Co-Creating Guidance and a Checklist for Rare Disease Value Research Through Meaningful Patient and Caregiver Engagement

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OBJECTIVE

Rare diseases present distinct challenges for comparative effectiveness research (CER) and health technology assessment (HTA), particularly in integrating patient-centered outcomes.
This study aimed to develop a Patient-Centered Value Research Guidance and Checklist for Rare Diseases, to systematically embed meaningful patient and caregiver engagement throughout the research process.

METHODS

In 2024, a Steering Committee of 15 members was formed to identify gaps in CER, HTA, and related methodologies that may create barriers to evaluating emerging rare disease therapies (**Figure 1**). To inform the development of the checklist, we conducted eight stakeholder discussions with 46 participants, including patients, caregivers, payers, manufacturers, employers, regulators, and researchers. A targeted and gray literature review was also conducted to help identify gaps, leading to a set of key recommendations for patient engagement in rare disease CER and HTA.

In 2025, we built upon these findings by developing a systematic guidance and checklist to ensure meaningful patient engagement in rare disease value research. A 19-member, multi-stakeholder Advisory Board and a smaller working group were convened. Several approaches were used to develop and refine the guidance and checklist, including six advisory board meetings, five working group meetings, post-meeting surveys, and a public comment period.

To validate and improve its applicability, case studies on three different rare diseases were conducted, including sickle cell disease, leukodystrophies, and generalized myasthenia gravis, allowing iterative refinements to enhance the checklist's relevance and impact. Each session included a structured walkthrough of the checklist, with targeted feedback on usability, relevance, and inclusivity .The goal was to develop a core guidance and checklist that can be applied across most rare diseases, assessing its applicability in diverse contexts by selecting diseases that differ from one another in diverse aspects.

RESULTS

To support researchers in integrating patient engagement across rare disease value research, we developed a Guidance and Checklist covering the following phases: **1) Initiation & Planning, 2) Execution, 3) Monitoring, and 4) Dissemination & Assessment** (**Figure 2**). Within each phase, **key considerations** are outlined with **corresponding questions** designed to guide reflection and assessment of patient engagement practices. The checklist includes both **CER and HTA** components, reflecting their interconnected nature. Questions are formatted using Likert-type **rating scales** to support structured assessment.

To ensure broad applicability across rare diseases, the checklist offers **high-level yet actionable guidance**, accompanied by brief explanations, relevant examples, and links to supporting tools and resources where available.

Key insights from engagement activities, including stakeholder discussions, Advisory Board meetings, public comment period, and case studies are summarized in **Table 1**, informing iterative refinements to the checklist and reinforcing its relevance, usability, and inclusivity.

Figure 1. Study Approach

Stakeholder Discussions + Literature Review
1. Steering Committee of 15 members was formed
2. Three roundtable discussions
3. Targeted and gray literature review
→ Result: Report with key recommendations for patient engagement in CER and HTA

Framework and Checklist Development
1. Six Advisory Board meetings held to convert recommendations into actionable checklist
2. Survey after each meeting to gather feedback
3. Public Comment Period to gather feedback

Case Studies for Validation
1.Advisory Board and Working Group guided development of case studies
2.Case studies on 3 different rare diseases conducted (sickle cell disease, leukodystrophies, generalized myasthenia gravis)
3.Guidance and Checklist refined via multiple rounds of review

Figure 2. Overview of the Checklist

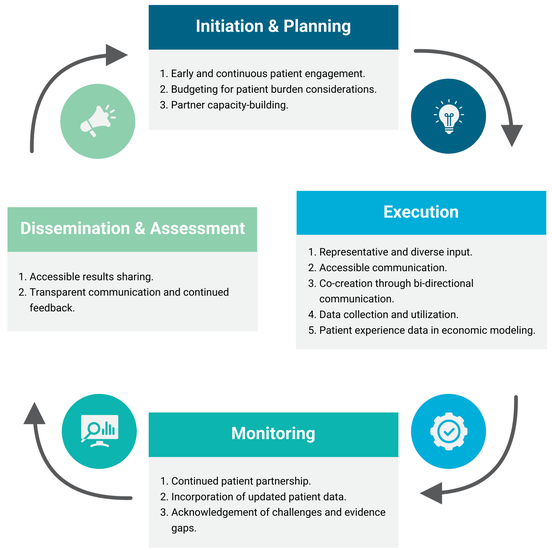

Table 1. Key Feedback from Stakeholder Engagements for Checklist Development

Section	Key Feedback
1. Initiation & Planning	- Incorporate recruitment strategies tailored to rare diseases - Ensure attention to literacy, language, and cultural sensitivity - Provide training for both researchers and patients - Add guidance on transparency, selection bias, frequency/mode of engagement and avoiding added patient burden
2. Execution	- Include recognition of hidden patient costs and time burden - Account for implications of rare disease biomarkers (e.g., link to disease progression, CER research) - Emphasize true co-creation as equal partnership - Plan proactively for managing missing data, knowledge gaps
3. Monitoring	- Provide guidance for addressing data gaps, e.g., economic burden data - Incorporate scenario analyses as ongoing monitoring practice - Encourage continued monitoring of patient/stakeholder feedback
4. Dissemination and Assessment	- Be transparent with evidence gaps to inform future research - Use plain language and multiple accessible formats for patients - Ensure research transparency, credit patient partners, and protect data privacy
Overall Feedback and Future Considerations	- Frame as "guidance" or "good practices" since it's not just a "check-the-box" exercise - Standardize response scales with clear instructions - Adapt for different research types and patient populations - Disseminate broadly through conferences, journals, and advocacy groups - Continue refining for clarity, inclusivity, and equity

CONCLUSION

The development of the Patient-Centered Value Research Guidance and Checklist for Rare Diseases was significantly strengthened through engagement with the rare disease community and input from diverse stakeholders. Findings underscore the need for flexible, accessible, and context-sensitive tools that reflect real-world experiences to support meaningful patient and caregiver engagement across all stages of value research, including CER and HTA. Next steps include broader dissemination and real-world testing of the checklist in future research and value assessment settings.

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