RARE DISEASE PATIENT ENGAGEMENT GUIDANCE AND CHECKLIST FOR VALUE RESEARCH

February 2026

PATIENT-CENTRICITY.
TRANSPARENCY.
EQUITY.

Center for Innovation & Value Research
107 S West Street, Suite 731
Alexandria, Virginia 22314

W : www.valueresearch.org

E : info@valueresearch.org

Funding for this project was provided by a Eugene Washington PCORI® Engagement Award (#EASCS-39046) and by Alexion, AstraZeneca Rare Disease.

Center for Innovation & Value Research

TABLE OF CONTENTS

INTRODUCTION

This document provides structured guidance and a checklist to support patient-centered value research in the context of rare diseases. The purpose is to ensure comprehensive integration of patient engagement throughout **Comparative Clinical Effectiveness Research (CER)** and **Health Technology Assessment (HTA)**, standardizing engagement processes while highlighting outcomes that matter most to patients. This resource is primarily designed for **value researchers**, the individuals who will be using the checklist to guide their rare disease research process.

OUR MISSION.

The **Center for Innovation & Value Research (Center)** is an independent non-profit research organization working to make sure all patients have access to the right care at the right time. Our mission is to advance the science, practice, and use of patient-centered HTA to support decisions that make healthcare more meaningful and equitable. [1]

ABOUT THE CHECKLIST

The checklist focuses on integrating patient engagement and **patient-centered** outcomes into CER and HTA for rare diseases. It is designed to help users systematically address key elements and best practices for patient engagement, including in study design, data selection, analysis, and stakeholder engagement, both when initiating planning and throughout the research process.[1] HTA-specific items in the checklist table are highlighted in **orange**.

HOW TO USE THE CHECKLIST

» STEP 1 «

SCAN THE CHECKLIST TABLE

Identify gaps quickly. Keep the guidance document accessible to support your review with relevant explanations and examples.

» STEP 2 «

WORK PHASE BY PHASE

Review Initiation & Planning, Execution, Monitoring, and Dissemination & Assessment. For each item, assign an owner and a date.

» STEP 3 «

TAILOR TO CONTEXT

Mark items as required, adapted, or not applicable for your study type. Note differences for **patient-reported outcomes (PRO)** development, clinical trials, or real-world evidence work.

» STEP 4 «

RECORD ACTIONS

For each item, document what you will do, what you did, and any changes made in response to partner input.

1 HTA includes and builds upon comparative clinical effectiveness research (CER) by incorporating additional dimensions such as cost-effectiveness, budget impact, and societal considerations. However, without robust CER, HTA would lack the necessary clinical evidence to make comprehensive value assessments. Therefore, this checklist addresses both CER and HTA as interconnected and complementary approaches to evaluating treatments and interventions.

RARE DISEASE PATIENT ENGAGEMENT CHECKLIST TABLE

INITIATION & PLANNING

Sub-Section	Objective	Checklist Question	Response Options	Notes
1. Early and Continuous Patient Engagement	Ensure patient and caregiver experiences are integrated from the start and sustained throughout the research lifecycle, shaping design, implementation, and decision-making.	Have patients, caregivers, and patient advocacy groups (PAGs) been engaged early and throughout the research process (e.g., from early research planning phase to dissemination & assessment phase)?	☐ Yes ☐ Partially ☐ No	
		Are key outcomes selected for the research shown to be relevant to patients and caregivers, reflecting lived experiences?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
2. Budgeting and Patient Burden Considerations	Ensure resources are allocated to support patient engagement, including fair compensation, expense coverage, and training, while keeping engagement credible, feasible, transparent, and minimizing unnecessary burden on patients and caregivers.	Is there a budget to support fair compensation, reimbursement of expenses, and stakeholder training, including training for patients and patient representatives?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Have transparency, frequency/mode of engagement, and strategies to reduce burden and bias been addressed?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
3. Partner Capacity-Building	Ensure patients, researchers, and others involved have the skills and knowledge for effective and meaningful engagement in the value research process.	Have you participated in training programs to support effective patient engagement?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Have you used training programs designed to help rare disease patients understand and engage in the value research process?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	

EXECUTION

Sub-Section	Objective	Checklist Question	Response Options	Notes
1. Representative Input and Diversity	Ensure diverse patient and caregiver representation to capture comprehensive experiences and needs.	Considering relevant target population demographics (socioeconomic status, race/ethnicity, sex/gender, culture, geography, age, disability), have a diverse group of patients been included?	☐ Not at All ☐ Somewhat[a] ☐ Moderately[b] ☐ Substantially[c] ☐ Reasonably Representative	
		Are caregivers or proxies engaged for patients who cannot themselves be engaged (e.g., too young, severely cognitively impaired, other health reasons)?	☐ Yes ☐ Partially ☐ No ☐ Not Applicable	
2. Accessible Communication	Ensure clear communication channels for all stakeholders, especially patients and caregivers from diverse backgrounds, so they are easily able to contribute to the value research process.	Are communication methods designed using plain language, translations, or accessible formats (font size, color contrast, numeracy support) to clearly communicate research purposes and potential outcomes to patients?	☐ Yes ☐ Partially ☐ No	
		Have communications been adapted for geographic, cultural, or accessibility barriers?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Have patients or patient representatives been engaged in designing communications, including content, methods, and dissemination plans (e.g., lay summaries and early sharing with communities)?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
3. Co-Creation through Bi-Directional Communication	Ensure co-creation and bi-directional communication between patients and researchers.	Is there a structured process for interactive collaboration between patients and researchers throughout the study?	☐ Yes ☐ No ☐ Planned	
		Have study materials and methods been co-created with patient partners wherever applicable?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	

[a] Representation on 1 dimension, but not others
[b] Representation on 2-3 dimensions, but not all
[c] Representation on >3 dimensions, but not all

EXECUTION (Continued)

Sub-Section	Objective	Checklist Question	Response Options	Notes
4. Data Collection and Utilization	Ensure transparency in data usage and ensure data used meaningfully benefits the rare disease patient community.	Are tailored approaches used to collect and apply patient experience data at different stages (pre-, during, post-treatment)?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Are patients and caregivers informed about how their data are used?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Are patient preferences or economic impacts (e.g., cost, access, and utilization) integrated into the research process?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Are longitudinal data incorporated to track outcomes over time wherever applicable?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Have you engaged patients, caregivers, or other experts to help identify appropriate data sources and ensure that the data were patient-focused and representative?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Are biomarker data considered, where relevant to disease progression and treatment response?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
5. Patient Experience Data **in Economic Modeling**	Ensure patient experience data are integrated and meaningfully inform the value assessment process.	When disease-specific outcomes are missing, have you explored using common outcomes across rare diseases, with disease-specific customization where needed?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Are robust methods (mixed methods, PROMs, DCEs) being utilized and appropriately incorporated into the HTA process?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Are patient preferences consistently integrated into the economic evaluation framework, ensuring alignment with what matters most to patients?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	

HTA-specific items in the checklist table are highlighted in orange.

MONITORING

Sub-Section	Objective	Checklist Question	Response Options	Notes
1. Continued Patient Partnership	Document meaningful patient partnership in value research and adherence to guidelines, ensuring it is monitored and adapted throughout.	Have you documented what you did or did not do (with a rationale) regarding patient engagement activities?	☐ Yes ☐ Partially ☐ No	
2. Incorporation of Updated Patient Data	Ensure that patient experience data is effectively integrated into value research and regularly updated as new data become available.	To what extent is evidence derived from patient experience data incorporated into value research?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Is there a plan to review and update findings as new patient experience data become available, or to conduct sensitivity analyses if updates are not feasible?	☐ Yes ☐ Partially ☐ No ☐ Not Applicable	
3. Acknowledgment of Challenges and Evidence Gaps	Acknowledge the unique challenges throughout rare disease value research and take specific actions to address these challenges.	Are the unique challenges of rare disease research clearly acknowledged in reports/ manuscripts/publications?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Have specific strategies been implemented to alleviate these challenges?	☐ Yes ☐ Partially ☐ No ☐ Not Applicable	
		Have regular check-in or updates of the monitoring items been planned/ made to support sustained engagement and adaptation as research progresses?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	

HTA-specific items in the checklist table are highlighted in orange.

DISSEMINATION & ASSESSMENT

Sub-Section	Objective	Checklist Question	Response Options	Notes
1. Accessible Results Sharing	Ensure that research results are shared back with patient and caregiver partners in meaningful, understandable, and culturally relevant ways, using multiple accessible formats (e.g., plain language, storytelling, videos, group discussions, or written summaries).	Have you documented what you did or did not do (with a rationale) regarding patient engagement activities?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Are patient and caregiver partners appropriately recognized and acknowledged as authors, in acknowledgments, as presenters, and through other methods?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Are dissemination outputs shared in a timely manner to ensure findings reach patients, caregivers, and stakeholders as early as feasible?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
2. Transparent Communication and Continued Feedback	Ensure clear, open, and timely communication of research goals, progress, findings, and the role of patient engagement to all stakeholders.	Are research goals, methods, and roles of patient engagement clearly communicated to all stakeholders at the start and through timely updates during and after the research process?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Are data gaps, data privacy, and conflict-of-interest disclosures included in communication and dissemination plans?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	
		Are patients and caregivers actively involved in dissemination activities and is feedback from them sought and integrated to improve relevance, clarity, and trustworthiness?	☐ Not at All ☐ Somewhat ☐ Moderately ☐ Substantially ☐ Fully	

CHECKLIST ITEMS IN DETAIL

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. The structure of the checklist aligns with the typical research process and is organized into four key phases: 1) Initiation & Planning, 2) Execution, 3) Monitoring, and 4) Dissemination & Assessment (see figure below). This section explains each of the phases in detail, along with examples.

1

Initiation & Planning

1. Early and Continuous Patient Engagement
2. Budgeting and Patient Burden Considerations
3. Partner Capacity-Building

2

Execution

1. Representative Input & Diversity
2. Accessible Communication
3. Co-Creation through Bi-Directional Communication
4. Data Collection & Utilization
5. Patient Experience Data in Economic Modeling

4

Dissemination & Assessment

1. Accessible Results Sharing
2. Transparent Communication and Continued Feedback

3

Monitoring

1. Continued Patient Partnership
2. Incorporation of Updated Patient Data
3. Acknowledgment of Challenges and Evidence Gaps

INITIATION & PLANNING

1. **Early and Continuous Patient Engagement:** Patient and caregiver experiences should be integrated from the very beginning of the research process and sustained throughout the entire lifecycle. Their input should actively shape study design, implementation, and decision-making.
2. **Budgeting and Patient Burden Considerations:** Resources must be allocated to support patient participation, including fair compensation, coverage of expenses, and access to training. Adequate budgeting signals the value placed on patient contributions and ensures equitable engagement, while also minimizing unnecessary burdens on patients and caregivers.
3. **Partner Capacity-Building:** All partners, including patients, researchers, and other stakeholders, should be equipped with the skills and knowledge needed for meaningful collaboration in rare disease value research.[2]

Example of Early and Continuous Patient Engagement

Before drafting the study protocol, the research team convenes a Patient Advisory Board made up of patients, caregivers, and advocates from the rare disease community.

1. They review draft inclusion/exclusion criteria to identify potential barriers (e.g., excluding patients who cannot travel long distances).
2. They recommend simplifying clinical visit schedules by combining multiple assessments into a single visit.
3. They highlight the importance of measuring "ability to attend school/work" as an outcome, which the researchers incorporate into the study.

Resources: PCORI Project Snapshot: Early & Ongoing Engagement [2]; PCORI Example 1. Learning to involve partners earlier in study planning [3]

Example of Budgeting and Patient Burden Considerations

In a rare disease clinical trial, the research team allocated funds to cover travel, lodging, and stipends for patient and caregiver advisory board members. Training sessions were provided to help participants understand study design, endpoints, and health economic modeling concepts. By budgeting for these resources up front, the team ensured that patient engagement was meaningful, accessible, and equitable.

Resource: The NHC's Patient Compensation Tools provides guidance on estimating costs and planning resources for patient involvement in research. [4]

2 Example Resources: Free training courses from CIHR and Kaiser Permanente Center for Health Research

EXECUTION

1. **Representative Input and Diversity:** Research teams should ensure that patient and caregiver voices are diverse and representative, reflecting the broad range of experiences and needs across rare disease communities.[3]
2. **Accessible Communication:** Communication channels must be clear, accessible, and inclusive so that all stakeholders, particularly patients and caregivers from varied backgrounds, can participate fully.
3. **Co-Creation through Bi-Directional Communication:** Engagement should be structured as a process of co-creation, with patients and researchers communicating openly and reciprocally to shape research together.
4. **Data Collection and Utilization:** Data practices should be transparent, ensuring that data collected are used responsibly and meaningfully to benefit the rare disease patient community.
5. **Patient Experience Data in Economic Modeling:** When feasible, patient experience data should be incorporated into economic modeling, ensuring that value assessments reflect outcomes that matter most to patients.

Example of Representative Input and Diversity

In a study of a rare neurological condition affecting fewer than 200 patients nationally, the research team collaborated with patient advocacy groups and international partners to broaden input. Within the recruitment criteria, participants were selected to reflect diverse age groups (children, young adults, older adults), disease stages (newly diagnosed vs. long-term), and caregiving roles (parents, spouses).

To avoid overburdening the same individuals, the team rotated participation in advisory meetings and supplemented engagement with short online surveys for patients who cannot commit to ongoing involvement.

Resources: PFDD Guidance 1 [5]; PFDD Hypothetical Case Examples [6]

Example of Accessible Communication

Study updates are shared through multiple formats (e.g., plain-language e-mails, short explainer videos, and translated summaries in Spanish and Mandarin) so all community members can follow the research regardless of language or literacy level.

Resource: The NHC Patient Engagement Best Practices provides tools, including a project coordinator guide, interview guide template, and health literacy toolkit, to support better communication. [7]

3 Due to the inherently small population size in rare diseases, achieving fully representative input can be challenging. Research teams should aim to capture as broad a range of patient experiences as possible while minimizing burden on participants. Where full representation is not feasible, efforts to include diverse perspectives through advisory boards, surveys, and collaboration with advocacy groups are recommended.

Example of Data Collection and Utilization

At the start of a Phase II clinical trial for a rare disease, patients are informed about how their data, including lab results and patient-reported outcomes, will be stored, analyzed, and shared. Throughout the trial, the research team provides regular updates showing how patient contributions have influenced protocol adjustments, endpoint selection, and upcoming publications, helping to build trust and demonstrate accountability.

Example of Patient Experience Data in Economic Modeling

Table 2 in Whittal et al. (2021) outlines key challenges and potential solutions when using patient-reported outcome measures for rare disease treatments, with implications for HTA. One example of a challenge is **mapping disease-specific patient-reported outcomes measures (PROMs) onto generic quality-of-life measures** to derive health state utility values, which is often difficult due to limited concordance between the two types of data. While mapping can be feasible in principle, the frequent lack of overlap means it may not be a viable solution for many rare diseases. In such cases, alternative approaches, such as referencing published literature or conducting *ad hoc* valuation studies should be considered. Further research is needed to develop methods that improve the reliability of mapping to make it more applicable in rare disease contexts, particularly for QALY-based HTA assessments. [8]

MONITORING

1. **Continued Patient Partnership:** Meaningful patient partnership should be documented and monitored throughout the research. Engagement should align with best-practice guidelines and adapt as projects evolve.
2. **Incorporation of Updated Patient Data:** Patient experience data should be effectively integrated into research and updated regularly as new information becomes available.
3. **Acknowledgment of Challenges and Evidence Gaps:** Researchers should explicitly recognize the unique challenges of rare disease research and take proactive steps to address them.

Example of Acknowledgment of Challenges and Evidence Gaps

In rare disease trial with very few eligible patients, the research team openly communicated recruitment and participation challenges. While it was not possible to include all patient subgroups, the team mitigated burden through **remote visits, flexible scheduling, and rotating advisory board participation**, and transparently noted limitations in engagement in the publications.

DISSEMINATION AND ASSESSMENT

1. **Accessible Results Sharing:** Research findings should be communicated in ways that are accessible, understandable, and culturally appropriate for patients, caregivers, and the broader community.
2. **Transparent Communication and Continued Feedback:** Results should be accompanied by clear and timely communication of research goals, progress, findings, and the role of patient engagement. Dissemination should be framed as part of an ongoing engagement process rather than a single event.

Example of Accessible Results Sharing

At the conclusion of all Center research projects, the team creates multiple formats for sharing results (e.g., a plain-language summary, infographic highlighting key outcomes, and presentations in patient-focused conferences). [9], [10], [11]

Example of Transparent Communication and Continued Feedback

Instead of only publishing results at the end of the study, the research team provides quarterly newsletters and mid-study webinars. Each update explains how patient feedback has shaped the study design, recruitment strategies, or data interpretation, emphasizing that engagement is an ongoing process rather than a one-time event.

REAL CASE EXAMPLES: RARE DISEASE PATIENT ENGAGEMENT

This section showcases real-world cases demonstrating how patient engagement has informed the evaluation process in rare diseases and directly shaped access decisions.

State Rare Disease Advisory Councils: Patients Informing Policy and Access

Rare disease advocates have championed the creation of Rare Disease Advisory Councils (RDACs) to give patients a formal voice in state health policy. By mid-2025, **32 states** have established an RDAC via legislation. These councils are comprised of patients, caregivers, clinicians, and other stakeholders. [12]

- **Patient Engagement:** RDACs advise state governments on issues affecting rare disease communities. They identify care gaps and propose solutions, often guiding policies on newborn screening expansions, Medicaid coverage criteria for costly rare therapies, drug affordability initiatives, emergency planning, and provider education. RDACs ensure that *lived experiences* and patient-preference data inform state-level decisions.
- **Outcome:** RDAC input has led to concrete changes, e.g., states adding new rare conditions to screening panels and revising insurance rules that had hindered access to specialist care. RDACs have made benefit designs and programs more attuned to rare disease needs, and the model is scaling nationwide. [13]

Copay Accumulator Bans: Advocacy Protects Out-of-Pocket Assistance

RD patients often rely on manufacturer/charity copay assistance to afford expensive medications. In recent years, however, insurers introduced “copay accumulator” programs that prevent these third-party payments from counting toward patients’ deductibles or out-of-pocket maximums. Therefore, a patient can exhaust copay aid and then face a second full deductible.

- **Patient Engagement:** Rare disease organizations mobilized a policy response, arguing that copay accumulators undermine access for those with high-cost conditions. Advocates shared personal stories with legislators about the financial peril caused by accumulators and formed coalitions (e.g., All Copays Count) to push for patient-friendly insurance laws.
- **Outcome:** Since 2019, over 20 U.S. states have enacted laws banning copay accumulator adjustments, ensuring any copay assistance counts toward a patient’s cost-sharing limits. Because of this advocacy-driven reform in benefit design, patients in those states are now protected from double-paying and can fully benefit from copay support. [14]

Cystic Fibrosis: Patient Input Drives Broad Access to Trikafta [15]

In 2020, an HTA review by ICER found the CFTR modulator *Trikafta* to dramatically improve health for most cystic fibrosis patients.

- **Patient Engagement:** Patients and caregivers shared personal stories during ICER's review, highlighting how CF *"robs them"* of normal life and how modulators transformed daily activities and future plans. This testimony underscored benefits beyond clinical metrics (e.g., ability to work, family life)
- **Outcome:** Final policy recommendations urged public and private payers to ensure all eligible CF patients can access Trikafta, removing coverage hurdles. Prior authorization criteria should be guided by clinical evidence *and input from patient groups* vs. cost alone. Patient engagement helped the HTA emphasize real-world quality-of-life gains and pushed payers toward broad coverage despite the therapy's high price tag. [16]

Spinal Muscular Atrophy: Newborn Screening Advocacy Enables Early Treatment

After SMA was added to the U.S. Recommended Newborn Screening Panel in 2018, the patient-led group Cure SMA launched nationwide advocacy for state implementation. They worked state-by-state to educate officials on the importance of early SMA detection and treatment.

- **Patient Engagement:** Families and advocates provided data, personal stories, and grants to jump-start screening programs. Grassroots campaigns urged policymakers to act quickly so babies born with SMA could be identified and treated before symptoms.
- **Outcome:** By mid-2022, all 50 states had adopted newborn screening for SMA. Because of persistent advocacy, infants with SMA are now diagnosed at birth and can receive life-saving therapies (like gene therapy *Zolgensma®* or *Spinraza®*) before irreversible damage occurs. Success demonstrated how patient engagement drove a policy change that expanded early access and improved outcomes in a RD. [17]

ALS: Patient Voices Accelerate Drug Approval

In 2022, an FDA advisory panel initially voted against approving Amylyx's ALS drug AMX0035 (*Relyvrio*) due to limited trial data. ALS patients and advocacy groups (e.g., ALS Association, I AM ALS) responded with a campaign for reconsideration.

- **Patient Engagement:** Dozens of patients, caregivers, and clinicians testified during the FDA's open hearing, sharing accounts of life with ALS and urging that AMX0035 be made available given the urgent unmet need. Public petitions and congressional pressure further amplified the community's voice.
- **Outcome:** The FDA took the unusual step of reconvening advisers, who *reversed* their stance (7-2 in favor) after hearing the patient testimony. The drug was approved in late 2022, making it only the third ALS therapy at the time. Early access to Relyvrio was achieved largely because patient advocacy made regulators reconsider their risk-benefit calculus. [18]

METHODS

The Center's rare disease project aims to address challenges in conducting comprehensive comparative clinical effectiveness research (CER) and health technology assessment (HTA) that incorporates the full spectrum of outcomes crucial to patients with rare diseases.

In 2023, the Center partnered with the EveryLife Foundation for Rare Diseases to convene patients, researchers, and other stakeholders to explore common patient-centered outcomes across rare diseases. The project focused on identifying evidence gaps and achieving consensus on approaches to address unique research challenges. This effort resulted in a report with prioritized recommendations for identifying patient-centered outcomes in rare disease research. [19]

In 2024, building on the 2023 findings, the Center established an advisory board of 19 stakeholders, including researchers, individuals with lived experience, and advocates dedicated to rare diseases. Guided by this board, the Center developed the patient-centered framework and checklist, ensuring meaningful patient engagement throughout the process. Stakeholder input informed both the selection of checklist items and the structure of the framework, ensuring relevance, feasibility, and alignment with patient-centered research principles.

In 2025, the Center collaborated with smaller working groups from the advisory board to conduct three case studies across different rare diseases to validate and enhance the checklist's applicability. These cases focused on sickle cell disease, leukodystrophies, and generalized Myasthenia Gravis. Each case study involved 1.5-hour focus group meetings with clinical researchers and researchers with modeling expertise, patients and caregivers, and representatives from patient advocacy groups. A public comment period also resulted in 10 comments from a diverse community, including patient representatives, pharmaceutical companies, other HTA organizations, and value researchers. This allowed for iterative refinements to enhance the checklist's relevance and impact. The overarching goal was to develop a core Guidance and Checklist that could be applied broadly across rare diseases while assessing its feasibility in diverse contexts by selecting diseases with distinct characteristics.

DISCUSSION

LIMITATIONS

While the Guidance and Checklist were developed through expert consensus and extensive engagement with the rare disease community, their applicability may vary depending on research objectives, specific disease characteristics, available data, and methodological constraints. Users are encouraged to tailor items as needed and document modifications transparently. Future updates may integrate new methodological insights, feedback from implementation, and perspectives from additional stakeholders.

CONCLUSIONS

The Rare Disease Patient Engagement (RDPE) Guidance and Checklist provides a structured framework to advance meaningful patient and caregiver participation in rare disease comparative effectiveness research (CER) and health technology assessment (HTA). The process of developing this resource underscored the importance of co-designing with stakeholders who possess diverse expertise and lived experience. This approach helps ensure that the guidance is practical, relevant, and broadly applicable across rare disease contexts.

The iterative, multi-stakeholder approach drawing on advisory board discussions, working group consultations, focus group meetings, public comments, and case studies helped identify core principles of patient-centered research that extend beyond individual disease contexts. Key themes emphasized the value of early and sustained engagement, transparent communication, and integration of patient experience across all stages of research. Together, these elements create a feedback loop that enhances trust, improves research quality, and increases the relevance of value assessments for patients and decision-makers.

Importantly, this work also demonstrated how structured engagement can help bridge evidence gaps in rare diseases, where small populations and limited data often constrain traditional methods. By including lived experiences and patient experience data, researchers can better interpret treatment effects and understand meaningful outcomes. These data also help inform models that capture a fuller spectrum of value, such as quality of life, caregiver burden, and long-term functional outcomes.

At the same time, the process revealed ongoing challenges in implementing patient engagement systematically. These include variability in capacity among stakeholders, limited funding and infrastructure to support engagement and longitudinal data collection, and uncertainty around how to integrate qualitative data into quantitative modeling frameworks. Addressing these barriers will require sustained collaboration among researchers, patient organizations, funders, and HTA bodies.

Future applications of the Rare Disease Patient Engagement Guidance and Checklist may include applying it to specific disease areas, development of educational programs, and refinement of indicators to measure impact and quality of engagement. Broader adoption could also support alignment with similar existing frameworks and regulatory agencies, promoting harmonization across the field of patient-centered value research.

ENDNOTES

1 "Advancing HTA - Center for Innovation & Value Research." Accessed: Oct. 09, 2025. [Online]. Available: https://valueresearch.org/what-we-do/advancing-hta/.

2 M. Maurer et al., "Understanding the Influence and Impact of Stakeholder Engagement in Patient-centered Outcomes Research: a Qualitative Study," J Gen Intern Med, vol. 37, pp. 6–13, Apr. 2022, doi: 10.1007/S11606-021-07104-W.

3 "Implementing the Expectation: Early & Ongoing Engagement | PCORI." Accessed: Oct. 09, 2025. [Online]. Available: https://www.pcori.org/engagement-research/engagement-resources/foundational-expectations/early-ongoing-engagement/implementing-expectation

4 "Access the NHC Patient Compensation Tools - National Health Council." Accessed: Oct. 09, 2025. [Online]. Available: https://nationalhealthcouncil.org/access-the-fmv-calculator/

5 "FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making | FDA." Accessed: Oct. 09, 2025. [Online]. Available: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

6 FDA and CDER, "Hypothetical Scenario - Qualitative Research Using a Single Focus Group". [Online]. Available: https://www.fda.gov/media/113666/download

7 "Patient Engagement - National Health Council." Accessed: Oct. 09, 2025. [Online]. Available: https://nationalhealthcouncil.org/issue/patient-engagement/

8 A. Whittal, M. Meregaglia, and E. Nicod, "The Use of Patient-Reported Outcome Measures in Rare Diseases and Implications for Health Technology Assessment," Patient, vol. 14, no. 5, p. 485, Sep. 2021, doi: 10.1007/S40271-020-00493-W.

9 "HTA Models - Center for Innovation & Value Research." Accessed: Oct. 09, 2025. [Online]. Available: https://valueresearch.org/what-we-do/hta-models/

10 "Economic Impacts - Center for Innovation & Value Research." Accessed: Oct. 09, 2025. [Online]. Available: https://valueresearch.org/what-we-do/defining-solutions/economic-impact/

11 "Rare Diseases - Center for Innovation & Value Research." Accessed: Oct. 09, 2025. [Online]. Available: https://valueresearch.org/what-we-do/defining-solutions/rare-diseases/

12 Rare Disease Advisory Council: Prader-Willi Syndrome Association | USA.

13 "MINNESOTA RARE DISEASE ADVISORY COUNCIL: ANNUAL REPORT 2024." Accessed: Nov. 18, 2025. [Online]. Available: https://mnraredisease.org/wp-content/uploads/2025/01/MNRDAC-Annual-Report-2024_FINAL_20241231b.pdf

14 "From plasma to copay accumulators, IDF achieves advocacy wins | Immune Deficiency Foundation." Accessed: Nov. 12, 2025. [Online]. Available: https://primaryimmune.org/resources/news-articles/plasma-copay-accumulators-idf-achieves-advocacy-wins

15 "ICER Releases Evidence Report on Treatments for Cystic Fibrosis - ICER." Accessed: Nov. 12, 2025. [Online]. Available: https://icer.org/news-insights/press-releases/cf_evidence_report_2020/

16 "ICER Issues Final Report and Policy Recommendations on Treatments for Cystic Fibrosis - ICER." Accessed: Nov. 12, 2025. [Online]. Available: https://icer.org/news-insights/press-releases

17 "Newborn Screening for SMA - Cure SMA." Accessed: Nov. 12, 2025. [Online]. Available: https://www.curesma.org/newborn-screening-for-sma/

18 "FDA advisers back Amylyx ALS drug, reversing earlier position | BioPharma Dive." Accessed: Nov. 12, 2025. [Online]. Available: https://www.biopharmadive.com/news/amylyx-als-fda-advisory-committee-second-vote/631354/

19 "Valuing Rare Disease Treatments in Healthcare: Real Experience, Real Impact," 2024. [Online]. https://everylifefoundation.org/wp-content/uploads/2024/02/2024-Rare-Disease-Project-Report-Final.pdf

20 Center for Innovation & Value Research, "A Blueprint for Patient-Centered Value Research". [Online]. Available: https://valueresearch.org/wp-content/uploads/2025/07/Blueprint-for-Patient-Centered-Value-Research_FINAL.pdf

21 "About PCORI | PCORI." Accessed: Oct. 19, 2025. [Online]. Available: https://www.pcori.org/about/about-pcori

22 "Health products policy and standards." Accessed: Oct. 19, 2025. [Online]. Available: https://www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-technology/medical-devices/assessment

23 "Patient-Focused Drug Development Glossary | FDA." Accessed: Nov. 19, 2025. [Online]. Available: https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary

24 "Discrete Choice Experiment (DCE) - York Health Economics Consortium." Accessed: Oct. 19, 2025. [Online]. Available: https://www.yhec.co.uk/glossary-term/discrete-choice-experiment-dce/

25 PCORI, "Engagement in Research: Foundational Expectations for Partnerships," 2025.

26 "Patient-Reported Outcome Measures Overview | The Measures Management System." Accessed: Oct. 19, 2025. [Online]. Available: https://mmshub.cms.gov/about-quality/types/proms/overview

ACKNOWLEDGMENTS

Authors (alphabetical):

- Becky Barnes, Patient Voices Matter
- Mousumi Bose, Montclair State University
- Richard Chapman, Center for Innovation & Value Research
- Shailesh Chavan, HepQuant
- Yuan-Yuan Michelle Cheng, Center for Innovation & Value Research
- Jose Delgado, ICHOM
- Vanessa Ferreira, Humanized Solutions
- Kavita Nair, University of Colorado
- Eleanor Perfetto, University of Maryland
- Dionne Stalling, Rare And Black

Special thanks to the following people and organizations for their input and collaboration:

- Kathryn Cowie, Nested Knowledge
- Geir Falck-Pedersen, Johns Hopkins University
- Victoria Gemme, National Organization for Rare Disorders
- Swapna Kakani, The Gutsy Perspective
- Annie Kennedy, EveryLife Foundation for Rare Diseases
- Joff Masukawa, Diligentia Strategy
- Charlene Son Rigby, Global Genes
- Paris Scott, American Red Cross
- Simu Thomas, Alexion, AstraZeneca Rare Diseases
- Marc Yale, International Pemphigus and Pemphigoid Foundation
- Dorota Zgodka, Experientia
- Alexion, AstraZeneca Rare Disease (Funding Sponsor)
- EveryLife Foundation for Rare Diseases (Partner Organization)
- Global Genes (Partner Organization)
- National Organization for Rare Disorders (NORD) (Partner Organization)
- Patient-Centered Outcomes Research Institute (PCORI) (Funding Sponsor)

APPENDIX A: DEFINITIONS

Value Research: Value research focuses on understanding the value of healthcare services, interventions, treatments, and policies. The "value" is determined by assessing outcomes relative to the costs involved. Value research is an umbrella term that may include one or more of the following components: comparative effectiveness research (CER), patient-centered outcomes research (PCOR), cost-effectiveness analysis (CEA), health technology assessment (HTA), or value assessment (VA). [20]

Comparative Clinical Effectiveness Research (CER): CER is a type of clinical research that compares two or more medical treatments, services, or health practices to help patients and others make better-informed decisions. [21]

Health Technology Assessment (HTA) or Value Assessment (VA): HTA refers to the systematic evaluation of properties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational, and ethical issues of a health intervention or health technology. The main purpose of conducting an assessment is to inform policy decision-making. [22] The Center uses the terms HTA and value assessment interchangeably.

Patient-Centered: Ensuring that patients' experiences, perspectives, needs, and priorities are meaningfully incorporated into decisions and activities related to their health and well-being (also referred to as patient-focused). [23]

Patient-Centered Value Research: Patient-centered value research is the meaningful and impactful partnership between patients and researchers in the design and conduct of value research, to ensure that every stage of the research process—from design to dissemination and implementation—is shaped by the experiences, needs, and preferences of those most impacted, aligning priorities and outcomes to generate meaningful and actionable insights. [20]

Patient-Centered HTA: This approach focuses on making sure that the needs and experiences of patients are at the center of the decision-making process. It ensures that new treatments or technologies help improve quality of life and health outcomes for patients. [20]

Discrete Choice Experiment (DCE): A quantitative method used in healthcare to elicit preferences from participants (patients, payers, commissioners) without directly asking them to state their preferred options. In a DCE, participants are typically presented with a series of alternative hypothetical scenarios containing a number of variables or "attributes" (usually ≤5), each of which may have a number of variations or "levels." Participants are asked to state their preferred choice between 2 or 3 competing scenarios, each of which consists of a combination of these attributes/levels. Typically, survey instruments include 5 to 10 such choices to be completed. Preferences are revealed without participants explicitly being asked to state their preferred level for each individual attribute. [24]

Patient Experience Data: Patient experience data can be interpreted as information that captures patients' experiences, perspectives, needs, and priorities related to (but not limited to): 1) the symptoms of their condition and its natural history; 2) the impact of the conditions on their functioning and quality of life; 3) their experience with treatments; 4) input on which outcomes are important to them; 5) patient preferences for outcomes and treatments; and 6) the relative importance of any issue as defined by patients. [23]

Patient Partners: People with lived experience, such as patients, family members, caregivers, community members, and organizations that represent a population of interest. They are engaged in planning, conducting, and disseminating the research. Patient partners should not be confused with study participants. [25]

Patient-Reported Outcome (PRO): Any report of the status of a patient's health condition or health behavior coming directly from the patient, without interpretation of the patient's response by a clinician or anyone else. [26]

APPENDIX B: SUPPLEMENTARY RESOURCES

Additional patient engagement frameworks, guidance, and tools for improving patient-centered value research.

1. Blueprint for Patient-Centered Value Research
2. NHC Patient Engagement Best Practices
3. NHC Patient-Centered Core Impact Set (PC-CIS)
4. NHC Fair-Market Value (FMV) Calculator
5. NHC Rubric for Patient Engagement
6. NHC Value Assessment Get-Ready Checklist
7. PCORI Partnerships in Research
8. FDA Patient Engagement Playbook
9. NORD IAMRARE® Program
10. EURORDIS Survey Design Toolkit
11. PFMD Patient Engagement Management Suite
12. NIH Patient Engagement Framework
13. CIHR Patient Engagement Framework
14. EveryLife Foundation: Guide to Patient Involvement in Rare Disease Therapy Development
15. PARADIGM Patient Engagement Toolbox
16. PARADIGM Framework with Metrics
17. Aspire4Rare Framework for Rare Disease Policy
18. Jonker et al. (2023): How to START? Four Pillars to Optimally Begin Orphan Drug Development
19. Klein et al. (2024): Measuring and Demonstrating the Value of Patient Engagement Across the Medicines Lifecycle
20. RARE-X Data Collection Program
21. Early and Often: Reimagining Patient Community Engagement to Improve Clinical Trials Feasibility
22. Puebla et al. (2025): A Comparative Analysis of Patient Participation in Health Technology Assessment Systems Worldwide: Trends and Practices
23. Awada N. et al. (2025): From Care to Cure: A Patient Engagement Framework for Rare Disease and Orphan Drug Research

The Center for Innovation & Value Research is a 501(c)(3) tax-exempt, non-profit research organization dedicated to advancing the science and improving the practice of health technology assessment through development of novel methods and the creation and application of enhanced health technology assessment models to support local decision-making needs in healthcare.

www.valueresearch.org