IVI INNOVATION AND VALUE INITIATIVE

EVERYLIFE FOUNDATION FOR RARE DISEASES

Valuing Rare Disease Treatments in Healthcare: Real Experience, Real Impact

This effort is partially supported by a Eugene Washington PCORI® Engagement Award (#EASCS-26726). This project is also supported by contributions from Alexion, AstraZeneca Rare Disease.

2024

ACKNOWLEDGMENTS

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IVI is also grateful to the many stakeholders who have shared their insight and experience through the roundtables. Their insights and recommendations led to rich discussions, new partners, and deeper understanding of what we should consider when we incorporate patient-centered outcomes into comparative effectiveness research in rare diseases. A special thank you to EveryLife Foundation partner, Annie Kennedy. Finally, thank you to the IVI team for their significant contributions to this work.

This project is funded through a Patient-Centered Outcomes Research Institute® (PCORI®) Eugene Washington Engagement Award (EASCS-26726) and support from Alexion, AstraZeneca Rare Disease.

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EXECUTIVE SUMMARY

Rare diseases collectively impact over 30 million people in the United States and impose a significant economic burden of $997 billion per year. However, due to the limited number of patients affected by any individual rare disease, conventional research methods face challenges in effectively studying them. Therefore, novel approaches to measuring outcomes and conducting research are needed. Lack of consensus on assessing the value and effectiveness of treatments for rare diseases hinders the establishment of an evidence base to inform healthcare decisions and limits patient access to innovative therapies.

The Innovation and Value Initiative (IVI) and the EveryLife Foundation for Rare Diseases are collaborated on a project titled, "Valuing Rare Disease Treatments in Healthcare: Real Experience, Real Impact." This project aimed to explore common patient-centered outcomes across rare diseases, identify evidence gaps, and achieve a consensus on addressing unique research challenges. The project team convened experts in patient-centered research and those with lived experience to examine the issues and build consensus on patient-centered outcomes.

The project was overseen by a diverse steering committee of 15 members, including patients/caregivers, clinicians, payers, industry experts, and other stakeholders. Three roundtable discussions were conducted, with participation from 46 attendees. These discussions aimed to achieve several key objectives, such as identifying expected outcomes significant to rare disease patients and caregivers, promoting communication between payer and patient stakeholders, and reaching a consensus on recommendations for enhancing patient-centered outcomes research. A literature review was also conducted through published literature and rare disease organization websites to obtain informative insights for this research.

From these engagements, key themes emerged on what matters most to patients, caregivers, and other stakeholders in developing approaches to comparative effectiveness research and value assessment, particularly in the context of understanding outcomes important to rare disease patients. **Key themes include: patient journey and time, caregiver journey, early and continuing engagement and communication, data and methods, economic impacts, scientific spillover, and identifying common patient-centered outcomes for economic modeling.**

In addition to discussing key themes and recommendations, the team examined patient-centered outcomes through a combination of literature reviews and consultations with patients and their families. As part of this analysis, the project team compared outcomes used in research on 11 different rare diseases. Certain outcomes such as physical functioning (motor, respiratory, and speech), fatigue, social relationships, pain, mental deterioration, mental health, employment/work, economic impacts, and sleep were common across more than half of these rare diseases. Additionally, outcomes based on the specific type of rare disease were explored, providing valuable insights into the diverse needs and priorities of patients and their families.

The IVI-EveryLife Foundation project has made progress in understanding the challenges of patient-centered outcomes research for rare diseases. **The findings will inform the development of more effective research approaches to patient engagement, leading to more informed selection of outcomes that are important for patients and their families.**

SEVEN KEY PROJECT THEMES

Patient Journey and Time

The patient journey and time, which include the disease's natural history and its evolving impact on patients, is important to consider when identifying and prioritizing outcomes important to rare disease patients.

Caregiver Journey

Throughout a patient's health journey, caregivers provide vital support, assistance, and advocacy for their loved ones. It is essential to understand the health and other impacts on caregivers.

Early and Continuing Engagement and Communication

Initiating and continuing patient/caregiver engagement with other stakeholders is critically essential to conducting fully patient-centered research and helpful for decision-making.

Data and Methods

Comprehensive, representative data plays an important role in value assessment and patient-centered outcomes research, especially when dealing with rare diseases. Collaboration should be encouraged to enhance data collection, and mixed (qualitative and quantitative) methods should also be promoted to incorporate lived experiences as meaningful input.

Economic Impacts

Understanding the economic impacts on patients and caregivers can help payers and other decision-makers to better design plans and strategies to ultimately improve patients' experiences and outcomes.

Scientific Spillover

Innovative treatments developed for one rare disease may be re-purposed or modified to treat additional rare diseases. Given the limited resources and data available for the study of rare disease treatments, the value of it could be especially beneficial.

Identifying Common Patient-Centered Outcomes for Economic Modeling

Identifying common patient-centered outcomes across rare diseases can help accelerate cross-cutting research, enhance our understanding of diseases themselves, patient perspectives, and potentially improve comparative effectiveness research methods.

BACKGROUND AND RATIONALE

Rare diseases represent a broad spectrum of illness. While each rare disease affects a relatively small patient population (defined as fewer than 200,000 individuals in the U.S.[1]), in aggregate, more than 30 million Americans live with rare diseases and disorders.[1] One study has estimated the total economic burden of rare diseases in the U.S. as $997 billion in 2019.[2]

Due to the small number of individuals affected by any specific rare disease, researchers often face challenges in meeting conventional standards for comparative effectiveness research (CER) and other scientific studies. The ability to identify, diagnose, and develop new therapies for rare diseases has been growing, necessitating new approaches to outcomes measurement, comparative effectiveness research, and patient-centered outcomes research (PCOR).

As the number of therapies being developed for rare diseases continues to grow, decision-makers within the U.S. healthcare system face the challenge of determining the comprehensive set of outcomes to consider when evaluating treatment options. Unfortunately, there is a lack of consensus in this field regarding how to assess comparative effectiveness and value for rare disease treatments.[3] This lack of agreement poses a significant barrier to building an evidence base on the effectiveness and value of emerging therapies, ultimately hindering patient access.

While many of these issues are relevant not only to rare diseases, but also to more common conditions, the complexity of developing therapeutics for rare diseases, and the often insufficient information available for decision-making at the time of approval, highlight the need to identify patient-centered outcomes early in the treatment development process.

Currently, the approach to evaluating rare disease treatments primarily focuses on one disease at a time due to the absence of consensus on common clinical and patient-reported outcomes across diseases. However, with an estimated 10,000+ rare diseases and disorders, this disease-centric approach is insufficient to keep pace with the increasing number of therapies being developed. Wagner et al. noted, **"One of the issues in rare diseases pertaining to these criteria is uncertainty or lack of consensus on the outcomes that need to be assessed in clinical studies."**[4]

METHODS

Beginning in 2023, the Innovation and Value Initiative (IVI) and the EveryLife Foundation for Rare Diseases (EveryLife Foundation) partnered to conduct a project, "Engaging Patients with Rare Disease in Identifying Meaningful Approaches to Comparative Effectiveness Research and Value Assessment," funded in part through a Patient Centered Outcomes Research Institute® (PCORI®) Eugene Washington Engagement Award (EASCS-26726) and a grant from Alexion Pharmaceuticals. The objectives of this project were to: **1) explore commonalities of attributes and patient-centered outcomes across rare diseases, 2) identify current emerging evidence gaps, and 3) develop consensus on opportunities for addressing challenges unique to research in rare diseases.**

The project involved six steering committee meetings and a series of roundtable discussions to identify challenges and opportunities in rare disease patient-centered outcomes research and comparative effectiveness research (see Table 1).

Table 1. Project Convenings

	Steering Committee	First Roundtable	Second Roundtable	Third Roundtable
Date	6 Meetings / Year	May 31, 2023	June 21, 2023	September 26, 2023
Purpose	Provide ongoing expertise, guidance, and insight	Identify key challenges in rare disease research and explore patient-centered outcomes	Facilitate patient-payer discussion to address existing evidence gaps and explore strategies to adopt cross-cutting outcomes for rare diseases	Prioritize and build consensus on key recommendations and identify steps needed for further outcomes research
Participants	17 Members	23 Participants	28 Participants	29 Participants
Stakeholder Perspectives	7 Patient/Caregiver 2 Payer 2 Researcher 3 Industry 1 Regulatory 1 Employer 1 Clinician	9 Patient/Caregiver 1 Payer 5 Researcher 7 Industry 1 Regulatory	12 Patient/Caregiver 5 Payer 4 Researcher 5 Industry 2 Regulatory	13 Patient/Caregiver 5 Payer 3 Researcher 7 Industry 1 Regulatory

Multi-Stakeholder Engagement

Steering Committee

A collaborative steering committee comprised of 17 stakeholders was formed to lead the initiative (see Table 1). This diverse steering committee met six times throughout 2023 to actively guide the project team in various aspects, including advising on the targeted literature review search strategy, refining key project objectives, identifying roundtable participants, and shaping and contributing to roundtable discussions.

First Roundtable

The first roundtable discussion was held on May 31, 2023 and focused primarily on exploring common outcomes important to patients and caregivers living with rare disease, and potential considerations when partnering with this important constituency. Twenty-three individuals representing a diverse range of stakeholder perspectives[i] (see Table 1) participated in a dynamic two-hour virtual discussion on rare diseases, where participants brought their expertise and experience in various conditions such as amyotrophic lateral sclerosis, sickle cell disease, ring chromosome 14 syndrome, rare epilepsy, and pediatric rare diseases.

To ensure efficiency and increased participation during the discussion, participants were divided into two separate breakout rooms, each focusing on different topics. Prior to the breakout sessions, a survey was conducted to gauge interest in attending the various topic discussion groups. Any remaining individuals were added to the groups to ensure stakeholder balance. Within the breakout sessions, participants engaged in discussions and shared their thoughts in response to specific questions. Additionally, to ensure participants were well-informed, supporting documents and reading materials were provided in advance.

The discussion sessions were divided into four main questions:

- What is important to know about engaging patients and caregivers to identify outcomes and impacts that matter to them?
- Among these identified patient-important outcomes, can we observe commonalities across different rare diseases or disorders?
- What outcomes and impacts should we be measuring in patient-centered outcomes research and comparative effectiveness research? Where can we identify common outcomes and impacts across rare conditions?
- What are best practices for stakeholder engagement to find and prioritize common patient-centered outcomes within diverse rare disease patient and family communities?

Second Roundtable

Held on June 21, 2023, the second roundtable discussion focused on payer perspectives regarding decision-making for rare diseases. The key objective of this convening was to facilitate constructive dialogue between payers, purchasers, and various stakeholders to address existing evidence gaps and explore strategies to promote the adoption and effective utilization of shared outcomes, if they are developed.

This dynamic two-hour virtual discussion included 28 individuals representing a diverse range of stakeholder perspectives (see Table 1). The roundtable consisted of two sections: a payer presentation, followed by a discussion session. The initial presentation aimed to provide insights into the challenges of rare diseases from payer perspectives. The focus of the subsequent discussion was on the challenges associated with assessing and making informed decisions about therapies for rare diseases. There were three separate discussion sessions, each lasting 20 minutes and focusing on a specific topic. The topics included the evidence required for comparative effectiveness, evidence for accelerated approval, and the adoption of cross-cutting outcomes for rare diseases. Participants actively engaged in these discussions and shared their thoughts in response to specific questions. The discussion sessions each focused on one of three topics:

- Exploring the necessity for evidence on comparative effectiveness of therapies for rare diseases,
- Exploring the types of evidence that can guide decision-making for drugs approved through the accelerated approval pathway, and

i The perspectives of the participants may not be mutually exclusive. However, for the purpose of interpretation, we have listed here one perspective per participant.

- Examining the requirements for promoting adoption and utilization of cross-cutting rare disease outcomes in decision-making processes.

Third Roundtable

The third roundtable, held on September 26, 2023, aimed to facilitate a final stakeholder discussion on key themes and recommendations emerging from project activities and convenings. The primary objective was to prioritize and build consensus on the incorporation of patient-centered concepts into value assessment for rare diseases.

There were 29 diverse stakeholders who participated in this final discussion (see Table 1). To ensure an effective engagement, we divided the discussion into two 45-minute sessions. The first session, "Integrating Patient-Centered Outcomes Data into Research and Value Assessment: Patient Engagement and Data Collection," addressed the following questions:

1. How should we prioritize recommendations (see Appendix Table 4) for patient (and caregiver) engagement and data collection?
2. What are best practices (i.e., when and how) for measuring these outcomes and preferences to ensure we can integrate them into comparative effectiveness research and value assessment?

The second discussion session, "Enhancing the Identification of Patient-Centered Outcomes," addressed three questions:

1. Based on the list of outcomes we collected from the literature, what outcomes (or types of outcomes) are missing?
2. What actions have been made, are currently in progress, or need to be made to ensure consistency in the outcomes being collected?
3. How can we help ensure these collected outcomes are used in decision-making and to inform further research?

Targeted Literature Review

In addition to multi-stakeholder engagement, we also conducted a targeted literature review on PubMed for English-language articles that focused on terms related to rare disease, health technology assessment, economic evaluation, and patient engagement. The goal of this review was to gain insight into the current state of research in this area. Articles were categorized into "rare disease in general" or "specific rare disease(s)" based on abstract screening. The search terms were refined by the steering committee and revised multiple times to ensure comprehensive coverage. The list of comprehensive search terms are provided in Appendix Table 1.

One of the challenges faced during this process was the concern that the general search method might overlook some relevant articles that could be identified through specific rare disease searches. To address this concern, we performed additional literature searches focusing on several specific rare diseases to cross-check the results (see Appendix Table 2). The 11 specific rare diseases were recommended by the steering committee and included Duchenne muscular dystrophy, spinal muscular atrophy, myasthenia gravis, amyotrophic lateral sclerosis, sickle cell disease, amyloidosis, cystic fibrosis, beta thalassemia, hemophilia, Sanfilippo syndrome, and Huntington's disease. The findings revealed that there were additional articles retrieved using specific rare disease search terms. Therefore, we included these additional articles into the outcomes search as well, and then eventually reviewed 92 outcomes related articles.

In addition to the literature review on PubMed, we also conducted a review of gray literature. We examined 30 rare disease advocacy organizations and collected outcomes mentioned on their websites. The list of these websites is provided in Appendix Table 4. The results related to patient-centered outcomes can be found in the Literature Review Results section.

KEY THEMES

Related to Comparative Effectiveness Research and Value Assessment for Rare Diseases


Patient Journey and Time


Caregiver Journey


Early and Continuing Patient and Caregiver Engagement


Data and Methods


Economic Impacts


Scientific Spillover

Identifying Common Patient-Centered Outcomes for Economic Modeling

Through the methods described in the previous section, several key concepts emerged, including the need for early engagement to incorporate the entire patient journey, data collection challenges, and the necessity of developing common patient-centered outcomes. These themes were explored in dialogue with stakeholders to better understand what patients[ii] and payers prioritize when conducting patient-centered comparative effectiveness research and value assessment, especially concerning outcomes significant to rare disease patients. The key themes are identified in detail below.

Patient Journey and Time

Patient participants emphasized that understanding the patient journey is crucial for identifying outcomes and impacts that matter to patients but may vary over time. They suggested that a comprehensive health journey map across the various stages of a patient's experience, from initial symptoms to diagnosis to treatment, recovery, and long-term management, can offer valuable insights into what outcomes are significant to patients and capture how needs and priorities change over time.

Understanding the patient journey requires exploring the natural history of diseases. While understanding natural history may provide crucial insights into disease progression and development, such information may be lacking due to multiple limitations in rare diseases. By studying how disease impacts change over time and the effects they have on patients' lives, we can better understand the outcomes that are most important to patients.

ii Throughout this document, we use the term "patient" or "patient advocate" to refer to a person who has had a significant encounter with the healthcare system and has lived expertise in the healthcare system. We do not suggest that a person is their disease or that is a person's only area of experience or expertise. We use this term in recognition of their lived experience and the importance of this experience to improving the healthcare system.

Case Example of Incorporating Patient Journey into Research

The National Health Council (NHC) has developed a Patient-Centered Core Impact Sets (PC-CIS) framework which provides essential guidance on integrating the concept of patient-centeredness into research. At the same time, organizations, including the National Health Council and National Organization for Rare Disorders (NORD), have developed patient journey maps to gain deeper insights into the patient experience, including the diagnostic odyssey. These valuable tools have been increasingly put into practice by various research groups and disease organizations to better understand the complexities of patients' journeys and ensure the patient is centered throughout their work.[5]

An example of an organization that applies existing patient-centered frameworks and guidance throughout their research is Sick Cells, a non-profit organization representing individuals and caregivers with lived experience. Sick Cells convened patients (sickle cell warriors), caregivers, clinicians, and other stakeholders to define outcomes that matter to sickle cell patients but are not typically measured in clinical research. The project utilized the NHC Patient-Centered Core Impact Sets (PC-CIS) to facilitate prioritization of patient outcomes. Additionally, Sick Cells partnered with the University of Southern California Hematology Utilization Group Studies (USC HUGS) and the Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute at the University of Washington School of Pharmacy to explore the feasibility of integrating these core outcomes into sickle cell disease research measures. The process involved ranking and weighting to understand the relative importance of these outcomes to patients and other stakeholders.

Caregiver Journey

Patients from the rare disease community place significant emphasis on recognizing the indispensable role of caregivers. Throughout a patient's health journey, caregivers provide vital support, assistance, and advocacy on behalf of their loved ones. Research has shown that there are significant health and economic impacts on caregivers.[6] However, the caregiver community is larger and more complex than is often reflected in research and more research is needed. In many ways, caregiver well-being is intrinsically linked to patient health outcomes. By actively engaging caregivers and understanding the caregiver journey, researchers and decision-makers can better capture the impacts of patients' conditions and more comprehensively identify the effects of a rare disease on patients' quality of life, emotional well-being, and economic impacts.

> *The role of caregivers is a pretty complicated one in the patient community, depending on the functionality of the patient, and the age of the patient also adds a level of complexity and dependency, e.g., dependency of children vs. adult patients on caregivers.*
>
> *— Roundtable Participant, Patient Perspective*

> *As an employer, the impact on caregivers is a really important one because our employees are experiencing that burden which impacts productivity/employability. Some quantitative review of that would be super helpful for our value assessment.*
>
> *— Roundtable Participant, Employer Perspective*

Early and Continuing Patient and Caregiver Engagement

All stakeholders acknowledged that initiating patient and caregiver engagement at the earliest stages in the treatment development process helps to ensure that research efforts align with patient needs and priorities. Additionally, continuing engagement among patients and other stakeholders is critically important to conduct research that is fully patient-centered and useful for decision-making, ultimately impacting patients' experiences and outcomes.

*One of the publications of the rare disease patient-focused drug development (PFDD) compendium workshop series, "**Guide to Patient Involvement in Rare Disease Therapy Development**," published in 2022, shared guidance for how patient engagement and patient experience data can be included throughout the product development process, from pre-clinical phase to post-marketing phase.*

Patient/Caregiver Engagement in Literature

According to Forsythe et al. (2014), in a systematic review of approaches for engaging patients in research on rare diseases, patients and other stakeholders were most commonly engaged in the preparatory (agenda setting) and study execution (study design and procedures, recruitment, data collection) stages. Less common was reported engagement for research translation, with a greater focus on dissemination than on evaluation of findings or implementation. Another notable finding is that only about half of studies described engagement at multiple stages, particularly those reporting on the role of patient organizations.[7]

Another research study explored the integration of patient-reported outcome (PRO) evidence into NICE appraisals for treatments of rare diseases and found that a majority of NICE rare disease appraisals did not utilize data collected alongside clinical trials. In approximately one-third of the appraisals investigated, patient surveys or input during appraisal committee meetings played a role in clarifying uncertainty or furnishing evidence regarding patient quality of life (QoL).[8]

> *We don't usually see what's missing from the picture. That's why we need people with lived experience at every stage. Not noticing the mental health impact on caregivers is an example. If we didn't ask, we would never know.*
>
> *— Roundtable Participant, Payer Perspective*

Data and Methods

The availability of comprehensive, representative data plays an important role in comparative effectiveness research and value assessment for any disease. Obtaining high-quality data is especially challenging for rare diseases. The small number of patients with each rare disease and paucity of active research or treatments often leads to limited data availability, making it difficult to gather sufficient sample sizes for comprehensive analyses. Additionally, the heterogeneity of rare diseases further complicates data collection and standardization efforts.[9]

The lived experiences of patients with rare diseases hold invaluable insights and perspectives that are often not fully captured in data collection for rare (and other) diseases or incorporated into research. **There is a need for researchers to apply mixed (quantitative and qualitative) methods to incorporate these experiences as meaningful input in comparative effectiveness research and value assessment decision-making processes.** This will allow for the development of more patient-centered care models and enhanced treatment plans that truly address the needs of patients.

Evidence exists regarding the current status of incorporating qualitative data from the literature. In a review article published in June 2023, researchers investigated the integration of qualitative methods in drug development and examined how qualitative evidence had been utilized in health technology assessments and product labeling.[10] From 2011 through 2022, they identified 27 clinical trials integrating interviews; seven guidelines gave recommendations about the use of patient input and qualitative research in clinical trials; and one drug label, two drug reports, and four health technology assessment (HTA) reports showed how qualitative interviews had been used by health authorities.

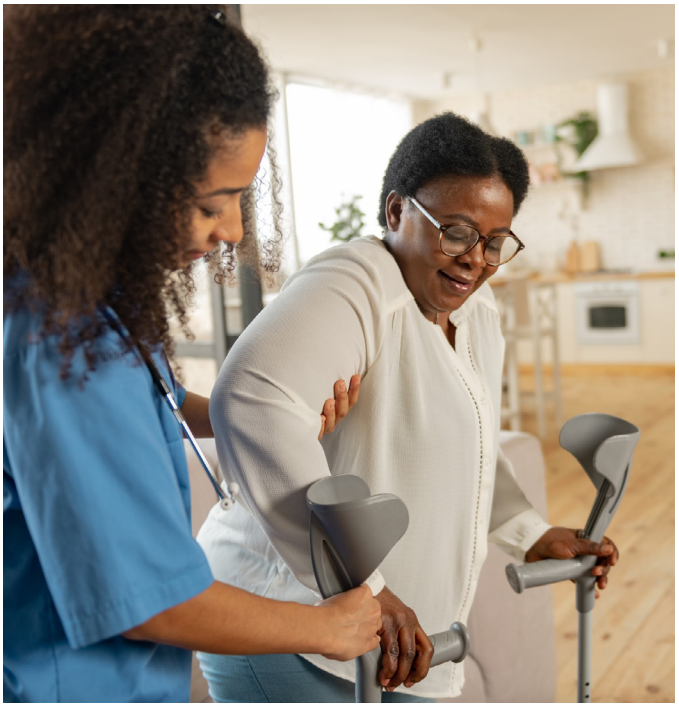
Another study conducted a review of the gray literature. The researchers explored documents from several HTA agencies, including the Canadian Agency for Drugs & Technologies in Health (CADTH), European Network for Health Technology Assessment (EunetHTA), National Institute for Health and Care Excellence (NICE), Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), Scottish Intercollegiate Guidelines Network (SIGN), and Scottish Medicines Consortium (SMC). Additionally, the review included professional societies such as the American Academy of Neurology and regulatory agencies such as the U.S. Food and Drug Administration (FDA) and European Medicine Agency (EMA). Notably, the results revealed limited cases of the incorporation of qualitative methods within the HTA and regulatory landscape. Only six HTA reports from CADTH, EunetHTA, and IQWiG, along with a single drug label, showed the integration of qualitative methods.[10]

Case Example of How the Nature of Disease and Endpoint Selection Can Affect Patients

Onasemnogene abeparvovec, a drug that treats spinal muscular atrophy (SMA) type 1 and Duchenne muscular dystrophy (DMD) were selected as case studies to illustrate how the nature of disease and endpoints in clinical trials can impact patient and payer decision-making. SMA type 1 is discussed as an example of a severe disease, characterized by significant muscle weakness with newborn presentation and rapid progression. Many children with SMA type 1 do not live past age two.[11] DMD, in contrast, is portrayed as a condition where patients often have a long diagnostic odyssey, slower disease progression, consistent decline of function, and progressive muscle weakness over time, and a life expectancy of 20 to 30 years.[12]

The different nature of these conditions emphasizes the significance of considering appropriate endpoints for evaluation. In the case of a treatment which treats patients with SMA, survival and the achievement of motor milestones are used as primary endpoints to assess the effectiveness of treatments.[13] However, for older patients with progressive diseases like DMD, survival may not be a reasonable or practical endpoint to measure treatment success. In the case of a DMD treatment, the endpoints such as the North Star Ambulatory Assessment (NSAA) and microdystrophin levels have been utilized.[14]

This example highlights the importance of understanding what matters to patients and ensuring that the chosen endpoints can genuinely reflect patient-centered outcomes.



> *By listening to this case, we know one indisputable fact is that the ability of these patients to take a single step or stand up represents a critical improvement.*
>
> *— Roundtable Participant, Payer Perspective*

Economic Impacts

*In May 2023, IVI and AcademyHealth published an **Economic Impacts Framework** that discusses the broader range of economic impacts affecting patients and caregivers. The framework focuses on how researchers can put patients, caregivers, and family members at the center of understanding economic impacts.*[15]

Understanding the economic impacts of rare diseases is crucial. For instance, payers may depend on this understanding to allocate resources efficiently and prioritize coverage decisions, focusing on interventions that have the most significant impact on patient outcomes. Additionally, for patients, economic impacts directly influence access to treatments and the financial burdens encountered.[5] By taking these impacts into consideration, payers can devise coverage options that reduce out-of-pocket costs and enhance affordability, ultimately ensuring improved access to necessary treatments for individuals with rare diseases. Stakeholders also emphasized that treatment costs and other economic impacts vary over time and across patient groups.

*The economic impact of a delayed diagnosis of a rare disease can result in up to $517,000 in avoidable costs per patient, according to a **health economics study** published in September 2023 from the EveryLife Foundation for Rare Diseases and the Lewin Group. On average, the report found, it takes more than six years and nearly 17 doctor visits, hospitalizations, and other health-related trips, to receive a rare disease diagnosis after symptoms begin. Shortening the diagnostic odyssey saves money for individuals, caregivers, and the healthcare system, while improving health outcomes.*

Scientific Spillover

Scientific spillover from research refers to the unintended benefits and broader knowledge gained that have implications and uses beyond the specific disease or treatment being studied.[16] Discovering successful treatments for rare diseases does not always require the development of entirely new drugs. While not widely recognized, the most promising prospect for numerous rare disease patients lies in the potential effectiveness of therapies already approved for different conditions. In addition, innovative treatments or technologies developed for one rare disease may be re-purposed or modified to treat additional rare diseases. Given the limited resources and data available for study of rare disease treatments, the value of scientific spillover in this field could be especially beneficial, and should be considered by funders, payers, and other decision-makers.

Identifying Patient-Centered Outcomes for Economic Modeling

Economic models can be invaluable tools for evaluating the value of interventions, including those for rare diseases. However, the unique characteristics of rare diseases, such as small patient populations, high heterogeneity, and limited data availability, can make conventional cost-effectiveness analysis (CEA) difficult to conduct or interpret. For instance, because of the nature of rare diseases, it is often difficult to characterize the uncertainty around efficacy and safety by using conventional CEA methods.

Furthermore, there is also criticism about the application of quality-adjusted life years (QALYs) in CEA for rare diseases, as some believe the QALY to have discriminatory impacts.[17, 18] Because of all these unique aspects of rare diseases, decision-making may require specialized economic models that account for these factors. Therefore, when assessing rare diseases, it may be more important to consider alternative approaches, such as multi-criteria decision analysis (MCDA), and account for different value elements such as disease severity, value of hope, real option value, and scientific spillover effects.[17]

LITERATURE REVIEW RESULTS

Following the methods mentioned in the previous section, of the 279 articles identified, more articles discussed "rare disease in general" than specific rare diseases, with more articles focused on HTA frameworks and methods and fewer with an emphasis on patient engagement processes, specifically (see Table 2).

To identify outcomes that are related to the 11 rare diseases we searched, 92 published articles on PubMed and 30 gray literature sources were reviewed (Appendix Table 3). Outcomes that are common across more than five out of the eleven specific rare diseases include physical functioning (motor, respiratory, speech, fatigue, social relationships, pain, mental deterioration, mental health, employment/work, economic impacts, and sleep (Figure 2).

Table 2. Results of the Abstract Review

Row Labels - Inclusion Criteria	Rare Disease in General	Specific Rare Disease(s)	Total	% of IN Count
HTA – Framework (e.g., conceptual resources, frameworks, key definitions, principles, guidance and recommendation)	37	5	42	18.4%
HTA – Method for Economic Evaluation (e.g., MCDA, CEA, cost of illness)	23	18	41	18.0%
HTA – Reimbursement and Pricing	31	6	37	16.2%
HTA – Method for CER/PCOR (e.g., PRO, patient-centered outcome)	15	18	33	14.5%
HTA – Tools (e.g., evaluation criteria, checklist)	16	2	18	7.9%
Policy	13	4	17	7.5%
HTA – Data	6	5	11	4.8%
HTA – Patient Engagement Process Specifically	6	4	10	4.4%
Budget Impact	4	2	6	2.6%
Diagnosis Issue	2	3	5	2.2%
HTA – Engagement Process	2	2	4	1.8%
Other	3	1	4	1.8%
Excluded	0	0	51	22.4%
Total	**158**	**70**	**279**	

Figure 2. Common Outcomes in Five or More of Eleven Rare Diseases

RECOMMENDATIONS

Through convening with different stakeholders and the literature review, we identified the key recommendations to consider when incorporating patient-centered outcomes into comparative effectiveness research. We then categorized these recommendations into several domains, recognizing that some recommendations may apply to multiple domains. With multiple recommendations per domain, we further conducted a ranking survey among steering committee members and rountable participants to derive a list of prioritized recommendations within each domain. The survey asks "how feasible is this recommendation to implement" (Feasibility) and "how urgent is it to put this recommendation into action" (Urgency) when it comes to incorporating patient-centered outcomes in comparative effectiveness research and value assessment for rare diseases. The prioritized recommendations are shown in Table 3. For the full table of recommendations, see Appendix Table 4.

For all recommendations in Table 3, the capability and accountability of different stakeholders needs to be considered, as well as ensuring that each stakeholder has the necessary resources to implement these recommendations. We would also like to note that many of these recommendations can and should apply to research and data collection for more common conditions as well as for rare diseases.

Table 3. Prioritized Recommendations for Integrating Patient-Centered Outcomes in Comparative Effectiveness Research

Domain	Prioritized Recommendations
Patient Journey and Time	2 out of 2 recommendations ranked similarly on both Urgency and Feasibility • Researchers developing clinical trials and other studies should collaborate with patients, patient advocacy groups, and rare disease organizations to include outcomes that are meaningful across the patient journey for individuals with rare diseases and high unmet need. • Researchers should include time to diagnosis, age at diagnosis, disease severity, delays in treatment, time spent on treatment, and time spent as caregiver as items which need to be explored and addressed as part of the patient journey.
Caregiver Journey	• Researchers should understand the caregiver journey as it relates to the journey of the individual with the condition and note which conditions that individual and their caregivers are diagnosed with over time.*

* Represents that this recommendation was added at the third roundtable.

Table 3 (Continued)

Domain	Prioritized Recommendations
Early and Continuing Engagement and Communication	2 out of 7 recommendations ranked high on both Urgency and Feasibility • Pharmaceutical companies and patient organizations should collaborate to begin patient/caregiver engagement earlier in the development timeline of drugs, to alleviate time and resource pressures for patient organizations, drug developers, and payers (early engagement). • Researchers and value assessment processes should employ virtual engagement strategies to facilitate participation of patients and caregivers who may face geographical or mobility challenges. +2 out of 7 recommendations ranked high on Urgency • Researchers, value assessors, and payers must dedicate resources to achieving direct patient interactions in research, value assessment, and coverage decision-making. • Researchers and value assessors should normalize the patient presence throughout agenda design, data collection, research design, and assessment processes, rather than relying solely on patient representatives at limited points in time (continuing engagement).
Data and Methods	3 out of 7 recommendations ranked high on both Urgency and Feasibility • Promote research outcomes considered important to patients and collect data on those outcomes over time.* • Data collection should include caregiver perspectives, as they can be essential to understanding what is meaningful and important to patients and their families, particularly in pediatric diseases with communication and cognitive challenges. • Studies should be designed to consider the natural history of rare diseases, including the broad spectrum of symptoms, changes in symptom severity over time, and the time of onset. +2 out of 7 recommendations ranked high on Urgency • Value assessments should recognize the unique data challenges of rare diseases, ensuring that the resultant uncertainty does not unfairly bias decision-making and is balanced against the needs of the patient and the state of standard care for those patients. • Payers should incorporate patient-centered outcomes in assessments and prior authorization criteria that play a role in determining treatment approval or coverage by payers.

* Represents that this recommendation was added at the third roundtable.

Table 3 (Continued)

Domain	Prioritized Recommendations
Economic Impacts	2 out of 2 recommendations ranked similarly on both Urgency and Feasibility • Value assessors and payers should account for variations in patients' conditions and differences in personal circumstances to mitigate the economic impacts of healthcare coverage and access decisions on rare disease patients and their families. • Researchers collecting and analyzing data should design studies to capture broad economic impacts that are important to patients, such as direct medical costs, non-clinical healthcare costs, caregiver impacts, social impacts, education and job impacts, and ability to work
Scientific Spillover	1 out of 5 recommendations ranked high on both Urgency and Feasibility • Research should evaluate the potential for scientific spillover effects resulting from rare disease research and treatments, including advancements that could impact common outcomes across rare disease areas and potential applications in more common diseases.
Identifying Common Patient-Centered Outcomes for Economic Modeling	2 out of 7 recommendations ranked high on both Urgency and Feasibility • Researchers should design surveys and conduct interviews with patients, caregivers, researchers, and clinicians to provide a patient-centered perspective on outcome priorities. • Value assessors should form partnerships with rare disease advocacy groups or organizations to gain valuable insights into diseases or treatments being evaluated (e.g., patient/caregiver advisory boards).

CONCLUSION

This final report presents a set of consensus-driven recommendations to assist stakeholders, especially researchers and decision-makers, in crafting more patient-centered research methods. With a solid commitment and broad consensus for a patient-centered approach, these recommendations provide a first-stage guide for considering outcomes important to rare disease patients in comparative effectiveness research and value assessment.

To ensure that patient-centered outcomes for rare diseases are identified and appropriately considered, researchers and other stakeholders should consider the following proactive steps:

- Early collaboration with patients, caregivers, patient advocacy groups, and rare disease organizations in the drug development process to identify and include outcomes meaningful throughout the patient journey for individuals with rare diseases,
- Continuously advocating for research on outcomes significant to patients and consistently collecting data on these outcomes over time, and
- Gaining insights into the caregiver journey by systematically collecting data on various aspects of their experiences.

Moving forward, we will need to develop processes to implement these recommendations into real-world practice and develop effective ways to measure cross-cutting outcomes that truly matter to patients, while striking a balance between developing common rare disease outcomes and acknowledging the uniqueness of each disease and each patient's lived experience.

APPENDIX

Appendix Table 1. Search Term Strategy and Results

Key Term	PubMed Results
((“ultra orphan*”[Title/Abstract] OR “ultra rare*”[Title/Abstract] OR “rare drug*”[Title/Abstract] OR “Rare Diseases”[MeSH Terms] OR “Orphan Drug Production”[MeSH Terms]) AND (“value assessment*”[Title/Abstract] OR “technology assessment, biomedical”[MeSH Terms] OR “economic evaluation*”[Title/Abstract] OR “cost benefit analysis”[MeSH Terms] OR “models, economic”[MeSH Terms] OR “Patient Outcome Assessment”[MeSH Terms] OR “comparative clinical effectiveness”[Title/Abstract] OR “comparative effectiveness research”[Title/Abstract])) AND (English[Filter])	279

Appendix Table 2. Search Term Strategy for Cross-Checking with Specific Rare Diseases

General Search Term	((“ultra orphan*”[Title/Abstract] OR “ultra rare*”[Title/Abstract] OR “rare drug*”[Title/Abstract] OR “Rare Diseases”[MeSH Terms] OR “Orphan Drug Production”[MeSH Terms]) AND (“value assessment*”[Title/Abstract] OR “technology assessment, biomedical”[MeSH Terms] OR “economic evaluation*”[Title/Abstract] OR “cost benefit analysis”[MeSH Terms] OR “models, economic”[MeSH Terms] OR “Patient Outcome Assessment”[MeSH Terms] OR “comparative clinical effectiveness”[Title/Abstract] OR “comparative effectiveness research”[Title/Abstract])) AND (English[Filter])
Specific Rare Disease Search Term	**((“Sickle Cell Disease”[Title/Abstract]))** AND (“value assessment*”[Title/Abstract] OR “technology assessment, biomedical”[MeSH Terms] OR “economic evaluation*”[Title/Abstract] OR “cost benefit analysis”[MeSH Terms] OR “models, economic”[MeSH Terms] OR “Patient Outcome Assessment”[MeSH Terms] OR “comparative clinical effectiveness”[Title/Abstract] OR “comparative effectiveness research”[Title/Abstract])) AND (English[Filter])

Note: Disease name varied for disease-specific searches.

Appendix Table 3. List of Websites Used for Gray Literature Search

Website
ALS Association
Amyloidosis Foundation
Amyloidosis Research Consortium
Bluebird Bio, Inc
Claire's Place Foundation
Cleveland Clinic
Conquer MG
Cure Sanfilippo Foundation
Cure SMA
Cystic Fibrosis Engagement Network
Cystic Fibrosis Foundation
Huntington's Disease Society of America
Les Turner ALS Foundation
Maryland Sickle Cell Disease Association
Mayo Clinic
Muscular Dystrophy Association
Myasthenia Gravis Association
Myasthenia Gravis Foundation of America
National Bleeding Disorders Foundation
NORD Amyloidosis Support Groups
NORD Thalassemia Support Foundation
Novo Nordisk
Pfizer DMD
Sanfilippo Children's Foundation
Sickle Cell Disease Coalition
Team Sanfilippo
The Cooley's Anemia Foundation
The SMA Foundation

Appendix Table 4. Full Set of Recommendations from Informational Roundtables

Domain	Recommendations (Prioritized Recommendations in Bold Text)
Patient Journey and Time	• **Researchers should include time to diagnosis, age at diagnosis, disease severity, delays in treatment, and time spent on treatment as items which need to be explored and addressed as part of the patient journey.** • **Researchers developing clinical trials and other studies should collaborate with patients, patient advocacy groups and rare disease organizations to include outcomes that are meaningful across the patient journey for individuals with rare diseases and high unmet need, including economic impacts, severity of disease, value of hope,[a] and real option value[b] throughout the patient journey.**[13, 19]
Caregiver Journey	• **Researchers should understand the caregiver journey as it relates to the journey of the individual with the various conditions and even what conditions the individual and caregivers diagnosed with over time.***
Early and Continuing Engagement and Communication	• **Pharmaceutical companies and patient organizations should collaborate to begin patient/caregiver engagement earlier in the development timeline of drugs, to alleviate time and resource pressures for patient organizations, drug developers, and payers (early engagement).** • **Researchers and value assessors should normalize the patient or caregiver presence throughout agenda design, data collection, research design, and assessment processes, rather than relying solely on patient representatives at limited points in time (continuing engagement).**[14] • Decision-makers conducting value assessments should pair patient advocates with clinicians to lead to a better combination of treatment context with patient perspectives. • Payers and employers should develop better mechanisms to learn what outcomes are important for employees and family members around rare diseases. The communication culture between payers and patients should be normalized. • **Researchers, value assessors, and payers must dedicate resources to achieving direct patient interactions in research, value assessment, and coverage decision-making.** • **Research and value assessment processes should employ virtual engagement strategies to facilitate participation of patients and caregivers who may face geographical or mobility challenges.**[20] • Best practices, guidance, or metrics for evaluating rare disease engagement practices and their effectiveness should be developed and widely put into practice.[14] • Establish a reliable platform for patients, caregivers, and other stakeholders to engage in open and trustworthy discussions. For example: Patient Engagement Resource Centre, a public platform that has been developed in joint collaboration with several organizations.* • During data collection, it is crucial to provide a clear explanation of the "why" behind data collection in order to establish trust.*

* Represents that this recommendation was added at the third roundtable.

[a] The concept of the "value of hope" refers to the notion that patients tend to favor treatments that offer a significant potential for positive outcomes.

[b] Real-option value applies when an existing treatment option prolongs survival or reduces disease severity of patients, which might subsequently enable them to benefit from future innovations that may be developed

Appendix Table 4 (Continued)

Domain	Recommendations (Prioritized Recommendations in Bold Text)

Data and Methods	• Clinical trials and other studies should be designed to include evidence-based, patient-centered clinical outcomes that reflect the evidence needs of purchasers (employers) for decision-making.
	• **Data collection should include caregiver impact, as they can be essential to understand what is meaningful and important to patients and their families, particularly in pediatric diseases with communication and cognitive challenges.**
	  ◦ For example, assessing the sleep quality of caregivers is crucial for understanding caregiver burden, but this data has not been routinely and easily collected in research.
	  ◦ For example, using existing mental health diagnostic tools probably can be a reliable way of assessing mental health impact of caregivers across rare diseases.[21]
	• **Value assessments should recognize the unique data challenges of rare diseases, ensure that resultant uncertainty does not unfairly bias decision-making, and is balanced against the needs of the patient and the state of standard care for those patients.**
	• Researchers should optimize recruitment using social media and communications through patient groups and advocacy organizations for geographically representative examples of individuals with rare diseases.[20]
	  ◦ A study on recruiting methods for gathering patient-reported outcomes from individuals with myeloproliferative neoplasms (MPNs) reveal that the most effective strategy was advertisements on social media platforms focus on MPNs, which accounted for 47.6% of respondents. Following this, e-mails (35.1%) and postcards (13.9%) sent through MPN advocacy groups were also successful in garnering participant responses.[22]
	• To enhance decision-making regarding healthcare access, it is crucial to incorporate patient experience data and outcomes into rare disease treatments' product labels. According to Lanar et al. (2020), only 17.4% of orphan drug labels contain a patient-reported outcome (PRO) measure. Additionally, less than half of pivotal trials conducted for orphan drugs have a PRO measure either as a primary or secondary endpoint.[23]
	• Research, value assessments, and decision-making for rare diseases should utilize valuable data sources beyond clinical trials, such as literature for relevant, related conditions, FDA staff reviews, qualitative data using mixed methods, and pipeline tracking services in data analysis.
	• Research funders and policy-makers should encourage the development of open-access databases and knowledge-sharing platforms to facilitate the transparent sharing of rare disease data and findings to ensure adequate data and exploration of potential for common, cross-cutting outcomes across rare diseases.
	• **Promote research on outcomes considered important to patients and collect data on those outcomes over time.**[*]
	• Recognize the challenges associated with data collection when disseminating your research. This approach helps highlight existing gaps and encourages ongoing efforts to collect important data.[*]
	• Keep collecting data and promote research on patient prioritized outcomes.[*]

[*] Represents that this recommendation was added at the third roundtable.

Appendix Table 4 (Continued)

Domain	Recommendations (Prioritized Recommendations in Bold Text)
Data and Methods (continued)	• Researchers should explore the increased use of common outcomes that apply to multiple rare diseases rather than disease- or study-specific outcomes. • Research and real-world evidence should include lived experiences in mixed methods analyses, going beyond relying solely on published quantitative evidence. Case studies have demonstrated frameworks for implementing combined qualitative and quantitative methods to elicit and prioritize patient experience value elements in rare diseases.[24] • To elevate the quality of information gathered, researchers should pose targeted inquiries about lived experiences. For example, instead of requesting patients to describe how a treatment enhances their quality of life (QoL), ask what a treatment needs to achieve to improve their overall lived experience.[25] • Researchers should adopt appropriate methodologies to assess comprehensive outcomes that matter to rare disease patients, moving beyond traditional cost-effectiveness analysis (CEA) approaches. For example, applying the multi-criteria decision analysis (MCDA) or the Generalized Risk-Adjusted Cost-Effectiveness (GRACE) approach to account for value elements that matter to rare disease patients, such as 'disease severity,' 'value of hope,' and 'scientific spillover' to evaluate cost and effectiveness.[26, 27] • **Studies should be designed to consider the natural history of rare diseases, including the broad spectrum of symptoms, changes in symptom severity over time, and the time of onset.** • For example, AMCP guidelines (2018) emphasize the importance of patient engagement in pre-approval information-gathering. In terms of data collection, patient registries can be a useful resource for researchers to study specific disease treatments and outcomes and incorporate these into design of clinical trials. • Researchers should pay attention not solely to the natural history of patients, but also seek to comprehend the "natural history of caregivers."* • **Payers should incorporate patient-centered outcomes in assessments and prior authorization criteria that play a role in determining treatment approval or coverage by payers.** • Payers should recognize that economic models to inform decision-making in rare disease will reflect maturing data in small populations with immediate need.
Economic Impacts	• **Value assessors and payers should account for variations in patients' conditions and differences in personal circumstances to mitigate the economic impacts of healthcare coverage and access decisions on rare disease patients and their families.** • **Researchers collecting and analyzing data should design studies to capture broad economic impacts that are important to patients, such as direct medical costs, non-clinical healthcare costs, caregiver impacts, social impacts, education and job impacts, and ability to work.**[13] • Broadening the scope of research to include the broader societal impact, such as caregiver burden and its implications for productivity and career changes.*

* Represents that this recommendation was added at the third roundtable.

Appendix Table 4 (Continued)

Domain	Recommendations (Prioritized Recommendations in Bold Text)
Scientific Spillover	• **Research should evaluate the potential for scientific spillover effects resulting from rare disease research and treatments, including advancements that could impact common outcomes across rare disease areas and potential applications in more common diseases.** • Funders and policy-makers should factor in the public good of scientific spillover when making funding decisions for rare disease drugs. • Value assessments should integrate scientific spillover effects to achieve a comprehensive evaluation of the impact and value of healthcare interventions.[19] • Economic evaluations of new rare disease treatments should include health effects on family members and caregivers to avoid undervaluing the benefits of diagnosis and management.[28, 29] • Research funders and policy-makers should encourage the development of open-access databases and knowledge-sharing platforms to facilitate the dissemination of rare disease data and outcomes, maximizing their potential for contributing to broader scientific understanding and progress.[30]
Identifying Common Patient-Centered Outcomes for Economic Modeling	• Researchers should utilize existing frameworks which already have components for rare diseases and engage each patient community in the exercise of identifying the 'common set' of outcomes relevant to their specific disease. • Researchers should explore using common outcomes across diseases, with customization based on types of rare disease (e.g., musculoskeletal, neurological). • Patient communities and researchers should identify and develop case studies which demonstrate frameworks for implementing a combined qualitative and quantitative method to elicit and prioritize patient experience value elements in rare diseases (e.g., as demonstrated in a case study of neuromyelitis optica spectrum disorder).[24] • Studies should be designed to capture broad patient-centered "impacts," which include not only health outcomes, but also all other meaningful concepts that patients might report as important to them. As an example, the National Health Council has introduced a valuable tool called the Patient-Centered Core Impact Sets (PC-CIS),[c] which is useful to identify core sets of outcomes that hold significance for patients, including financial burdens and caregiver stresses.[31] • Funders should encourage development of guidance to researchers regarding methods for developing common, cross-cutting patient-centered outcome measures for rare diseases. • **Researchers should design surveys and conduct interviews with patients, caregivers, researchers, and clinicians to provide a patient-centered perspective on outcome priorities.**[32] • **Value assessors should form partnerships with rare disease advocacy groups or organizations to gain valuable insights into diseases or treatments being evaluated. Establishing advisory boards for patients and caregivers within these organizations will provide a platform to capture unique experiences and perspectives directly from affected individuals and their caregivers.**[31]

[c] Patient-Centered Core Impact Sets (PC-CIS) is a patient-derived and patient-prioritized list of impacts a disease and/or its treatments have on a patient (and/or their family and caregivers).

References

1 "Rare Diseases Act of 2002 (2002; 107th Congress H.R. 4013) - GovTrack.us." Accessed: Jul. 11, 2023. [Online]. Available: https://www.govtrack.us/congress/bills/107/hr4013.

2 G. Yang, I. Cintina, A. Pariser, E. Oehrlein, J. Sullivan, and A. Kennedy, "The national economic burden of rare disease in the United States in 2019," Orphanet J Rare Dis, vol. 17, no. 1, pp. 1–11, Dec. 2022, doi: 10.1186/S13023-022-02299-5/FIGURES/2.

3 T. Morel et al., "Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: A comparative study of managed entry agreements across seven European countries," Orphanet J Rare Dis, vol. 8, no. 1, pp. 1–15, Dec. 2013, doi: 10.1186/1750-1172-8-198/FIGURES/5.

4 M. Wagner, H. Khoury, J. Willet, D. Rindress, and M. Goetghebeur, "Can the EVIDEM Framework Tackle Issues Raised by Evaluating Treatments for Rare Diseases: Analysis of Issues and Policies, and Context-Specific Adaptation," Pharmacoeconomics, vol. 34, no. 3, pp. 285–301, Mar. 2016, doi: 10.1007/S40273-015-0340-5.

5 "Burden of Rare Disease Study - EveryLife Foundation for Rare Diseases." Accessed: Jul. 30, 2023. [Online]. Available: https://everylifefoundation.org/burden-study/.

6 M. Brandt, L. Johannsen, L. Inhestern, and C. Bergelt, "Parents as informal caregivers of children and adolescents with spinal muscular atrophy: a systematic review of quantitative and qualitative data on the psychosocial situation, caregiver burden, and family needs," Orphanet J Rare Dis, vol. 17, no. 1, pp. 1–30, Dec. 2022, doi: 10.1186/S13023-022-02407-5/TABLES/2.

7 L. P. Forsythe et al., "A Systematic Review of Approaches for Engaging Patients for Research on Rare Diseases," J Gen Intern Med, vol. 29, no. Suppl 3, p. 788, 2014, doi: 10.1007/S11606-014-2895-9.

8 E. Nicod, M. Meregaglia, A. Whittal, S. Upadhyaya, K. Facey, and M. Drummond, "Consideration of quality of life in the health technology assessments of rare disease treatments," Eur J Health Econ, vol. 23, no. 4, pp. 645–669, Jun. 2022, doi: 10.1007/S10198-021-01387-W.

9 M. Wagner et al., "HTA challenges for appraising rare disease interventions viewed through the lens of an institutional multidimensional value framework," https://doi.org/10.1080/14737167.2023.2161513, vol. 23, no. 2, pp. 143–152, 2022, doi: 10.1080/14737167.2023.2161513.

10 A.-S. Michel et al., "Integrating qualitative interviews in drug development and the use of qualitative evidence in product labelling and health technology assessments: a review," Front Med (Lausanne), vol. 10, p. 1197529, Jun. 2023, doi: 10.3389/FMED.2023.1197529/BIBTEX.

11 "Spinal Muscular Atrophy (SMA) | Boston Children's Hospital." Accessed: Oct. 12, 2023. [Online]. Available: https://www.childrenshospital.org/conditions/spinal-muscular-atrophy-sma.

12 J. Broomfield, M. Hill, M. Guglieri, M. Crowther, and K. Abrams, "Life Expectancy in Duchenne Muscular Dystrophy: Reproduced Individual Patient Data Meta-analysis," Neurology, vol. 97, no. 23, pp. E2304–E2314, Dec. 2021, doi: 10.1212/WNL.0000000000012910.

13 J. W. Day et al., "Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial," Lancet Neurol, vol. 20, no. 4, pp. 284–293, Apr. 2021, doi: 10.1016/S1474-4422(21)00001-6.

14 J. S. Chamberlain et al., "Microdystrophin Expression as a Surrogate Endpoint for Duchenne Muscular Dystrophy Clinical Trials," Hum Gene Ther, vol. 34, no. 9–10, p. 404, May 2023, doi: 10.1089/HUM.2022.190.

15 "A Research Framework to Understand the Full Range of Economic Impacts on Patients and Caregivers," 2023, Accessed: Jul. 20, 2023. [Online]. Available: https://thevalueinitiative.org/wp-content/uploads/2023/06/05-2023-Economic-Impacts-Framework-Report_FINAL.pdf.

16 D. N. Lakdawalla, J. A. Doshi, L. P. Garrison, C. E. Phelps, A. Basu, and P. M. Danzon, "Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report [3]," Value Health, vol. 21, no. 2, pp. 131–139, Feb. 2018, doi: 10.1016/J.JVAL.2017.12.007.

17 H. I. Hyry, A. D. Stern, T. M. Cox, and J. C. P. Roos, "Limits on use of health economic assessments for rare diseases," QJM: An International Journal of Medicine, vol. 107, no. 3, pp. 241–245, Mar. 2014, doi: 10.1093/QJMED/HCU016.

18 M. J. Postma et al., "Assessing the value of orphan drugs using conventional cost-effectiveness analysis: Is it fit for purpose?," Orphanet J Rare Dis, vol. 17, no. 1, p. 157, 2022, doi: 10.1186/s13023-022-02283-z.

19 R. Fischer et al., "Title: Healthcare Stakeholder Perspectives on a Value Assessment Approach for Duchenne Muscular Dystrophy Therapies Running title: Value Assessment Perspectives for Duchenne", doi: 10.1101/2023.07.11.23292507.

20 J. Yu, D. Paranagama, and S. Parasuraman, "Recruitment strategies and geographic representativeness for patient survey studies in rare diseases: Experience from the living with myeloproliferative neoplasms patient survey," PLoS One, vol. 15, no. 12, Dec. 2020, doi: 10.1371/JOURNAL.PONE.0243562.

21 T. Conijn, S. C. M. Nijmeijer, H. A. van Oers, F. A. Wijburg, and L. Haverman, "Psychosocial functioning in parents of MPS III patients," JIMD Rep, vol. 44, pp. 33–41, 2019, doi: 10.1007/8904_2018_119/COVER.

22 J. Yu, D. Paranagama, and S. Parasuraman, "Recruitment strategies and geographic representativeness for patient survey studies in rare diseases: Experience from the living with myeloproliferative neoplasms patient survey," PLoS One, vol. 15, no. 12, Dec. 2020, doi: 10.1371/JOURNAL.PONE.0243562.

23 S. Lanar, C. Acquadro, J. Seaton, I. Savre, and B. Arnould, "To what degree are orphan drugs patient-centered? A review of the current state of clinical research in rare diseases," Orphanet J Rare Dis, vol. 15, no. 1, Jun. 2020, doi: 10.1186/S13023-020-01400-0.

24 R. B. McQueen et al., "Framework for Patient Experience Value Elements in Rare Disease: A Case Study Demonstrating the Applicability of Combined Qualitative and Quantitative Methods," Pharmacoecon Open, vol. 7, no. 2, p. 217, Mar. 2023, doi: 10.1007/S41669-022-00376-W.

25 R. Sharma, S. Ahmed, J. Campagnari, W. Huff, and L. Lloyd, "Embedding Patient-Centricity by Collaborating with Patients to Transform the Rare Disease Ecosystem," Pharmaceut Med, vol. 37, no. 4, p. 265, Jul. 2023, doi: 10.1007/S40290-023-00474-Y.

26 D. N. Lakdawalla and C. E. Phelps, "Health Technology Assessment With Diminishing Returns to Health: The Generalized Risk-Adjusted Cost-Effectiveness (GRACE) Approach," Value in Health, vol. 24, no. 2, pp. 244–249, Feb. 2021, doi: 10.1016/j.jval.2020.10.003.

27 M. J. Postma et al., "Assessing the value of orphan drugs using conventional cost-effectiveness analysis: Is it fit for purpose?," Orphanet J Rare Dis, vol. 17, no. 1, p. 157, Dec. 2022, doi: 10.1186/S13023-022-02283-Z.

28 Y. Wu et al., "Parental health spillover effects of paediatric rare genetic conditions," Qual Life Res, vol. 29, no. 9, pp. 2445–2454, Sep. 2020, doi: 10.1007/S11136-020-02497-3.

29 N. J. Simon et al., "Health utilities and parental quality of life effects for three rare conditions tested in newborns," J Patient Rep Outcomes, vol. 3, no. 1, Dec. 2019, doi: 10.1186/S41687-019-0093-6.

30 N. Denton et al., "Sharing is caring: a call for a new era of rare disease research and development," Orphanet J Rare Dis, vol. 17, no. 1, p. 389, Dec. 2022, doi: 10.1186/S13023-022-02529-W.

31 E. M. Perfetto et al., "A Foundation for Patient-Centered Core Impact Sets: Key Learnings from Past and Existing Approaches," Patient, vol. 16, no. 4, pp. 293–300, Jul. 2023, doi: 10.1007/S40271-023-00630-1/METRICS.

32 E. Mayo-Wilson et al., "Methods to identify and prioritize patientcentered outcomes for use in comparative effectiveness research," Pilot Feasibility Stud, vol. 4, no. 1, pp. 1–12, Apr. 2018, doi: 10.1186/S40814-018-0284-6/FIGURES/3.

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