2

Preference Research: Case Studies Utilizing a Community Engaged Process

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A Community-Engaged Approach to Quantifying Caregiver Preferences for the Benefits and Risks of Emerging Therapies for Duchenne Muscular Dystrophy

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ABSTRACT

Background: There is growing agreement that regulators performing benefit-risk evaluations should take patients' and caregivers' preferences into consideration. The Patient-Focused Drug Development Initiative at the US Food and Drug Administration offers patients and caregivers an enhanced opportunity to contribute to regulatory processes by offering direct testimonials. This process may be advanced by providing scientific evidence regarding treatment preferences through engagement of a broad community of patients and caregivers.

Objective: In this article, we demonstrate a community-engaged approach to measure caregiver preferences for potential benefits and risks of emerging therapies for Duchenne muscular dystrophy (DMD).

Methods: An advocacy oversight team led the community-engaged study. Caregivers' treatment preferences were measured by using best–worst scaling (BWS). Six relevant and understandable attributes describing potential benefits and risks of emerging DMD therapies were identified through engagement with advocates (n = 5), clinicians (n = 9), drug developers from pharmaceutical companies and academic centers (n = 11), and other stakeholders (n = 5). The attributes, each defined across 3 levels, included muscle function, life span, knowledge about the drug, nausea, risk of bleeds, and risk of arrhythmia. Cognitive interviewing with caregivers (n = 7) was used to refine terminology and assess acceptability of the BWS instrument. The study was implemented through an online survey of DMD caregivers, who were recruited in the United States through an advocacy group and snowball sampling. Caregivers were presented with 18 treatment profiles, identified via a main-effect orthogonal experimental design, in which the dependent variable was the respondents' judgment as to the best and worst feature in each profile. Preference weights were estimated by calculating the relative number of times a feature was chosen as best and as worst, which were then used to estimate relative attribute importance.

Results: A total of 119 DMD caregivers completed the BWS instrument; they were predominately biological mothers (67.2%), married (89.9%), and white (91.6%). Treatment effect on muscle function was the most important among experimental attributes (28.7%), followed by risk of heart arrhythmia (22.4%) and risk of bleeding (21.2%). Having additional postapproval data was relatively the least important attribute (2.3%).

Conclusions: We present a model process for advocacy organizations aiming to promote patient-centered drug development. The community-engaged approach was successfully used to develop and implement a survey to measure caregiver preferences. Caregivers were willing to accept a serious risk when balanced with a noncurative treatment, even absent improvement in life span. These preferences should inform the Food and Drug Administration's benefit–risk assessment of emerging DMD therapies. This study highlights the synergistic integration of traditional advocacy methods and scientific approach to quantify benefit–risk preferences. (*Clin Ther.*

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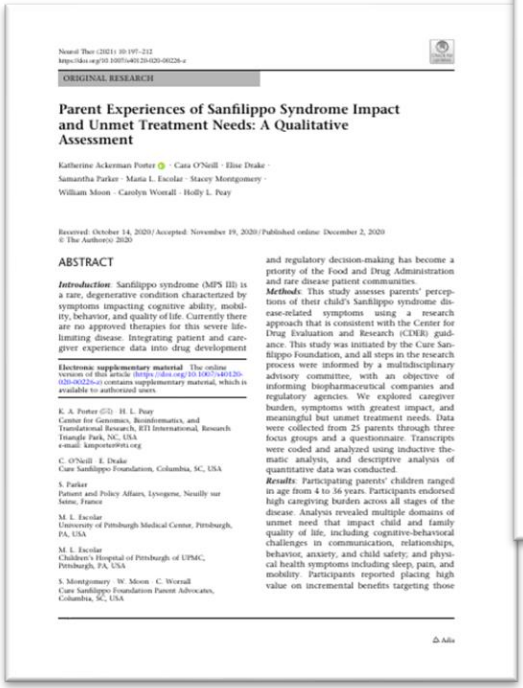
Community-Engaged Approach

- Research co-led by advocacy and researchers
- Objective and aims defined based on stated needs of disease community
- Multiple impacted parties involved in each step
- Method & attribute selection based on feasibility, meaningfulness, understandability, and relevance
- Dissemination driven by community needs

Example 1.
Sanfilippo syndrome



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ORIGINAL RESEARCH

Parent Experiences of Sanfilippo Syndrome Impact and Unmet Treatment Needs: A Qualitative Assessment

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ABSTRACT

Introduction: Sanfilippo syndrome (MPS IIIi) is a rare, degenerative condition characterized by symptoms impacting cognitive ability, mobility, behavior, and quality of life. Currently there are no approved therapies for this severe life-limiting disease. Integrating patient and caregiver experience data into drug development and regulatory decision-making has become a priority of the Food and Drug Administration and rare disease patient communities.

Methods: This study assesses parents' perceptions of their child's Sanfilippo syndrome disease-related symptoms using a research approach that is consistent with the Center for Drug Evaluation and Research (CDER) guidance. This study was initiated by the Cure Sanfilippo Foundation, and all steps in the research process were informed by a multidisciplinary advisory committee, with an objective of informing biopharmaceutical companies and regulatory agencies. We explored caregiver burden, symptoms with greatest impact, and meaningful but unmet treatment needs. Data were collected from 25 parents through three focus groups and a questionnaire. Transcripts were coded and analyzed using inductive thematic analysis, and descriptive analysis of quantitative data was conducted.

Results: Participating parents' children ranged in age from 4 to 36 years. Participants endorsed high caregiving burden across all stages of the disease. Analysis revealed multiple domains of unmet need that impact child and family quality of life, including cognitive-behavioral challenges in communication, relationships, behavior, anxiety, and child safety; and physical health symptoms including sleep, pain, and mobility. Participants reported placing high value on incremental benefits targeting those

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RESEARCH Open Access

Caregivers' assessment of meaningful and relevant clinical outcome assessments for Sanfilippo syndrome

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Abstract

Objectives: Sanfilippo syndrome is a rare multisystem disease with no approved treatments. This study explores caregiver perspectives on the most impactful symptoms and patient-relevant clinical outcomes assessments. The pediatric onset and progressive neurodegenerative nature of Sanfilippo limits use of self-report in clinical research. This study obtains Sanfilippo caregiver data to support the selection of fit-for-purpose and patient-relevant clinical outcome assessments (COAs).

Methods: We conducted an asynchronous online focus group (*n* = 11) followed by individual interviews with caregivers (*n* = 19) of children with Sanfilippo syndrome. All participants reported on the impact of disease symptoms and level of unmet treatment need across Sanfilippo symptom domains. Focus group participants reviewed existing assessments relating to 8 symptom domains (13 total assessments) and provided feedback on meaningfulness and relevance. Focus group data were used to reduce the number of assessments included in subsequent interviews to 8 COAs across 7 symptom domains: communication, eating, sleep, mobility, pain, behavior and adapting. Interview respondents provided data on meaningfulness and relevance of assessments. Data were coded using an item-tracking matrix. Data summaries were analyzed by caregivers' responses regarding meaningfulness, relevance to Sanfilippo syndrome, and based on caregiver indication of missing or problematic subdomains and items.

Results: Participants' children were 2–24 years in age and varied in disease progression. Caregivers reported communication and mobility as highly impactful domains with unmet treatment needs, followed closely by pain and sleep. Domains such as eating, adaptive skills, and behaviors were identified as impactful but with relatively less priority, by comparison. Participants endorsed the relevance of clinical outcome assessments associated with communication, eating, sleep, and pain, and identified them as highly favorable for use in a clinical trial. Participants specified some refinements in existing assessments to best reflect Sanfilippo symptoms and disease course.

Discussion: The identification of impactful symptoms to treat and relevant and meaningful clinical outcome assessments supports patient-focused drug development. Our results inform targets for drug development and the selection of primary and secondary outcome assessments with high meaningfulness and face validity to Sanfilippo syndrome caregivers. Assessments identified as less optimal might be refined, replaced, or remain if the clinical trial necessitates.

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Key Summary Points

Why carry out this study?

Sanfilippo syndrome (MPS III) is a rare, pediatric-onset, multi-symptom disorder with no approved therapies.

Integrating patient-focused drug development and the collection of patient experience data into drug development and regulatory decision-making by the Food and Drug Administration (FDA).

Our study objectives included (1) exploring caregiver perspectives on unmet treatment needs relating to managing the symptoms of Sanfilippo syndrome, and (2) describing what constitutes meaningful treatment benefits for children with Sanfilippo syndrome and their families.

What was learned from the study?

Parents reported high burden and high unmet treatment need across physical health and cognitive/behavioral/psychological domains, some with differential impact on the child and the caregivers.

Participants advocated for clinical trials that shift focus from primary cognitive outcomes to other multisystem endpoints, and perceptions of non-curative therapies revealed a preference for treatment options that stop or slow the disorder progression to maintain the child's current function to ensure quality of life; thus parents express high risk tolerance and a desire for broader inclusion criteria for trials.

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Table 2 Characteristics of participants' child with Sanfilippo syndrome

Oldest child with Sanfilippo syndrome	Median	Range
Age (in years)	8	(4–36)
	Number	%
Sanfilippo subtype		
Type A	17	68%
Type B	6	24%
Type C	2	8%
Type D	0	0%
Ever participated in a clinical treatment trial	5	20%

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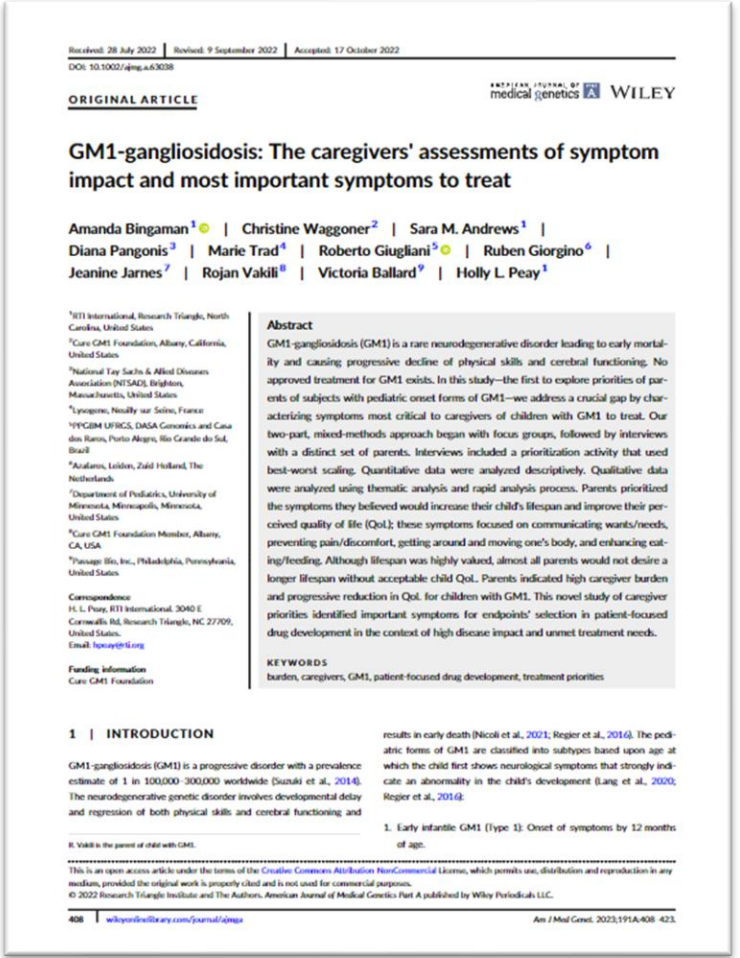
Table 3 Domains and themes: unmet treatment needs

From: Parent Experiences of Sanfilippo Syndrome Impact and Unmet Treatment Needs: A Qualitative Assessment

Domain	Symptoms	Most significant impact on…
Cognitive/behavioral/psychological impact		
	Communication	Child and family
	Relationship and social deficits	Family
	Frustration	Child
	Impulse control/aggressive behaviors	Family
	Hyperactivity	Child and family
	Unsafe behaviors	Family
	Anxiety/unhappiness in child	Child
	Sleep disturbance/nighttime waking[a]	Family
Physical health impact		
	Pain/headaches (experienced and anticipated)	Child and family
	Mobility	Child and family
	Sleep problems[a]	Child
	Illness/vulnerability to illness	Child and family
	Seizures	Child
	Feeding and maintaining nutrition	Child
	Digestive issues and toileting	Family

Example 2. GM1-gangliosidosis



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ORIGINAL ARTICLE

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GM1-gangliosidosis: The caregivers' assessments of symptom impact and most important symptoms to treat

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Abstract

GM1-gangliosidosis (GM1) is a rare neurodegenerative disorder leading to early mortality and causing progressive decline of physical skills and cerebral functioning. No approved treatment for GM1 exists. In this study—the first to explore priorities of parents of subjects with pediatric onset forms of GM1—we address a crucial gap by characterizing symptoms most critical to caregivers of children with GM1 to treat. Our two-part, mixed-methods approach began with focus groups, followed by interviews with a distinct set of parents. Interviews included a prioritization activity that used best-worst scaling. Quantitative data were analyzed descriptively. Qualitative data were analyzed using thematic analysis and rapid analysis process. Parents prioritized the symptoms they believed would increase their child's lifespan and improve their perceived quality of life (QoL); these symptoms focused on communicating wants/needs, preventing pain/discomfort, getting around and moving one's body, and enhancing eating/feeding. Although lifespan was highly valued, almost all parents would not desire a longer lifespan without acceptable child QoL. Parents indicated high caregiver burden and progressive reduction in QoL for children with GM1. This novel study of caregiver priorities identified important symptoms for endpoints' selection in patient-focused drug development in the context of high disease impact and unmet treatment needs.

KEYWORDS
burden, caregivers, GM1, patient-focused drug development, treatment priorities

1 | INTRODUCTION

GM1-gangliosidosis (GM1) is a progressive disorder with a prevalence estimate of 1 in 100,000–300,000 worldwide (Suzuki et al., 2014). The neurodegenerative genetic disorder involves developmental delay and regression of both physical skills and cerebral functioning and results in early death (Nicoli et al., 2021; Regier et al., 2016). The pediatric forms of GM1 are classified into subtypes based upon age at which the child first shows neurological symptoms that strongly indicate an abnormality in the child's development (Lang et al., 2020; Regier et al., 2016):

1. Early infantile GM1 (Type 1): Onset of symptoms by 12 months of age.

R. Vakili is the parent of child with GM1.

TABLE 4 Interviews: Oldest child with GM1-gangliosidosis (GM1) characteristics ($n = 26$)

Number of children with GM1 by type	Count	
Type 1—Early infantile	9	
Type 2A—Late infantile	9	
Type 2B—Juvenile	8	
Number of children with GM1 by gender	**Count**	
Female	10	
Male	16	
Current age of oldest child with GM1/age at death (all subtypes)	**Median**	**Range**
Age of oldest living child ($n = 21$)	7 years	1–33 years
For deceased children: Age of child at death ($n = 5$)	1 year	5 months–11 years
Age at first concerns about development	**Median**	**Range**
Type 1—Early infantile	4 months	1 month–1 year
Type 2A—Late infantile	1 year	7 months–2 years
Type 2B—Juvenile	4 years	2–5 years
Age of child at diagnosis	**Median**	**Range**
Type 1—Early infantile	10 months	1 month–2 years
Type 2A—Late infantile	2 years	1–5 years
Type 2B—Juvenile	10 years	4–12 years
Time between symptom onset and age at diagnosis	**Median**	**Range[a]**
Type 1—Early infantile	5 months	0–12 months
Type 2A—Late infantile	1 year	0–4 years
Type 2B—Juvenile	6 years	2–8 years

[a]0 indicates no time difference reported between first symptoms and age at diagnosis.

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TABLE 5 GM1-gangliosidosis Type 1: Pre-interview prioritization activity using best-worst scaling to rank importance of features/symptoms to treat ($n = 9$)

"Importance to treat" ranking of feature/symptoms
• Lifespan[a]
• Child expressing needs/wants[a]
• Pain/discomfort
• Eating/feeding
• Muscle tone
• Moving his/her body
• Senses: vision and hearing
• Child's awareness of environment and caregivers
• Fine motor skills/grasp and hold

[a]These items were tied, yielding the same mean priority score.

TABLE 6 GM1-gangliosidosis Types 2A and 2B: Pre-interview prioritization activity using best-worst scaling to rank importance of features/symptoms to treat

"Importance to treat" ranking of feature/symptoms	
Type 2A ($n = 9$)	**Type 2B ($n = 8$)**
• Lifespan	• Child expressing needs/wants
• Child expressing needs/wants	• Lifespan
• Getting around/mobility	• Getting around/mobility
• Eating/feeding	• Pain/discomfort
• Pain/discomfort	• Fine motor skills/grasp and hold
• Child reacting to environment and caregivers	• Eating/feeding
• Seizures	• Child reacting to environment and caregivers
• Fine motor skills/grasp and hold	• Clumsy/falls
• Muscle tone	• Seizures
• Clumsy/falls	• Sleep
• Sleep	• Muscle tone

Engagement learnings: Barriers and facilitators

Development:

- Time and resources
- Complexity
- Concept match
- Shared philosophy
- Priorities clearly defined
- Processes clearly defined

Interpretation:

- Diverse motivations
- Complexity
- Inclusion

Dissemination:

- Priority audiences
- Preferred approaches
- Timelines
- Community empowerment