounding and biases on inferences by using rigorous design and statistical techniques.
O	Design: Heterogeneity of treatment effect	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.
P	Design: registry	When relevant, investigators follow best practices for establishing and maintaining a registry.
Q	Reproducibility	The investigators demonstrate reproducibility of results from the study by conducting alternative and sensitivity analyses, and/or using other data sources.
R	Reporting	The results and analytic code are submitted for peer review using a reporting guideline appropriate for the design.
S	Replication	The reporting is structured to enable replication by a regulator, payor, or another research team.
T	Sharing	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.

	Tag	Requirement Version 2a, For Key Informants
U	Regulation	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.
V	Regulation	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.

CED = Coverage with Evidence Development; CFR = Code of Federal Regulations; CMS = Centers for Medicare & Medicaid Services; FDA = United States Food and Drug Administration

In Table 2, we show our comparison of the existing requirements and the proposed requirements that were presented to the KIs, showing that we moved from 13 requirements to 22 requirements, including the two requirements that cite specific regulations (U and V). The increase in the count of requirements was partially due to our decomposing the content of some of the existing requirements so that each requirement reflected a single concept with the goal of improved clarity. Additionally, we included recommendations that more completely reflect contemporary best practices regarding transparency and reproducibility.

Table 2. Evolution from Initial Criteria to Final Proposed Requirements

Tag for Requirement	Existing Requirements (version 2014)	Changes and Rationale for Changes after Initial Literature Review	Revised Proposed Requirements Presented to Key Informants (KIs) (version 2a)	Changes and Rationale for Changes after KI Panel Input	Revised Proposed Requirements after KI Panel Input (This Version was Posted for Public Comment) (version 3a)	Changes and Rationale for Changes after Public Comment	Final Proposed Requirements after Public Comments (version 3b)
Experts	e. The study is sponsored by an organization or individual capable of completing it successfully.	Perceived need to add "resources and skills," as both will contribute to success. Removed "organization".	A. The study is sponsored 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."	A. The study is **conducted** by investigators with the resources and skills to complete it successfully.	Public commenters noted that studies may be conducted by the sponsors or by external investigators, and both should be acknowledged; Thus, we expanded "investigators" to "sponsors/investigators" and made this change throughout.	A. The study is conducted by **sponsors/investigators** with the resources and skills to complete it successfully.
Communication	No existing requirement	Perceived need to add a requirement for a written plan for milestones to increase likelihood of timely completion.	**B. A written plan describes scheduled communication by the investigators with CMS throughout the evidence generation period for review of 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."	B. A written plan describes the **schedule for completion of key study milestones**.	Public commenters requested that we clarify the intent of a milestone driven process, so we added "to ensure timely completion of the CED process."	B. A written plan describes the schedule for completion of key study milestones **to ensure timely completion of the CED process.**
Governance	No existing requirement	Perceived need to add explicit data governance and protections, as these are best practices.	**C. The information governance and data protection requirements are established in writing and included in the study protocol.**	The KI Panel suggested reordering of the sentence to improve clarity.	F. **The protocol describes** the information governance and data protection requirements that have been established.	Public commenters requested clarity about the intent of this requirement; therefore, we clarified that this is meant to highlight data security concerns.	F. The protocol describes the information governance and **data security provisions** that have been established.
Context	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.	Perceived efficiency to combine Requirements b and c, as they are both about context and could be combined without loss of clarity	D. The rationale for the study is supported by scientific and medical evidence and its results are expected to fill a 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."	C. The rationale for the study is supported by scientific evidence and study results are expected to fill the **specified** knowledge gap.	Public commenters noted the need for attention to both harms and clinical benefits in the evidence generation process, and thus we added the phrase "net benefit."	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.**
Context	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.	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.	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.	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.	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**.	Public commenters noted the importance of patient input (e.g., preferences regarding outcomes and risk tolerance).	D. Sponsors/investigators establish an evidentiary threshold for the primary outcome(s) so as to demonstrate clinically meaningful differences with sufficient precision.
Outcomes	No existing requirement	Perceived need that the outcomes should be patient- relevant, and that, if a surrogate is used, this should be explicitly recognized.	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.**	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.	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.	Public commenters suggested that we remove the word "key" because it has no actual meaning in trial design; we changed "key outcomes" to "primary outcomes." Note that there were some comments that suggested we were advocating for patient reported outcomes but that is not the case. Patient-important outcomes may or may not be patient-reported (e.g., death).	I. The **primary** outcome(s) for the study are clinically meaningful and important to patients. A surrogate outcome that reliably predicts these outcomes may be appropriate for some questions.

Tag for Requirement	Existing Requirements (version 2014)	Changes and Rationale for Changes after Initial Literature Review	Revised Proposed Requirements Presented to Key Informants (KIs) (version 2a)	Changes and Rationale for Changes after KI Panel Input	Revised Proposed Requirements after KI Panel Input (This Version was Posted for Public Comment) (version 3a)	Changes and Rationale for Changes after Public Comment	Final Proposed Requirements after Public Comments (version 3b)
Protocol	h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements. 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).	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.	**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.**	The KI Panel requested that the sentence be reordered for clarity.	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.	Public commenters recommended against public posting of the complete protocols due to the risk of disclosing proprietary information. They indicated that registering the study with ClinicalTrials.gov is provides transparency and that additional protocol information could be provided to CMS directly without public posting. We added "registered with ClinicalTrials.gov" and also "a complete protocol is delivered to CMS."	E. The CED study is **registered with ClinicalTrials.gov** and a **complete protocol is delivered to CMS**.
Population	No existing requirement	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.	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.**	The KI Panel noted that the requirement needed revisions for clarity and conciseness, while maintaining the intended purpose.	J. The study population reflects the **demographic and clinical complexity among the Medicare beneficiaries who are the intended users** of the product.	Public commenters requested clarity about the essential demographic characteristics that the study population should reflect. We added "This includes attention to the intended users' racial and ethnic backgrounds, gender, and socio-economic status, at a minimum.**"**	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.**
Consent	No existing requirement	Perceived need for an explicit statement about informed consent.	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.**	After discussion with the KI Panel, this requirement was deemed unnecessary, as Institutional Review Board includes informed consent requirements.	Deleted requirement.	N/A	N/A
Generalizable	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.	Perceived need for beneficiaries to be studied in their usual sites of care to better reflect the effectiveness of the product or service.	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.**	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."	H. Data for the study comes from patients **treated in the usual sites of care delivery for the product.**	Public commenters generally supported the requirement for data coming from patients in usual care settings. They also noted that clinical trial participation may be required but is often challenging for patients outside of urban settings or outside of academic settings. The requirement does not explicitly acknowledge this challenge. We expect that diversity in care settings might be required in the 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.

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Data quality	No existing requirement	Perceived need to ensure that the data are sufficient to expediently generate the needed evidence.	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.**	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.	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.	Public commenters questioned whether the requirements would conflict with FDA's post-approval study requirements. We are uncertain if a study can meet both the needs of a CED study and FDA's post-approval needs as these differ. Public commenters also suggested that studies seek to assure that benefits are durable, and we added "to demonstrate durability of results."	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.
Data use	No existing requirement	Perceived need for a data validity requirement to improve scientific integrity with the goal of high strength 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.**	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.	K. When using **secondary data**, investigators provide information about the performance of the algorithms used for measurement of key exposures and outcomes.	Public commenters noted that validity is also essential when using primary data. We revised the wording to be inclusive of primary and secondary data. We also clarified that secondary data are "existing data."	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.
Design	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.	Perceived need to clarify about study design selection for the generation 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.**	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."	L. The study design is selected **to efficiently generate valid evidence. If a contemporaneous comparison group is not included, this choice must be justified.**	Public commenters requested that we clarify what is mean by efficient. There were also suggestions to assure that the data collection process is safe for patients. "Efficient" is meant to encompass both timeliness and inclusion of the minimum number of participants required to generate valid evidence. We added "safely and efficiently for decision making by CMS."	L. The study design is selected to generate valid evidence **safely and efficiently for decision making by CMS.** If a contemporaneous comparison group is not included, this choice must be justified.
Design	g. All aspects of the study are conducted according to appropriate standards of scientific integrity.	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."	N. The investigators **minimize the impact of confounding and biases on inferences by using rigorous design and statistical techniques**.	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."	M. The investigators minimize the impact of confounding and biases on inferences with **appropriate statistical techniques, in addition to rigorous design**.	Public commenters recommended reversing the order of the wording to mention rigorous design before statistical techniques; we reordered to "rigorous design and appropriate statistical techniques."	M. The sponsors/investigators minimize the impact of confounding and biases on inferences with **rigorous design and appropriate statistical techniques.**

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Design- subpopulations	I. 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.	Perceived need to reflect best practices for understanding heterogeneity in treatment effectiveness led to revised recommendations about evaluating subpopulations responses.	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.	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 effecting 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.	N. In the protocol, the investigators **describe considerations for analyzing demographic subpopulations as well as clinically relevant subgroups as motivated by existing evidence**.	Public commenters suggested adding specificity by defining the minimum requirements for subgroup analyses. We also added a sentence to encourage exploratory analyses as appropriate.	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 not required**.
Design- registry	No existing requirement	Perceived need to add explicit attention to registries given expectation that CED studies may involve registries.	P. **When relevant, investigators follow best practices for establishing and maintaining a 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.	Deleted	N/A	N/A
Reproducibility	No existing requirement	Perceived need to demonstrate reproducibility of results as a best research practice	Q. **The investigators demonstrate reproducibility of results from the study by conducting alternative and sensitivity 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.	O. The investigators demonstrate **robustness** of results by conducting alternative analyses, and/or using other data sources.	Public commenters expressed concern that this requirement would require two trials, which was not the intent. We revised the wording to clarify that this requirement is applicable when" using secondary data" and doing observational studies (i.e., "using more than a single source of data").	O. Sponsors/investigators using secondary data will demonstrate robustness of results by conducting alternative analyses and/or using supplementary data.

Tag for Requirement	Existing Requirements (version 2014)	Changes and Rationale for Changes after Initial Literature Review	Revised Proposed Requirements Presented to Key Informants (KIs) (version 2a)	Changes and Rationale for Changes after KI Panel Input	Revised Proposed Requirements after KI Panel Input (This Version was Posted for Public Comment) (version 3a)	Changes and Rationale for Changes after Public Comment	Final Proposed Requirements after Public Comments (version 3b)
Reporting	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).	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.	R. The results and analytic code are submitted for peer review using a reporting guideline appropriate for the design.	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.	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.	Public commenters questioned the purpose of peer review, and thus we added "with the goal of publication." They also expressed opposition to supplying analytic code, as they believed that it may include proprietary information; thus, "analytic code" was removed	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.
Replication	No existing requirement	Perceived need for reporting sufficiency with the goal of replication.	**S. The reporting is structured to enable replication by a regulator, payor, or another research team.**	The KI Panel suggested this could be merged with R, which we did.	Merged with R	N/A	N/A
Sharing	No existing requirement	Perceived need for requirement about sharing with CMS to allow replication and verification of results.	**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.**	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.	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.	Public commenters expect that the data sharing requirement will make recruitment of participants difficult. We combined the existing two sentences. We added wording about timing of sharing and about HIPPAA compliance as recommended by commenters. We also added that there may be limitations imposed by the data vendor.	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).**

Tag for Requirement	Existing Requirements (version 2014)	Changes and Rationale for Changes after Initial Literature Review	Revised Proposed Requirements Presented to Key Informants (KIs) (version 2a)	Changes and Rationale for Changes after KI Panel Input	Revised Proposed Requirements after KI Panel Input (This Version was Posted for Public Comment) (version 3a)	Changes and Rationale for Changes after Public Comment	Final Proposed Requirements after Public Comments (version 3b)
Legal	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.	No change made.	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.	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.	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.	Public commenters noted that some CED studies are likely to be for evaluation of devices with *lower* toxicity. We added a sentence to better characterize what we understand to be the intent of such studies.	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).
Legal	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.	Perceived continued need to specify requirement for compliance with applicable Federal regulations, although text about consent was moved to a unique requirement.	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.	No comments received or changes made.	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.	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.

AHRQ = Agency for Healthcare Research and Quality; CED = Coverage with Evidence Development; CFR = Code of Federal Regulations; CMS = Centers for Medicare & Medicaid Services; CMS = Centers for Medicare & Medicaid Services; FDA = United States Food and Drug Administration; RoPR = Registry of Patient Registries

Results of the Key Informants Call

Twelve KIs provided rich comments about the proposed requirements. The ratings of the proposed requirements by 11 KIs, which ranged from essential (2 points) to important (1 point) to not important (0 points), indicated that all were considered important or essential [Appendix 4]. (Table 3)

Table 3. Ratings of Importance of Proposed Requirements by the Key Informants (2 = essential; 1 = important; 0 = not important)

Requirement Version 2a For Key Informants	Mean Rating of Importance*	Number of Zeros
D. The rationale for the study is supported by scientific and medical evidence and its results are expected to fill a knowledge gap.	2.0	0
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.	2.0	0
A. The study is sponsored by investigators with the resources and skills to complete it successfully.	1.9	0
C. The information governance and data protection requirements are established in writing and included in the study protocol.	1.9	0
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.	1.9	0
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.	1.9	0
S. The reporting is structured to enable replication by a regulator, payor, or another research team.	1.9	0
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.	1.8	0
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.	1.8	1

Requirement Version 2a For Key Informants	Mean Rating of Importance*	Number of Zeros
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.	1.8	0
N. The investigators minimize the impact of confounding and biases on inferences by using rigorous design and statistical techniques.	1.7	1
R. The results and analytic code are submitted for peer review using a reporting guideline appropriate for the design.	1.7	0
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.	1.6	1
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.	2.0	0
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.	1.6	0
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.	1.5	1
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.	1.5	0
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	1.5	2

Requirement Version 2a For Key Informants	Mean Rating of Importance*	Number of Zeros
cohort studies with contemporaneous comparators nested within registries.		
P. When relevant, investigators follow best practices for establishing and maintaining a registry.	1.5	1
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.	1.4	2
Q. The investigators demonstrate reproducibility of results from the study by conducting alternative and sensitivity analyses, and/or using other data sources.	1.4	1
B. A written plan describes scheduled communication by the investigators with CMS throughout the evidence generation period for review of study milestones.	1.3	1

CFR = Code of Federal Regulations; CMS = Centers for Medicare & Medicaid Services

*11 KIs voting

In the discussion during the KI meetings, the KIs generally agreed that the proposed requirements as written did not seem to be excessively burdensome. Most of the KIs favored splitting multipart requirements into separate requirements rather than bundling several recommendations into a single requirement. It was felt that more granular requirements may be easier to act upon. Based on the discussion with the KIs, the proposed requirements were amended and re-ordered. The rationales for the amendments are included in Table 2.

Upon review of the amended requirements, nine KIs responded and all nine remained supportive of all the requirements. The mean ratings of the amended requirements ranged from 1.3 (for J and N) to 2.0 (for A, C, L, S, and V). The KIs suggested only minor further alterations to the wording of the requirements. Table 4 displays the resulting amended requirements along with the mean ratings [which also are displayed in Appendix 3]. None of the KIs rated any of these requirements as a zero. One KI strongly suggested that examination of demographic subpopulations be required for every CED. However, there remained disagreement regarding whether demographic subpopulations should be studied in every CED, the focus should simply be on clinically relevant subpopulations, or whether this should remain flexible based on prior evidence from studies of related interventions or earlier studies of the given intervention.

Table 4. Amended Requirements Based on the Recommendations of the Key Informants (2 = essential; 1 = important; 0 = not important)

Requirement Version 3a for Public Posting	Mean Rating of Importance*
A. The study is conducted by investigators with the resources and skills to complete it successfully.	2.0
B. A written plan describes the schedule for completion of key study milestones.	1.6
C. The rationale for the study is supported by scientific evidence and study results are expected to fill the specified knowledge gap.	2.0
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.	1.9
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.	1.8
F. The protocol describes the information governance and data protection requirements that have been established.	1.9
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.	1.9
H. Data for the study comes from patients treated in the usual sites of care delivery for the product.	1.4
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.	1.8
J. The study population reflects the demographic and clinical diversity among the Medicare beneficiaries who are the intended users of the product.	1.3
K. When using secondary data, investigators provide information about the performance of the algorithms used for measurement of key exposures and outcomes.	1.7

Requirement Version 3a for Public Posting	Mean Rating of Importance*
L. The study design is selected to efficiently generate valid evidence. If a contemporaneous comparison group is not included, this choice must be justified.	2.0
M. The investigators minimize the impact of confounding and biases on inferences with appropriate statistical techniques, in addition to rigorous design.	1.8
N. In the protocol, the investigators describe considerations for analyzing demographic subpopulations as well as clinically relevant subgroups as motivated by existing evidence.	1.3
O. The investigators demonstrate robustness of results by conducting alternative analyses and/or using other data sources.	1.7
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.	1.7
Q. The investigators commit to sharing de-identified data, methods, and analytic code with CMS or with a trusted third party. Other sharing is to follow the rules of the funder and the institutional review board.	1.7
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.	1.4
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.	2.0

*9 KIs voting; CFR = code of federal regulations, CMS = Centers for Medicare & Medicaid Services; KI = key informant

Results from Public Comments

We received 27 public comments, some of which came from allied groups. Seventeen commenters offered specific suggestions for editing one or more of the requirements. There were 137 remarks about specific requirements, with requirements K, L, and Q garnering the most remarks. After collating the public comments, we revised many of

the proposed requirements, as shown in Table 2 and 5. Some of the commenters do not believe that every requirement is necessary for every CED decision. We recommend that all the proposed requirements be considered for every CED, based on the previous importance ratings from the KIs as shown in Table 4.

In Appendix 2, we summarize the main topics of public comments. Some comments, such as comments relating to the *process of CED*, were outside the scope of this project. Within the comments related to the revised requirements as a set, a common concern was that increasing the number of requirements would place increased administrative and financial burden on sponsors. Some commenters suggested that CMS ought to waive certain requirements or prioritize the requirements depending on the technology under consideration, evidence gaps, and outcomes. Other commenters suggested that the requirements should give attention to the ethical and equity issues that can arise when implementing CED programs, such as when access is limited to centers with the resources to conduct randomized trials. Another common theme was support for the addition of real-world evidence options in the requirements, while also suggesting improvements for how real-world evidence might be developed and used by CMS.

Some comments focused on the methodology of the report. Some respondents voiced concerns about the process for selecting the KI Panel, and the exclusion of industry representation in the Panel. The selection followed the Program's standard protocol, thereby including input from the EPC, AHRQ, and partners, as well as a screening process for potential conflicts of interest. Although the primary focus of the KI Panel members was CED expertise, a broader list of stakeholders, including industry stakeholders, were directly notified when the draft report was posted for public comment to increase awareness of the opportunity. Some commenters felt that the three-week public comment period was too short; however, the period followed the standard protocol and could not be extended due to contractual requirements. Some commenters also expressed concern about a lack of transparency regarding the identities or interests represented by KIs at the time of public posting; the AHRQ EPC protocol is to de-identify report authors and panel members when the final product is publicly shared, and not beforehand. Finally, a few comments expressed concern that the literature review to inform the revision of requirements was too restrictive and too heavily reliant on published literature. The search strategy focused on the project scope and was supplemented by stakeholder input and public comments.

Table 5. Final Proposed Requirements after Incorporating Suggestions from Public Comments

Requirement Version 3b After Public Comments
A. The study is conducted by sponsors/investigators with the resources and skills to complete it successfully.
B. A written plan describes the schedule for completion of key study milestones to ensure 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.
D. Sponsors/investigators establish an evidentiary threshold for the primary outcome(s) so as to demonstrate clinically meaningful differences with sufficient precision.
E. The CED study is registered with ClinicalTrials.gov and a complete protocol is delivered to CMS.
F. The protocol describes the information governance and data security provisions that have been established.
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.
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.
I. The **primary** outcome(s) for the study are clinically meaningful and important to patients. A surrogate outcome that reliably predicts these outcomes may be appropriate for some questions.
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.
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.
L. The study design is selected to generate valid evidence safely and efficiently for decision making by CMS. If a contemporaneous comparison group is not included, this choice must be justified.

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M. The sponsors/investigators minimize the impact of confounding and biases on inferences with rigorous design and appropriate statistical techniques.
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 not required.
O. Sponsors/investigators using secondary data will demonstrate robustness of results by conducting alternative analyses and/or using supplementary data.
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.
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).
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).
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.

CED = Coverage with Evidence Development; CFR = Code of Federal Regulations; CMS = Centers for Medicare & Medicaid Services; FDA = United States Food and Drug Administration; HIPAA = Health Insurance Portability and Accountability Act

Considerations from Guiding Questions

In approaching this task, we looked to the *guiding questions* as we developed a strategy to generate this new set of requirements. We considered the strengths and limitations of the existing requirements and we sought to learn what requirements are used by other coverage decision-making bodies. The existing requirements have not been formally evaluated, making it challenging to comment objectively on their strengths and limitations. Our review of the documentation of completed studies for a CED or studies underway does not allow for comprehensive assessment of adherence to the requirements. There has not been a requirement for public posting of *protocols*, and we have not seen peer reviewed and published CED protocols, although they may exist. We are not recommending public posting given the risk of disclosure of proprietary information. Peer reviewed CED study *results* are often available, and the methods sections of such reports provide information about study design and conduct. Of the 23 CEDs for which registries and/or trials were used, 16 (62%) had some publicly available results, including 6 in which results were posted on ClinicalTrials.gov.[8] We suggest that immediately valuable work would be a review, similar to that conducted by the EU Horizon 2020 COMED, to assess the historical adherence of studies to the existing requirements. This would then inform the implementation and evaluation of amended requirements.

The evaluation of the *impact* of the existing set of requirements requires assessment of whether a decision was made based on the generated evidence, as well as what the decision was. In the recent review by Zeitler and colleagues, an action based on the results of CED studies was infrequent. In only 5 of the 26 CEDs has there been an outcome.[8] For 3 CEDs, the CED was retired when the evidence was deemed to be adequate: carotid artery stenting, implantable cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death, and magnetic resonance angiography/magnetic resonance imaging in patients with a cardiac implantable electronic device. Two CEDs, artificial hearts and home oxygen for cluster headaches, progressed to retirement of the CED and deferral of coverage decisions to MACs. The remaining CEDs are considered ongoing, suggesting that the studies have not yet generated the evidence needed for a coverage decision other than that provided by the CED. Whether this is due to the existing study requirements or due to other elements of the CED program cannot be easily determined. The addition of a requirement establishing milestones at the initiation of the CED should improve the completion rate. Many of the public comments suggested that clarity regarding the evidentiary threshold and a timeline to work toward reaching this threshold would be valuable.

The guiding question about requirements used by other CED decision-making bodies was valuable in pushing us to search for international publications on the topic as well as domestic publications from organizations that conduct health technology assessment. We found extensive literature describing processes, but very little that is granular enough to be considered recommendations for study requirements. Given that CMS is not authorized to consider the costs of items or services in coverage decisions, we limited our extraction of recommendations from the literature to those that could be applied to CMS policy. For that reason, the literature about managed-entry agreements

and risk-sharing was not on-target with our needs. We also learned that with decision-making bodies having greater access to data from diverse sources over the past decade, and the expansion of methods for drawing inferences from observational data, older literature about study design was less valuable to our revision of the requirements. However, many of the principles, including transparency and reproducibility of results, are evergreen.

Led by the guiding questions, we then addressed the key questions that were posed by AHRQ on behalf of CMS.

Key Questions

KQ1: What Revisions to the CED Criteria ("Requirements") May Best Address the Limitations While Preserving the Strengths

We suggest that the proposed requirements, although lengthier, 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. Many of the existing requirements are important and were retained. We suggest that the process of separating some of the requirements, which included multiple goals, into more discrete requirements improves the clarity. The inclusion of additional requirements reflects our understanding of the limitations of the existing requirements from our review of the literature. The existing requirements did not address the need for a governance plan, the quality of the data, validation of exposures and outcomes in the data, reproducibility of inferences, and publication of results. Most of the proposed requirements are applicable across study designs and across varied sources of data.

Our suggestion about the use of real-world data when feasible is reflected in amended requirement H, which describes the inclusion of patients in their usual care settings. The focus on real-world data to generate real-world evidence was intentional; this is often the appropriate evidence for a coverage decision (in contrast to a regulatory decision).[40, 41] Additionally, the focus on use of data generated in the usual care of patients may help assure the inclusion of a population generalizable to all Medicare beneficiaries who may be impacted by the coverage decision, and may help with the inclusion of sufficient beneficiaries representing subpopulations of interest.

Although real-world evidence is often sought for coverage decisions, for some CED decisions, we expect there will continue to be the need for more traditional trials. This largely arises because the therapies recommended for CED are often devices or diagnostics, rather than drugs or biologics, or are therapies being used for novel indications, without FDA-approval for marketing for these indications. In these situations, there may not be the extensive clinical trial record that is generated during regulatory approval of pharmaceuticals. Even Class III devices may be released from FDA's pre-market approval process if the sponsor successfully petitions for reassignment of the device to allow for the 501(k) process, which does not require the generation of extensive clinical evidence of efficacy or safety. Therefore, decision-makers at CMS may require the generation of new evidence to inform the coverage

decision and this may require a more traditional clinical trial. These trials can still be expected to follow the criteria presented here.

KQ2: How Might the Amended Criteria be Evaluated in the Future

We are unaware of any previous evaluation of the existing criteria so what we propose here is unique. The amended requirements might be evaluated with attention to both process and outcome metrics. If protocols that are developed by sponsors of the product, or by other investigators, are described with sufficient detail in ClinicalTrials.gov, it will facilitate external evaluation. This is consistent with what was recommended in an Organisation for Economic Co-operative and Development (OECD) Health Working Paper[42] "that as many features of [CED-like] schemes as possible should be in the public domain, apart from confidential items such as the details of any financial settlement made following the scheme (e.g., on the price of the device). Features of schemes that could be made public are the study design and methodology, the new evidence generated by the scheme, and any policy recommendations that were made following the scheme." CMS and/or AHRQ might review the protocols for their attention to the amended requirements. The sponsors might be encouraged to use a checklist to confirm attention to the requirements at the time of protocol preparation. While we largely expect that each requirement should be attended to, it is possible that a given requirement may not be appropriate in a specific instance; this will need to be documented when embarking upon a study. Upon completion of the proposed work, the published results might again be reviewed by CMS for adherence to the requirements.

The impact of the requirements on outcomes can be evaluated by an assessment of the value of the evidence that is produced. Does the evidence generated in a study or series of studies allow CMS to end a CED with a coverage or non-coverage decision or with deferral to a MAC? If the evidence is insufficient for these decisions, this would be a poor outcome as the studies should have been designed and adequately powered to generate the needed evidence. We expect that studies that adhere to the requirements will be more efficient; this will allow more rapid generation of evidence with involvement of the fewest patient participants as is needed to answer the question. 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 decision by CMS.

Conclusion

We reviewed published literature about best practices for generating evidence as is appropriate for a coverage decision. We found 27 articles to be relevant to the update, yielding 172 recommendations to distill into a parsimonious set of revised requirements. We circulated 22 revised requirements to the KIs. After incorporating their feedback, we had 19 amended requirements that were posted for public comment. We received a total of 137 comments from representatives of the life sciences industry and other stakeholders about the amended requirements. We responded to the numerous specific suggestions by making additional edits in the amended requirements that will be presented to the MEDCAC for their consideration. The new additions include

requirements for a milestone driven process, improved clarity regarding data selection and data security, attention to clinically important outcomes and to the diversity of Medicare beneficiaries, demonstration of robustness of results, and sharing of results. The amended requirements make explicit the expectations for studies that are designed to generate needed evidence for CMS. The requirements pertain to observational studies and traditional trials which may be sources of evidence for future CED decisions, depending on the clinical context. We propose that the impact of these requirements might be evaluated by assessment of the value and timeliness of evidence produced. Does the evidence generated in a study or series of studies allow CMS to efficiently and more predictably end a CED with a coverage or non-coverage decision? This is the test of the effectiveness of the requirements. In Table 5, we present a full set of proposed new criteria that have been amended to incorporate input from a distinguished panel of experts in the field as well as public comments from important stakeholders.

References

1. Medicare Program; Medicare Coverage of Innovative Technology (MCIT) and Definition of ‘‘Reasonable and Necessary’’(CMS–3372–F). In: Centers for Medicare & Medicaid, editor: Federal Register; 2021. p. 2987-3010.

2. Guidance for the public, industry, and CMS staff: coverage with evidence development. Baltimore, MD: Centers for Medicare & Medicaid Services; 2014. https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?mcdid=27&keyword=guidance&keywordType=starts&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&dateOption=effect&startDate=01/02/2007&endDate=01/02/2007&sortBy=relevance&bc=1. Accessed on June 24, 2022.

3. Medicare Announces Draft Guidance for National Coverage Determinations with Evidence Development. Baltimore, MD: U.S. Centers for Medicare & Medicaid Services; 2005. https://www.cms.gov/newsroom/press-releases/medicare-announces-draft-guidance-national-coverage-determinations-evidence-development. Accessed on July 1, 2022.

4. Straube BM. How changes in the Medicare coverage process have facilitated the spread of new technologies. Health Aff (Millwood). 2005 Jan-Jun;Suppl Web Exclusives:W5-314-w5-6. doi: 10.1377/hlthaff.w5.314. PMID: 15975989.

5. Tunis SR, Pearson SD. Coverage options for promising technologies: Medicare's 'coverage with evidence development'. Health Aff (Millwood). 2006 Sep-Oct;25(5):1218-30. doi: 10.1377/hlthaff.25.5.1218. PMID: 16966717.

6. Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development Baltimore, MD: U.S. Centers for Medicare & Medicaid Services; 2014. https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27. Accessed on July 1, 2022.

7. National Bioeconomy Blueprint. White House. 2012. https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/national_bioeconomy_blueprint_april_2012.pdf

8. Zeitler EP, Gilstrap LG, Colylewright M, et al. Coverage with evidence development: where are we now? AJMC. 2022;28(8):In Press.

9. Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease. CAG-00460N. Baltimore, MD: U.S. Centers for Medicare & Medicaid Services; 2022. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&NCAId=305. Accessed on July 1, 2022.

10. Brügger U. A Review of Coverage with Evidence Development (CED) in Different Countries: What Works and What Doesn’t. 2014. https://htai.org/wp-content/uploads/2018/02/CED_Report_Bruegger_Final_Version.pdf. Accessed on July 12, 2022.

11. Diaby V, Goeree R. Coverage with Evidence Development in Comparative Effectiveness Research. Comp Eff Res Heal Serv. 2015doi: 10.1007/978-1-4899-7586-7.

12. Federici C, Reckers-Droog V, Ciani O, et al. Coverage with evidence development schemes for medical devices in Europe: characteristics and challenges. Eur J Health Econ. 2021 Nov;22(8):1253-73. doi: 10.1007/s10198-021-01334-9. PMID: 34117987.

13. Framework for FDA's Real-World Evidence Program US Food & Drug Administration. Silver Spring, MD: 2018. https://www.fda.gov/media/120060/download

14. National Evaluation System for health Technology Coordinating Center (NESTcc) Data Quality Framework: A Report of the Data Quality Subcommittee of the NEST Coordinating Center - An initiative of MDIC NEST Coordinating Center. 2020. https://mdic.org/wp-content/uploads/2020/02/NESTcc-Data-Quality-Framework.pdf

15. National Evaluation System for health Technology Coordinating Center (NESTcc) Methods Framework: A Report of the Methods Subcommittee of the NEST Coordinating Center - An initiative of MDIC NEST Coordinating Center. 2020. https://mdic.org/wp-content/uploads/2020/02/NESTcc-Methods-Framework.pdf

16. Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. Pharmacoepidemiol Drug Saf. 2017 Sep;26(9):1033-9. doi: 10.1002/pds.4297. PMID: 28913966.

17. Wang SV, Schneeweiss S, Berger ML, et al. Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0. Pharmacoepidemiol Drug Saf. 2017 Sep;26(9):1018-32. doi: 10.1002/pds.4295. PMID: 28913963.

18. RWE for Regulatory Decision Making. Bethesda, MD: International Society for Pharmacoepidemiology; 2022. https://www.pharmacoepi.org/strategic-initiatives/rwe-for-regulatory-decision-making/. Accessed on June 22, 2022.

19. National Academies of Sciences E, Medicine, Health, et al. The National Academies Collection: Reports funded by National Institutes of Health. Real-World Evidence Generation and Evaluation of Therapeutics: Proceedings of a Workshop. Washington (DC): National Academies Press (US). Copyright 2017 by the National Academy of Sciences. All rights reserved.; 2017.

20. National Academies of Sciences E, Medicine, Health, et al. The National Academies Collection: Reports funded by National Institutes of Health. Examining the Impact of Real-World Evidence on Medical Product Development: II. Practical Approaches: Proceedings of a Workshop—in Brief. Washington (DC): National Academies Press (US). Copyright 2018 by the National Academy of Sciences. All rights reserved.; 2018.

21. National Academies of Sciences E, Medicine, Health, et al. The National Academies Collection: Reports funded by National Institutes of Health. In: Shore C, Gee AW, Kahn B, Forstag EH, eds. Examining the Impact of Real-World Evidence on Medical Product Development: Proceedings of a Workshop Series. Washington (DC): National Academies Press (US). Copyright 2019 by the National Academy of Sciences. All rights reserved.; 2019.

22. Towse A, Chalkidou K, Firth I, et al. How Should the World Pay for a Coronavirus Disease (COVID-19) Vaccine? Value Health. 2021 May;24(5):625-31. doi: 10.1016/j.jval.2020.12.008. PMID: 33933230.

23. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices US Food & Drug Administration. Silver Spring, MD: 2017. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices

24. Use of Electronic Health Record Data in Clinical Investigations Guidance for Industry US Food & Drug Administration. Silver Spring, MD: 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-health-record-data-clinical-investigations-guidance-industry

25. Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics Guidance for Industry US Food & Drug Administration. Silver Spring, MD: 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drugs-and-biologics-guidance

26. Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products US Food & Drug Administration. Silver Spring, MD: 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory

27. Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry US Food & Drug Administration. Silver Spring, MD: 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-registries-support-regulatory-decision-making-drug-and-biological-products

28. Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products US Food & Drug Administration. Silver Spring, MD: 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug

29. Data Standards for Drug and Biological Product Submissions Containing Real-World Data US Food & Drug Administration. Silver Spring, MD: 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-standards-drug-and-biological-product-submissions-containing-real-world-data

30. GRACE Principles: A validated checklist for evaluating the quality of observational cohort studies for decision-making support GRACE Initiative. https://www.graceprinciples.org/doc/GRACE-Checklist-v5.1.pdf

31. Dreyer NA, Bryant A, Velentgas P. The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness. J Manag Care Spec Pharm. 2016 Oct;22(10):1107-13. doi: 10.18553/jmcp.2016.22.10.1107. PMID: 27668559.

32. Pearson SD, Dreitlein WB, Towse A, et al. A framework to guide the optimal development and use of real-world evidence for drug coverage and formulary decisions. J Comp Eff Res. 2018 Dec;7(12):1145-52. doi: 10.2217/cer-2018-0059. PMID: 30427724.

33. Berger M, Daniel G, Frank K, et al. A Framework for Regulatory Use of Real-World Evidence Duke Margolis Center for Health Policy. 2017. https://healthpolicy.duke.edu/sites/default/files/2020-08/rwe_white_paper_2017.09.06.pdf

34. 21st Century Cures Act, Public Law 114–255. In: United States Congress, editor. Washington, DC: U.S. Government Publishing Office; 2016.

35. Meeting Minutes of the Center for Medicare and Medicaid Services Medicare Evidence Development and Coverage Advisory Committee U.S. Centers for Medicare and Medicaid Services. Baltimore, MD: 2012. https://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/Downloads/id65b.pdf

36. Drummond M, Federici C, Reckers-Droog V, et al. Coverage with evidence development for medical devices in Europe: Can practice meet theory? Health Econ. 2022 Feb 26doi: 10.1002/hec.4478. PMID: 35220644.

37. Specification for Cancer Drugs Fund data collection arrangements. National Institute for Health and Care Excellence. https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/data-collection-specification.pdf. Accessed on June 22, 2022.

38. The Innovative Medicines Fund Principles. National Health Service; 2022. https://www.england.nhs.uk/publication/the-innovative-medicines-fund-principles/. Accessed on June 22, 2022.

39. Reckers-Droog V, Federici C, Brouwer W, et al. Challenges with coverage with evidence development schemes for medical devices: A systematic review. Health Policy and Technology. 2020;9:146-56. doi: 10.1016/j.hlpt.2020.02.006.

40. Garrison LP, Jr., Neumann PJ, Erickson P, et al. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. Value Health. 2007 Sep-Oct;10(5):326-35. doi: 10.1111/j.1524-4733.2007.00186.x. PMID: 17888097.

41. Hampson G, Towse A, Dreitlein WB, et al. Real-world evidence for coverage decisions: opportunities and challenges. J Comp Eff Res. 2018 Dec;7(12):1133-43. doi: 10.2217/cer-2018-0066. PMID: 30411972.

42. Wenzl M, Chapman S. Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward OECD Publishing. Paris: 2019.