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ORIGINAL RESEARCH ARTICLE

Framework for Patient Experience Value Elements in Rare Disease: A Case Study Demonstrating the Applicability of Combined Qualitative and Quantitative Methods

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Abstract

Background and Objective Several novel methods have been suggested to extend a conventional value assessment to capture a more comprehensive perspective of value from a patient perspective. The objective of this research was to demonstrate a framework for implementing a combined qualitative and quantitative method to elicit and prioritize patient experience value elements in rare diseases. Neuromyelitis optica spectrum disorder was used as a case study.

Methods The method for eliciting and prioritizing patient experience value elements involved a three-step process: (1) collecting potential patient experience value elements from existing literature sources followed by deliberation by a multi-stakeholder research team; (2) a pre-workshop webinar and survey to identify additional patient-reported value elements; and (3) a workshop to discuss, prioritize the value elements using a swing weighting method. Outcomes were prioritized value elements with normalized weights for patients considering a treatment for neuromyelitis optica spectrum disorder.

Results A literature review and deliberation resulted in the following initial value elements: ability to reach important personal milestones, patient's financial burden, value of hope/balance or timing of risks and benefits, Uncertainty about long-term benefits and safety of the treatment, Patient empowerment through therapeutic advancement and technology, Caregiver/family's financial burden, patient experience related to treatment regimen, Therapeutic options, and Caregiver/family's quality of life. Eight patients with neuromyelitis optica spectrum disorder participated in the case study. In the online survey, participants found the nine proposed patient experience value elements both understandable and important with no additions. During the workshop, 'Uncertainty about long-term benefits and safety,' 'Patient experience related to treatment regimen,' and 'Patient's financial burden' were found to be the most important patient experience value elements, with a respective weight of 25%, 19.2%, and 14.4% (out of total 100%).

Conclusions This case study provides a framework for eliciting and prioritizing patient experience value elements using direct patient input. Although elements/weights may differ by disease, and even in neuromyelitis optica spectrum disorder, additional research is needed, value frameworks, researchers, and manufacturers can use this practical method to generate patient experience value elements and evaluate their impact on treatment selection.

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Key Points for Decision Makers

A conventional value assessment may not capture the full spectrum of value for patients.

This paper describes a practical method to engage patients in eliciting and prioritizing patient experience value elements.

A rare neurological disease, neuromyelitis optica spectrum disorder, was used as a case study.

1 Introduction

The increasing public pressure about rising drug prices highlights the importance of assessing the value of health technologies. Two main questions are raised regarding the value of new healthcare technologies: (1) what value elements are important for different stakeholders, including patients, caregivers, healthcare professionals, and payers/insurance? (2) What is a fair price premium for the added value of new technologies? A common critique of conventional value assessment is the lack of formal representation of additional value elements beyond regulatory approval endpoints such as patient-centered and societal value elements [1]. Several alternative methods have been suggested to broaden a conventional value assessment in capturing a more complete perspective on value. In recent years, multiple value frameworks have been published or updated to capture a broader list of potential value elements [2–5]. Methods to include these additional value elements in value assessment applications are emerging and include an augmented cost-effectiveness analysis and a multi-criteria decision analysis (MCDA) [6–11].

Guidance documents suggest that multiple stakeholders, including payers/decision makers, healthcare providers, academic researchers, and patients and informal caregivers should be involved to elicit the relative importance of value elements as various stakeholders have different perspectives and decision contexts [12–14]. Different decision contexts may exacerbate information asymmetry, for example, decision makers may not be aware of patient experiences (PEx) related to different health technologies. According to the guidance of the US Food and Drug Administration, PEx data may be collected by any persons and are intended to provide information about PEx with a disease, or the related treatment [15]. While conventional value elements derived largely from regulatory approval studies (e.g., survival, safety) are included in value assessment applications and weighed by a multi-stakeholder group (where patients and their family caregivers are also represented) [16], the relative importance of subdomains within patient-centered value should be determined by patients and their families [17].

The dearth of PEx value elements in value assessment applications is even more apparent for therapies focused on treating patients with rare diseases. Many novel technologies for rare disease, such as cell and gene therapies, are approved based on limited evidence (e.g., single-arm studies, small sample sizes) at the regulatory approval stage compared to non-rare diseases [18, 19]. Further, novel treatments can raise significant affordability concerns, even in high-income countries. The combination of data gaps and affordability concerns can lead to significant uncertainty for both patients and payers. An example case of a rare disease where the recent approval of breakthrough treatments has limited evidence and may benefit from further data on patient insights is neuromyelitis optica spectrum disorder (NMOSD) [20–22]. Neuromyelitis optica spectrum disorder is a rare recurrent inflammatory disorder of the central nervous system that commonly presents with recurrent attacks of optic neuritis and transverse myelitis and affects approximately 0.5–4/100,000 patients globally, making the recruitment of patients for both pivotal clinical trials and post-marketing research a challenge [23]. Neurologic injury in NMOSD is often severe, leading to blindness and/or paralysis. As a result, its impact on patients and their families, as well as society, is substantial. However, the impact of NMOSD on patients and their families is not well documented and understood. To fill gaps in the NMOSD literature on PEx, we used common MCDA weighting methods to prioritize the multiple criteria that drive treatment decisions in NMOSD and compare the relative value of PEx value elements. Specifically, the objective of this research was to implement a combined qualitative and quantitative approach to elicit and prioritize the most important PEx value elements for patients with rare disease, with NMOSD as a case study.

2 Materials and Methods

Our method for eliciting and prioritizing PEx value elements involves a three-step process: (1) collecting potential PEx value elements from existing literature sources identified in a targeted literature review, and preparing an initial list of value elements through deliberation by the multi-stakeholder research team; (2) a pre-workshop webinar and surveys to identify additional PEx value elements; and (3) a workshop to prioritize the value elements using the swing weighting method commonly used in MCDA.

2.1 Patient Experience Value Element List Development

The sources of the initial PEx value element list are shown in Fig. 1. Identification of the initial list of value elements was based on two foundation works of US value frameworks: the International Society for Pharmacoeconomics and Outcomes Research Value Flower [2, 4] and the Institute for Clinical and Economic Review Value Assessment Framework [3]. These were extended with the results of two previously published studies: a systematic literature review that aimed to collect and analyze PEx value elements in published value frameworks [24] and an original research article applying mixed methods [5]. In the paper by Inotai et al. [24], based on the systematic literature review, a multidisciplinary research team developed five potential PEx value elements

that were challenged, discussed, and approved by a panel of international payer experts. The original research article by dosReis et al. [5] aimed to identify patient-informed value elements that can be used to make value assessments more patient centered. This mixed-method study, including one-on-one discussions with patients from a diverse set of disease areas, identified 42 value elements organized into five domains: short-term and long-term effects of treatment, treatment access, cost, life impact, and social impact [5].

Initial selection and merging overlapping value elements from the four included papers to minimize redundancy was conducted iteratively through deliberations by a multi-stakeholder research team. The team included an NMOSD clinical expert (USA), a European Patients' Academy on Therapeutic Innovation-trained [25] non-NMOSD patient expert (Hungary), and four academic researchers (from the USA and Hungary) experienced in value framework and MCDA development, in compliance with the International Society for Pharmacoeconomics and Outcomes Research MCDA Emerging Good Practices Task Force report's principles [26]. Value elements were then flagged as (1) conventional value elements, (2) additional PEx value elements, and (3) additional societal value elements. Description and categorization of value elements were challenged by members of the research's Steering Committee including internationally recognized health economists. Domains of PEx value elements (as described in this paper) were ranked and weighted by patients with NMOSD in a workshop, societal value elements will be ranked and weighted by a multi-stakeholder group in a future workshop.

2.2 Case Study Population

Patients with NMOSD (aged ≥ 18 years) who were positive for serum aquaporin-4 autoantibodies and fluent in English were recruited at the University of Colorado Anschutz Medical Campus (Protocol #21-3409). Participants received a gift card for their time and effort in the research.

2.3 Pre-workshop Webinar and Online Survey

The pre-workshop webinar, embedded to an anonymous online survey (using SurveyMonkey [27]), provided a concise lay-language audio-visual summary of the rationale of value assessment of health technologies and the study objective. The main research question—what do patients consider to be valuable when selecting a treatment for NMOSD?—was made explicit to participants of the case study at every stage of the process. The introduction was followed by short audio-visual explanations for each of the nine value elements, backed up with illustrations and real-life examples to ease understanding. After watching the short video for each value element, participants were asked to (1) rate the level of understanding of the value element

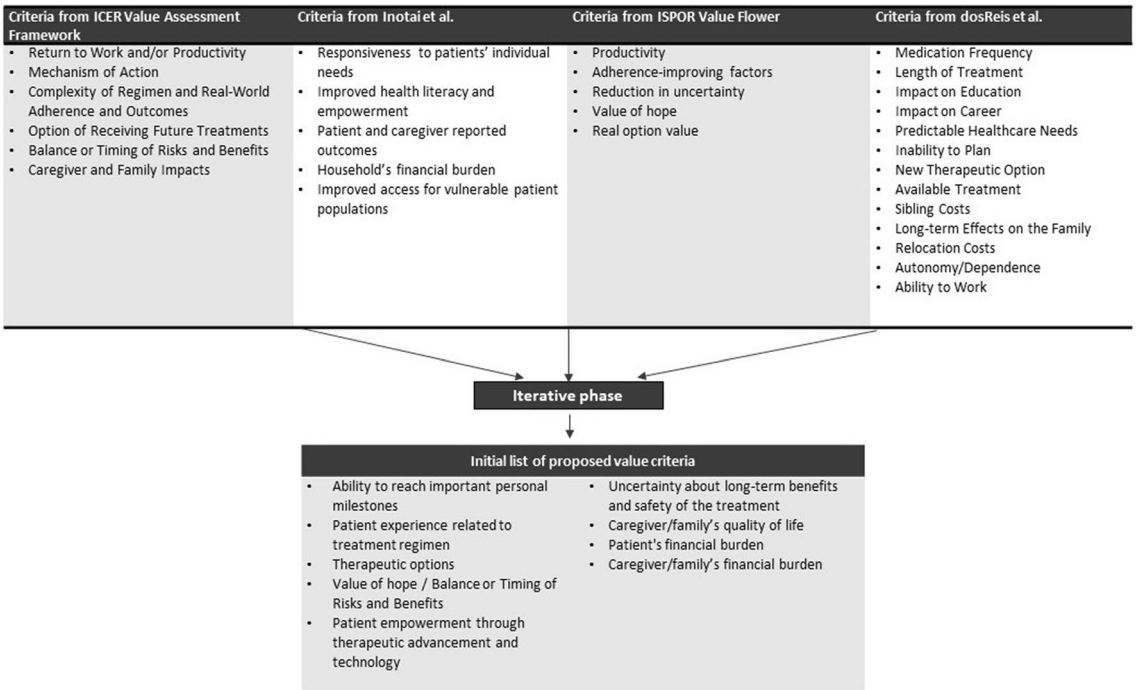

Fig. 1 Sources and selection of patient experience value elements. *ICER* Institute for Clinical and Economic Review, *ISPOR* International Society for Pharmacoeconomics and Outcomes Research

on a five-level discrete rating scale (where 1 is "Very poor" and 5 is "Excellent"), with the opportunity to provide suggestions or comments for the concept or wording in a free text format, (2) rate the level of importance of each value element for themselves in their treatment decisions (where 1 is "Not important at all" and 5 is "Extremely important"), with the opportunity to add any personal experience on why it is, or why it is not important for people with NMOSD and their families. Finally, (3) participants were asked whether they think the list of value elements presented cover all important aspects of a new treatment for patients with NMOSD and their families, and if not, what might be missing. This step ensured that participants had the opportunity to propose additional value elements to extend findings from the literature. During the online survey, participants had the opportunity to pause and re-watch the prerecorded short videos on the value elements and navigate forward and backward among the questions. The pre-workshop webinar and online survey were pilot tested with two patients with NMOSD (who did not participate in the research) who were then interviewed to capture their impressions and suggestions. The voting exercises of the workshop were tested with university students for technical difficulties and feasibility.

2.4 Workshop

Participants were asked to contribute to the subsequent workshop only if they watched the pre-workshop webinar and completed the anonymous online survey. The workshop was held in a hybrid form, i.e., participation was possible face-to-face (onsite) or virtually (Zoom). The first part of the workshop was a group discussion, moderated by a trained facilitator, aimed to discuss (1) the objective of the research, (2) each value element (with a special focus on those items with a fair or worse understanding in the online survey), and (3) NMOSD-specific experience of participants gathered from the survey results and the comprehensiveness of the list of value elements.

The second part of the workshop was the ranking and weighting exercise, aiming to elicit participants' preferences on the relative importance of the PEx value elements by anonymous voting through Mentimeter [28]. Mentimeter is an interactive polling software that allows users to develop advanced ranking and weighting exercises. To test participants' understanding on voting questions and to make sure their Mentimeter was operating properly, both ranking and weighting exercises were preceded with similar questions on an everyday topic (i.e., important value elements of a good night's sleep). To reduce the cognitive burden of the ranking exercise, participants were asked to select the three most important value elements in the first voting. These items (ranked by the entire group) were then removed from the list and participants were asked to repeat the voting and again select the next three most important value elements from the remainder of six. Finally, in a third voting, they were asked to rank the remainder value elements. Draws were acceptable voting outcomes.

The swing weighting method conducted is a commonly used preference elicitation technique in MCDA development to weight ranked value elements [29]. Participants were asked to indicate how much more a value element is important to them compared to the one ranked just below. First, a value element ranked #8 regarding its relative importance was compared to a value element ranked #9; then a value element ranked #7 was rated relative to #8, until the value element considered the most important #1 was compared to #2. In their votes for relative importance between each value element pairs, responders could select a value on a continuous scale between 0% (i.e., equally important) and + 50% (i.e., huge difference). Relative importance (mean of differences in percent) between element pairs were then converted to weights, summing up 100% for the total of nine value elements [9]. The final weights were then presented to the participants and discussed together with the moderator of the workshop.

3 Results

3.1 Participants

Eleven patients with NMOSD agreed to participate in the case study. Ten patients completed the pre-workshop survey and watched the webinar between 9 July and 19 July, 2021, and eight patients participated in the workshop on 22 July, 2021, allowing 3–13 days to consider the value elements. One participant could not take part in the ranking and weighting part of the workshop because of the accessibility issues of the voting platform (not accessible for the severely visually impaired). Out of eight participants who completed all steps of the case study, 50% were non-white and 25% of Hispanic origin. Over 35% had a time from diagnosis greater than 15 years, and 75% identified as female. The full description of the demographics and disease background of participants is provided in Table 1.

3.2 List of Value Elements

Table 2 describes the short descriptions and the Appendix in the Electronic Supplementary Material (ESM) shows the additional illustrations of the nine value elements presented to research participants both throughout the online survey and the workshop. In the pilot and during the online survey and the workshop, all responders confirmed the

completeness of the list of value elements (i.e., no additional elements were proposed, and no recommendations were received regarding textual phrasing).

3.3 Understandability and Importance of Value Elements (Quantitative Results)

In the online survey, responders found the value elements understandable (range 4.3–4.7 out of a maximum 5), which was also reflected in their minimum scores not less than 3 ("Fair") for any of the value elements. The online survey discovered the responders' individual perception on the importance of each element on a 5-point scale, while the workshop revealed the relative importance of the value elements (i.e., the group's mean percent difference) in the ranking and weighting exercise according to the group's preference. Quantitative results are summarized in Table 3.

Table 1 Descriptive characteristics of patients with neuromyelitis optica spectrum disorder involved

Characteristics	Patients ($N = 8$) *n* (%)
Age, years	
18–30	2 (25)
31–50	4 (50)
51–70	2 (25)
Sex	
Female	6 (75)
Male	2 (25)
Race	
American Indian or Alaska Native	0
Asian	1 (12.5)
Black or African American	2 (25)
Native Hawaiian or other Pacific Islander	0
White	4 (50)
Other	1 (12.5)
Ethnicity	
Hispanic	2 (25)
Non-Hispanic	6 (75)
Stage of disease	
Mild	6 (75)
Moderate	2 (25)
Time from diagnosis, years	
0–5	2 (25)
5–10	3 (37.5)
10–15	2 (25)
15–20	1 (12.5)
Type of participation	
Virtual	6 (75)
In-person	2 (25)

3.4 Participants' Quotes on the Value Elements (Qualitative Results)

Participants were asked to reflect on each value element and their importance also in a free text format: first in the online survey, then in the group discussion part of the workshop. Table 4 contains the most illustrative participant quotes (edited for grammar, clarity, and brevity while maintaining intended content) associated with each value element from the online survey (S) and the workshop (W), respectively.

3.5 Additional Themes from the Workshop Discussion

In the online survey, workshop participants addressed some additional themes not directly related to the value elements discussed. Two participants stated their preferences for value elements are different at the time of the workshop as compared with earlier stages of the disease: (1) "Those were my three most important. Maybe it'll change years down the line." (2) "I'm looking at it through a filter of where I'm at today in terms of my disease progression and if there's any clinical or subclinical concerns. Whereas prior, I would have considered the filter of where my values were at the point, where I was in an acute state or recently navigating the diagnosis. I don't know but the value shift is very dynamic." Participants also reflected on the significance of the relative importance of the value elements: "I think this has been great. Thinking back to attributes of each element and the magnitude of difference between them. I think it's always a false choice to choose one versus the other, but I don't think I've ever thought about the space between my top choices." For some patients, participating in the workshop offered new connections to other patients with NMOSD and emphasized the value of personal connections with peers who are having similar PEx.

4 Discussion

4.1 Ensuring Completeness of Value Elements

We applied multiple steps to ensure the completeness of the final list of value elements, including robust literature sources, multiple iterations with stakeholders (steering committee, pilot), and providing multiple opportunities for participants to revise the list of value elements or propose new elements while (1) completing the online survey (individual

Table 2 Description of patient experience value elements (see Appendix in the ESM for graphical illustrations designed for participants)

Name	Description
Ability to reach important personal milestones	Patients' ability to achieve major life goals related to education, work, family affairs (e.g., pregnancy), and social integration
Patient's financial burden	The financial impact of the disease and treatment on the patient including drug cost, medical costs of treatment and disease management (e.g., hospitalization), and nonmedical costs (e.g., transportation costs, absence from work) borne by the patients
Value of hope/balance or timing of risks and benefits	Potential of a treatment to provide the chance of "cure" at a great risk
Uncertainty about long-term benefits and safety of the treatment	Uncertainty about the long-term benefit and safety
Patient empowerment through therapeutic advancement and technology	Therapeutic advancement or improved technology (e.g., digital health tools) combined with the treatment to empower patients in self-management and to allow their involvement as equal partners through their patient journey (e.g., through shared decision making)
Caregiver/family's financial burden	The financial impact of the disease and treatment on the caregiver(s) (e.g., travel costs, absence from work)
Patient experience related to treatment regimen	The patient's experience related to the management of the condition with available therapies (e.g., infusion-related reactions, site of injection reaction, pain, frequency of taking the treatment, location, and time needed for administration) and the potential of the new treatment to influence it
Therapeutic options	The treatment provides the first/only option for the patient and/or extends current or future treatment options, for example, by promoting the possibility of individualized therapy
Caregiver/family's quality of life	The caregiver's general perception of how the patient's disease and treatment affect their own physical, physiological and social aspects of everyday life (e.g. anxiety, social isolation, exhaustion, health consequences)

feedback) and (2) sharing their experiences in the workshop (group interaction). Consequently, in the online survey, we observed high scores on understandability (Table 3), relevant NMOSD-specific examples and, during the workshop, no emergence of missing value concepts.

4.2 Consistency of Quantitative Results in the Online Survey and the Workshop

Individual preferences regarding the importance of value elements in the pre-workshop online survey and group ranking during the workshop were overall consistent. For example, the two value elements considered to be the most important by responders (Patient's financial burden, 4.6; and Uncertainty about long-term benefits and safety of the treatment, 4.5) were also ranked in the top 3 during the workshop by the group, where participants had to make trade-off decisions during a priority setting. Interestingly, in Ranking Vote 1, 2 and 3, although value elements changed their rankings, they tended to maintain their rank groupings (i.e., being ranked within #1–3, 4–6 or 7–9).

4.3 Importance of Qualitative Data

In research on PEx, collecting quantitative evidence is desirable but may not show the full picture without supplementary qualitative data. Patients, even with the same disease area and stage, might have completely different experiences with their condition and how it is affecting their own life. Individual patient quotes may reveal additional aspects of value otherwise hidden in numbers. We therefore recommend that regardless of the decision tool (i.e., conventional value assessment, MCDA), the collection of both qualitative and quantitative data is essential.

4.4 Conducting Patient-Centered Research

A major part of the framework was ensuring that patients are engaged in a truly meaningful manner through multiple steps: (1) patient-centric design of research through the involvement of a trained patient expert; (2) piloted each step with patients with NMOSD; (3) invested time to translate terminology into lay language and to create helpful visual tools for patients; (4) allocated fair compensation for participants for their time; and (5) considered the maximum time spent with tasks requiring concentration (which may depend on the nature of the disease). Methodology ensured

Table 3 Individual scores on understandability and importance, and group ranking and weighting of value elements

Value element	Online survey		Workshop, ranking			Workshop, swing weighting		
	Understandability mean (range)	Importance mean (range)	Vote 1	Vote 2	Vote 3	Relative importance [mean percent difference between element pairs (range)]	Relative scores for swing weighting (total: 24.07 = 100%)	Weight of value element (total: 100%)
Uncertainty about long-term benefits and safety of the treatment	4.5 (3–5)	4.5 (3–5)	**1**	NA	NA	NA	6.03	25.0%
Patient experience related to treatment regimen	4.3 (3–5)	4.3 (3–5)	**2**	NA	NA	30.5% (0–50)	4.62	19.2%
Patient's financial burden	4.7 (4–5)	4.6 (3–5)	**3**	NA	NA	33.1% (0–50)	3.47	14.4%
Ability to reach important personal milestones	4.7 (4–5)	4.2 (3–5)	6	**4**	NA	34.0% (11–50)	2.59	10.8%
Patient empowerment through therapeutic advancement and technology	4.4 (3–5)	4.1 (3–5)	7	**5**	NA	24.7% (0–50)	2.08	8.6%
Therapeutic options	4.3 (3–5)	4.3 (3–5)	5	**6**	NA	18.4% (0–35)	1.75	7.3%
Value of hope/balance or timing of risks and benefits	4.7 (4–5)	4.4 (2–5)	4	8	**7**	21.3% (0–50)	1.45	6.0%
Caregiver/family's financial burden	4.4 (3–5)	4.4 (3–5)	8	7	**8**	34.0% (12–50)	1.08	4.5%
Caregiver/family's quality of life	4.4 (4–5)	4.2 (3-5)	9	9	**9**	7.9% (0–26)	1	4.2%

Bolded rank numbers represent final rankings of value elements.

NA not applicable.

all participants have a chance to (1) think about the value elements thoroughly, (2) interact with others to facilitate discussion and create consensus, and (3) share an informed view on PEx value elements. We commend the National Health Council on their recommendations and confirm the use of the Patient Engagement Rubric [30] helped enrich our study.

4.5 Cognitive Burden of the Study

Concerns have been raised on the cognitive burden of certain preference elicitation methods and its effect on the reliability of results [31]. We addressed this limitation by dividing the ranking into three consecutive votes, asking only for the top three of the 9, 6 and 3 value elements, respectively. (Notably, this did not only reduce the cognitive burden of participants, but also enabled them to change their priorities reflecting the group dynamics).

4.6 Relation to Other Research on Patient Value

The specific role of patient preferences in value assessment applications is still emerging [13, 31Previous research continues to test ways of incorporating patient preferences (e.g., discrete choice experiments) into decision contexts such as early-phase clinical development, benefit-risk assessment (regulatory specific), and health technology assessments [32]. For example, Bouvy et al. suggested presenting patient preference research as a stand-alone and distinct evidence source alongside a conventional cost-effectiveness analysis, instead of attempting to incorporate those preferences into modeling efforts [33]. Overall, our exercises are quite similar in nature to such efforts in the field, with some differences that highlight the nuance of the PEx through qualitative discussions, rankings, and weighting all in one session.

Table 4 Illustrative quotes from patients on the value elements from the online survey (S) and the workshop (W)

Name of value element	Patient quote
Ability to reach important personal milestones	(S) "Getting out of the house more and do basic activities, have social interaction and maybe being able to work more consistently. These are goals I look forward to having." (S) "When I lost the use of my legs right after I had my daughter and I couldn't take care of her." (S) "NMO diagnosis and infusions have had a huge impact on putting personal milestones on hold and focusing on health, recovery from infusions and not letting the NMO flare." (W) "I was an avid runner, and I am very, very active. So, for me not being able to do that has probably been the most detrimental."
Patient's financial burden	(S) "The stress that comes with having NMO and how it has financial been the worst burden on me and others around me." (S) "With healthcare sky rocketing and out of pocket expenses being as high as they are, absolutely the cost is important. As well as the impact of treatment i.e. a whole day lost at work, etc."
Value of hope / Balance or Timing of Risks and Benefits	(S) "If the "cure" is potentially worse than the illness then I would not be interested in the treatment." (S) "So far I feel like I've lost so much from NMO even though I have a lot of ability still. I have one eye, limited endurance and medical needs—so the risk to do more damage is pretty scary to consider." (W) "When I was diagnosed 16 years ago, I was told within 10 years they'd have a cure, so I didn't really worry too much about the fact that I've had this long-lasting illness. Sixteen years later I don't think they're any closer to a cure."
Uncertainty about long-term benefits and safety of the treatment	(S) "This value is important to me because let's face it, who wants to have serious complications later in life due to a treatment that was done. With that being said though, I am someone that is for the here and now. I want a better quality of life now. I want to experience things now and get back to as normal of a life as I can. Is it really even realistic to understand the lasting effects of such a rare disease that hasn't been studied nearly long enough to even provide information on 20 or 30 years of treatments? We are not there yet, so why do I even want to think of so far down the road." (S) "The long term safety of treatment concerns me. I often wonder if the drugs to treat the illness will do more irreparable damage to my body than the illness might do." (W) "My last flare up was in 2013 so I have been somewhat non affected for eight years. I've pushed the envelope in terms of how often I get my treatment to see how long I go without getting into trouble. (…) It's not because I don't believe in the treatment, it's simply that we just don't know, so I've become my own test case."
Patient empowerment through therapeutic advancement and technology	(S) "Since we are the ones dealing with this disease day in and day out, it is important for our doctors to sympathize and include us in decision making, but also take the time to make sure that we understand things completely. I have brain fog a lot and sometimes I cannot grasp all the information at once. Takes a minute for things to register and I get overwhelmed with anxiety not knowing what is being said or how I should be reacting." (S) "I do not feel empowered because I have to rely on a caregiver for the first time in my adult life. I have a great doctor and understand my medical data, but the decisions and day in and day out it's up to me to keep up with my medical needs, limitations, deal with insurance, schedule the checkups (I have 7 doctors) and attend all appointments. It became a part-time job to manage NMO and I have had to slow down to take care of it the best I can. If there were systems like mediation at home, that would be a huge advancement."

Table 4 (continued)

Name of value element	Patient quote
Caregiver/family's financial burden	(S) "The health insurance is under my caregiver/husband and there is an impact on schedules especially from infusions. I hate being such a burden to the person assisting me." (S) "For me, this is extremely important. I cannot stand to see my family suffer with me in this. It leaves me awake at night. If any type of treatment could help them as well as myself, then those are options I would love to have in front of me, even if some other risk factors are higher."
Patient experience related to treatment regimen	(S) "I think reducing the number of times having to go to infusion centers is always a bonus when discussing treatments. In the long run though for me, I will deal with a little pain from infusion sites or any inconvenience from time spent on treatments, if the end result is preventing future attacks." (S) "I am self employed. Having to take an entire day off for treatment is not always convenient. Also many times I drive over to [Name of city] from the [Name of region] (6+ hours round trip) and that can pose issues as well."
Therapeutic options	(S) "Any treatment that can help multiple auto immune's at the same time can be extremely beneficial, especially since these usually run in two or three's." (S) "I also have Lupus along with NMO and the current clinical trial I am in and the treatment I have received so far seems to be helping with the inflammation of my Lupus as well." (W) "If we actually have a drug that's designed for just NMO, and it would just answer all the questions. Since it's just for NMO, we don't have all these other experimental things happening."
Caregiver/family's quality of life	(S) "My diseases have taken a toll on my family members, especially when I am going through stages of my bad days with the disease. Not being to do anything for myself. The pain they have to watch me go through sometimes on a day to day basis. It is exhausting. It can break up relationships, cause too much social distancing and hard physically on all involved." (S) "When my husband still had to work and take care of the house & kids when I was sick so he had to carry a heavier burden bc he had to take care of my duties as a mother and wife as well as his normal duties as a dad and a husband and a provider." (W) "The burden or any of my family watching me go through the nerve pain and the suffrage, it puts so much stress on me. I cannot handle it because I'm very much a caregiver to other people." (W) "Caretaker quality of life is important. I am visually impaired, and I can do things, that's not too much of a problem. Since I'm in a wheelchair, I require a lot of assistance from my family. So their quality of life is very important because, you know, when they're down, I'm down, basically. One year we all got sick, my brother got sick first, then me, and then it went my mom and then it was my dad, and we're all down. It was hard because when I needed something to like, no one wanted to do it for me." (W) "Sometimes I think my friends and family worries more about what's going on than I do."

(S) The quote comes from the online survey responses; (W) The quote comes from the discussions during the workshop.

4.7 Applicability in Value Assessment

Value elements proposed in this framework could be used to support deliberative decision making by standardizing and prioritizing the list of value attributes to consider if aiming to understand the impact of health technologies on patients in a holistic manner. Alternatively, value elements can be integrated within existing value assessment frameworks through an augmented cost-effectiveness analysis, by including patient-centric domains in the calculation of incremental costs or effectiveness, or using them as cost-effectiveness threshold modifiers. Finally, value elements

could be incorporated into existing or future MCDA tools with an explicit decision rule to guide decision making [24]. For developers, the inclusion of these value elements in decision making would provide a signal for additional evidence generation in a holistic manner and, if benefit claims are supported by adequate scientific evidence, those efforts will be rewarded [9, 12].

4.8 Limitations

There are some limitations of this research. First, eliciting PEx elements from existing frameworks as an initial step may introduce a selection bias toward what constitutes value. Second, while sample size is challenging in rare disease, the sample size of the current case study can be considered small. The dropout of the patient with visual difficulties highlights a potential selection bias with a possible impact on results (patients' priorities may vary with progressing disease; however, the proposed methodology may be applicable primarily in mild or moderate disease stage), as well as a lesson to be learned for future studies including patients with severe symptoms. Nevertheless, there was another patient with NMOSD participating in the program who was blind and was still able to fully take part remotely even in the voting, using assistive devices at home. Where possible in future research, increased efforts should be made to account for recruitment and accessibility issues especially in rare diseases. It should be noted, however, that in a combined qualitative and quantitative session, larger sample sizes may increase the complexity and lose the nuance of the discussion. In addition, because NMOSD is a rare disease with treatments that were approved based on approximately 40 patients per study arm, we made every attempt to ensure a broader representation in descriptive characteristics (i.e., across age, race, and disease stage); however, a small sample size did not allow assessment of the heterogeneity of quantitative data. In terms of sample size, our case study is consistent with other patient involvement efforts such as the study by dosReis et al. where the analysis included 14 patients (representing various disease areas) [5]. Regardless, we plan to expand our analysis to at least two more rare disease areas to compare the importance of value elements across rare diseases.

Third, although this study represents engagement rather than a conventional research study that seeks to extract quantitative data alone, there were limitations to the extent patients were engaged throughout the design of the case study. One patient expert has been involved from the very beginning, but ideally, a panel of patients with NMOSD could have served as an advisory board for the research team during the full process. The pilot with two patients with NMOSD could partly counterbalance this limitation.

Fourth, the discussion during the workshop did not blind participants to the ranking results between the three consecutive cycles of voting. However, this is considered a minor source of bias, as part of the objective of the moderated discussion and voting exercises was to facilitate a consensus on the worth of PEx value elements at a group or averaged level.

Finally, NMOSD has a large representation of Spanish-speaking patients in the USA. We plan to update our framework with Spanish language materials to ensure we represent all communities not only with NMOSD but in other rare diseases moving forward.

4.9 Next Steps

The research will continue aiming to test the hypothesis if patients with different rare diseases (with variations across the nature of disease and age at onset) have different preferences towards PEx value elements. Additionally, the relative importance of conventional value elements, including clinical outcomes (i.e., survival, safety, quality of life) and cost, and the aggregate weight of additional PEx (where relative importance of PEx elements are estimated per disease basis, following the method proposed in this study) and societal value elements will be determined by a multi-stakeholder group (involving patients and their family caregivers, but also payers/decision makers, healthcare providers, academic researchers). The-long term objective is to complete a value framework for health technologies for rare diseases inclusive of PEx, societal, and conventional value elements.

We demonstrated that a combined qualitative and quantitative method is feasible and efficient, even in a rare disease such as NMOSD. For example, prioritized PEx value elements may inform value assessment applications through improving deliberations on "Other Benefits and Contextual Considerations" [3]. Specifically, instead of relying on deliberation panels to perceive the additional benefits of PEx value elements, patients can prioritize and weight those PEx value elements themselves as a separate exercise during the appraisal process. Continued applications of the proposed process will produce efficiencies over time and reduce current study duration from 6 months to 2–3 months. Furthermore, the PEx value elements need not be confined to deliberation. The findings may also flow to an "impact inventory" of all PEx value elements important to patients, providing a valuable resource for future researchers in value assessments [34–36]. Disease-specific impact inventory tables may inform an augmented cost-effectiveness analysis and MCDA applications in addition to overall evidence generation for future health technologies.

5 Conclusions

This research provides a framework for prioritizing the most important PEx value elements with a case study in rare disease. Using the method described in this study, we have demonstrated this method to be both feasible, efficient, and acceptable by patients. The process can inform value framework applications and may facilitate PEx evidence generation in early phases of health technology development to ultimately improve PEx with relevance specifically to rare diseases.

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Declarations

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Conflict of interest R. Brett McQueen, Nicholas D. Mendola, and Kavita V. Nair received funding for this work through the PhRMA Foundation Center of Excellence Grant—Center for Pharmaceutical Value (pValue), paid for by the University of Colorado. R. Brett McQueen received a grant paid to the University of Colorado by Eli Lilly and consulting fees from the Monument Analytics and Institute for Clinical and Economic Review. Kavita V. Nair received grants through the University of Colorado by Genentech, Biogen, Novartis, Gilead Sciences, Bristol Meyers Squibb, and Rocky Mountain MS Center, received consulting fees from Biogen, Novartis, and Celgene, honoraria from Sanofi, and support for attending meetings from the American Academy of Neurology and Consortium of Multiple Sclerosis Centers. Kavita V. Nair reports a leadership role as the Vice Chair at Payment, Policy and Coding Subcommittee, American Academy of Neurology. Ivett Jakab, Bertalan Németh, András Inotai, and Zoltán Kaló are employed by Syreon Research Institute. Syreon Research Institute received funding from the University of Colorado for this work. Ivett Jakab reports leadership positions as a member of the Board of Trustees, European Patients' Academy on Therapeutic Innovation Foundation, and the President of European Patients' Forum Youth Group. Jeffrey Bennett received institutional grants or contracts from Novartis, Mallinckrodt, Alexion, and the National Institutes of Health. Jeffrey Bennett reports both institutional and personal royalties or licenses and a patent of Aquaporumab, and consulting fees from MedImmune/Viela Bio/Horizon Therapeutics, Alexion, Chugai, Genentech, Genzyme, Mitsubishi-Tanabe, Reistone Biopharma, Roche, Beigene, and Abbvie. Jeffrey Bennett reports participation on a data safety monitoring board/advisory board of Roche/Genentech and Clene Nanomedicine.

Ethics approval This study was deemed exempt by the Colorado Multiple Institutional Review Board under protocol #21.340.

Availability of data and material The manuscript and the ESM contain all data generated during the study.

Code availability Not applicable.

Authors' contributions RBM, IJ, BN, AI, and ZK made contributions to the concept and design of the study. The manuscript was drafted by RBM, IJ, and AI. Analysis and interpretation of data were performed by BN, IJ, and AI. Critical revision of paper for important intellectual content was conducted by RBM, ZK, JB, and KVN. RBM, KVN, JB, and NM contributed to the provision of the patients, and administrative, technical, and logistic support. RBM, ZK, and JB supervised the study.

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