# Topic Refinement

## Analysis of Requirements for Coverage :ith Evidence Development (CED) – Topic Refinement

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department

# 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 (EPC). 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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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

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

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

Century Cures Act[34]

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. |
| [redacted] | 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. |
| | | [redacted] key elements of design, at a minimum, is publicly posted on the CMS website. |

| | 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. |

| | 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 I nitial L iterature Review | Revised Proposed Requirements Presented to Key Informants (KIs) (version 2a) | Changes and Rationale for Changes after KI Panel Input | Revised Proposed |
|---|---|---|---|---|---|

| Tag for Requirement | Existing Requirements |
| --- | --- |
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| Tag for Requirement | Existing Requirements (version 2014) | Changes and Rationale for Changes after I nitial L iterature 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 P osted for Public Comment ) (version 3a) | Changes and Rationale for Changes after Public Comment | Final Proposed Requirements after Public Comments (version 3b) |
|---|---|---|---|---|---|---|---|
| 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 | | | |

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Requirement

| Tag for Requirement | Existing Requirements (version 2014) | Changes and Rationale for Changes after I nitial L iterature Review | [redacted] |
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| Tag for Requirement | Existing Requirements (version 2014) | Changes and Rationale for Changes af ter I nitial L iterature Review | Revised Proposed Requirements Presented to Key Informants (KIs) (version 2a) | Changes and Rationale for Changes af ter KI Panel Input | Revised Proposed Requirements after KI Panel Input (This Version was P |
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## 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. | | |

| Requirement Version 2a For Key Informants | Mean Rating of Importance * | Number of Zeros |
|---|---|---|
| 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. | 1.5 | 2 |
| P. When relevant, investigators follow best practices for establishing and maintaining a registry. | | |

prior evidence from studies of related interventions or earlier studies of the given intervention.

| Requirement V ersion 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 | |

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

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

| Requirement V ersion 3b After Public C omments |
|---|
| 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 iBMC 1 g ieso |

| Requirement V ersion 3b After Public C omments |
| --- |
| 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. |

## 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

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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 evi Td (as)-1emee BT /P <<-4 (e.001 Tc 0.001 Tw [(ex)-1 (t (et)-3.1 (hodo0.001 Tc 0.e c)-1.1

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.70.5 706.2 471 a1 ( 1 (e f)- >>BDC  0 g / 47151 ( 18.615 0

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# Appendix 1

PubMed search strategy

| Search numbers | Search terms |
| --- | --- |
| Targeted Search [#1- #6] | |

# Appendix 2 : CED Compiled Public Comment Themes

Located in associated Excel files.

# Appendix 3: Data Abstraction

Located in associated Excel files.

# Appendix 4: Ratings of Importance of Proposed Requirements

Table 1. Amended Requirements- Frequency of assigned value of importance by the key informants [9 Key Informants]

Figure 1. Amended Requirements - Frequency of assigned value of importance by the key informants [9 Key Informants]