Journal of Child Neurology
1-8

DOI: 10.1177/08830738211028388
journals.sagepub.com/home/jcn
SAGE

Development of a Quality-of-Life Survey for Patients With Succinic Semialdehyde Dehydrogenase Deficiency, a Rare Disorder of GABA Metabolism

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Abstract

Succinic semialdehyde dehydrogenase deficiency (SSADHD), a rare disorder of GABA metabolism, presents with significant neurodevelopmental morbidity. Although there is a growing interest in the concept of quality of life through patient reports as a meaningful outcome in rare disease clinical trials, little is known about the overall impact of SSADHD from the patient/family perspective. The purpose of this study was to determine issues related to quality of life and patient/family experience through a focus group discussion with family caregivers of patients with SSADHD. The discussion included the input of 5 family caregivers, and highlighted concerns related to physical function, cognitive and intellectual function, psychological and behavioral function, social function, and family impact. These themes represent appropriate starting points in the development of a quality-of-life survey that may serve as a meaningful clinical tool in future studies of SSADHD.

Keywords

inborn errors of metabolism, quality of life, outcome, intellectual disability, behavior

Received December 7, 2020. Received revised June 3, 2021. Accepted for publication June 9, 2021.

Introduction

Succinic semialdehyde dehydrogenase deficiency (SSADHD) is an ultra-rare autosomal recessive (chromosome 6p22) disorder that disrupts the normal metabolism of gamma aminobutyric acid, the major central inhibitory neurotransmitter. SSADHD is characterized by hypotonia (infantile-onset), developmental delay, cognitive impairment, expressive language deficit, ataxia and sleep disturbances. Additional clinical features may include epilepsy, as well as hyperkinetic behavior, aggression, self-injurious behaviors, and hallucinations.[1] Although the various symptoms of SSADHD have been characterized in multiple case studies, the cumulative impact of SSADHD on patients remains largely unknown.

There has been a growing interest in the assessment of quality of life (QOL) in individuals affected by rare genetic diseases to determine well-being, functioning, effectiveness of treatment options, and overall health care needs. Recently, the Food and Drug Administration has described the importance of validated patient- and observer-reported outcomes for health-related quality of life as clinically meaningful outcomes in the understanding of natural history and clinical trials.[2] Moreover, both the Food and Drug Administration and independent task forces have provided guidance on the creation of observer-reported outcome assessments in diseases where the patient cannot self-report due to functional and communication limitations, such as in SSADHD.[2,3] In rare diseases that have used observer-reported outcome instruments for determination of quality of life, most are dependent on the report of the primary family caregiver (parent, stepparent, or legal guardian)

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due to their intensive experience with their children their children.

Previous studies have demonstrated quality of life is negatively impacted in children with conditions and symptoms associated with SSADHD, including developmental delays,[4] epilepsy,[5] and sleep disturbances.[6] To date, however, there are no current research studies evaluating quality of life specifically in SSADHD.

According to the Food and Drug Administration, one of the first considerations in the development of a survey instrument intended for patient or observer reports in clinical trials is establishing content validity using feedback from the target population for determination of the relevant concepts to measure.[2] The purpose of this study was to determine what concepts in SSADHD would be appropriate starting points related to quality-of-life measures in patients. To address this, we conducted a focus group among family caregivers of patients diagnosed with SSADHD.

Materials and Methods

Preliminary SSADHD Focus Group

Approval for the study was granted by the Montclair State University Institutional Review Board (IRB-FY20-21-2241). The first steps for this project sought feedback from 2 researchers with clinical expertise in SSADHD and 2 family caregivers of patients diagnosed with SSADHD on an initial conceptual framework for a quality-of-life survey instrument (Supplementary Figure). Once finalized, this initial framework was used to create questions for the focus group interview guide. The focus group interview guide was semi-structured, consisting of primarily open-ended questions to elicit feedback from caregivers about key symptoms and signs that would serve as valid concepts in the development of a SSADHD quality-of-life survey, without targeted probing from the interviewer. Broad topics that were addressed in the interview guide included the impacts of SSADHD such as physical/clinical, cognitive/intellectual, social, and psychological impacts as well as disease burden on day-to-day living for both patients and family.

The preliminary focus group took place during a conference call that included the research team, and 5 family caregivers of patients diagnosed with SSADHD. At the beginning of the conference call, the purpose, goals, and format of data collection were described, including the broad topics that would be covered during the session. The focus group lasted 90 minutes and was conducted in English. One member of the research team served as facilitator and moderator, and took notes on the discussion. Another research team member served as assistant moderator, and took minutes and additional notes on the focus group discussion to be used in the subsequent analysis. To reduce the risk of personal bias from the facilitator and encourage participant-to-participant interactions, the facilitator's role was limited to reading the questions, distributing response turns, and encouraging personal experience sharing. Follow-up prompts to encourage further discussion were used when needed.

Data Analysis

All notes from both the moderator and assistant moderator were carefully reviewed and response patterns were documented. Notes were analyzed using a combination of deductive (based on the initial conceptual framework) and inductive content analysis techniques.[7] Common themes were identified, using words and phrases that caregivers used to describe their observations and experiences. For content validity, multiple techniques including peer debriefing and member checking were used to ensure that the themes were generated rigorously.[8,9] Briefly, the moderator and assistant moderator met to discuss their individual analyses using the notes taken during the focus group session. This discussion involved the addition, removal, merging, or splitting of themes based on consensus agreement. After consensus on focus group themes, the research team shared their preliminary analysis with a stakeholder family caregiver within the SSADHD community, to ensure that the identified themes were appropriate and meaningful to the target population. These validation approaches served to reduce bias and comprehensively generate appropriate concepts to inform on quality of life in SSADHD as observed by the family caregivers.

Results

A total of 5 participants (4 mothers and 1 father) representing 7 patients (ranging from ages 3 years to 28 years old) with SSADHD participated in the study. Analysis of focus group discussion, as captured by notes taken by the moderators, confirmed 5 broad categories related to quality of life in patients, including physical function, cognitive and intellectual function, social and emotional function, psychological and behavioral function, and family impact. Further analysis revealed specific subthemes within the broad categories which were subsequently supported by additional stakeholder input (Table 1). Overall, the focus group discussion showed that symptoms and other clinical impacts varied from patient to patient and that the majority of symptoms and other clinical impacts appeared to become debilitating with age. The initial framework was revised based on the themes generated from the focus group discussion (Figure 1).

Physical Function

All participants shared concerns related to physical function. Problems related to motor coordination, sleep patterns and fatigue, sensory processing, and seizures were discussed (Table 1). With respect to motor coordination, 3 participants specifically mentioned crawling, walking, and feeding as challenges to individuals with SSADHD, particularly in younger children. One participant mentioned that their child "falls a lot" while another stated that "crawling was dis-coordinated" for their child. Sensory processing issues usually manifested in the form of self-stimulating behaviors. On this topic, 3 participants described oral, tactile, aural, and other whole-body behaviors for self-stimulation or self-soothing. One participant stated how their child used "her hand to hit at something constantly"; another also described "hand-slapping" as a common occurrence in their children.

Although most participants in the focus group provided care for children who did not experience seizures, one caregiver

Table 1. Generated Themes From Focus Group With Family Caregivers of Patients With SSADHD.

Broad Category	Code/Theme	Supporting Quotes
Physical function	Motor skills / coordination / musculoskeletal	• Symptoms/challenges ○ "Hypotonia/hyporeflexia" ○ "Poor balance" ○ "Falls a lot" ○ "Motor planning is the hardest, brain-body connection is the worst." ○ "Reflexes and motor skills are bad." • Walking: "Couldn't walk through a door without hitting one side of it. " • Crawling ○ "Crawling is very dis-coordinated" ○ "Has to move arms first, then legs" • Feeding ○ "Doesn't chew well"
	Fatigue	• "Significant fatigue in doing whole body movements" • "Tired, drowsy all day." • "Checked out all day, tired" • "Wiped out, couldn't do anything" • "Sometimes fatigue takes over intentional control" (regarding potty training) • What happens on a good day? ○ "When she has stamina." ○ "So she has enough energy through the day to dance and sing, all the things she likes to do" • Sleep ○ Patterns ▪ "One week where she'll sleep solid all night, other weeks when she has a party in her bed." ▪ "She's just up, not upset. For the first few years she would be up for a few hours. She's chatty, playing with her bear in bed" ▪ "Recently it's been hard to get her to go to bed. Bedtime is 8 pm but she's been getting down at 11:30 pm. Not enough sleep since she gets up at 5 am." ▪ Difficulty falling asleep, staying asleep, and getting up. ○ Impact on daily activities ▪ "Falling asleep, up early," ▪ "Fallen asleep on her horse at hippotherapy" ▪ "Sometimes they pass out in the middle of the day" ○ What happens on a good day? ▪ "Slept well" ▪ "Sleeping solid through the night"
	Sensory processing / self-stimulatory behavior	• Hands ○ "Waves her hand" ○ "[My child] will open and close her hands" • Striking something with hands/arms ○ "Hand slapping" ○ "Use her hand to hit at something constantly" ○ "Hit her hand on the side of her bed" ○ "She'll put her arms down and bang them on the tray of her high chair" • Whole Body ○ "Twirling around" ○ "Sways side to side" • Oral ○ "Thumb in her mouth," • Aural ○ "Makes a high-pitched moaning sound" • Head ○ "Cock their head a little to the side" ○ "Head cocked to one side" • Self-harm ○ "She will self-harm (poke her eyes really hard)." ○ "Throw her body into the wall." • Stimuli ○ "When she's excited the hand behaviors increase"

(continued)

Table 1. (continued)

Broad Category	Code/Theme	Supporting Quotes
	Seizures	• "Many times it happens after puberty, a lot of time with girls. I know quite a lot of families with young children who have seizures." • "A lot of families struggle with seizures. From a really young age they need to be battling seizure medications. One . . . [parent's] daughter (who was pretty high functioning) has seizures to a point where it wiped out all the progress she's made. There's things she can't do now that she was able to do for 25 years. I think it's as high as 90% for the rate of seizures in the literature. It's life changing to start getting seizures during puberty."
Cognitive/ intellectual	Developmental milestones	• Potty training ○ "Issues with potty training" ○ "Toilet training came years later compared to a typical child" • "Little over 3 but is not walking"
	Processing	• "Intellectually he can't keep up with the other kids (needs more processing time" • "IQ test are very misleading because it doesn't take into account processing speed, apraxia, etc" • What happens on a good day?: "when the apraxia isn't so bad"
Psychological/ behavioral	Greater issue in older children compared to younger children, where physical issues are more urgent	• "But now that she's older it's more about the disobedience." • "The behaviors of the older children is hard to explain to others."
	Mood	• Good day: "She's able to sit calmly and play alone with herself." • Bad day: "Being very uncooperative (in terms of potty training). Refusal to eat, refusal to obey, listen, in any form."
	Secondary disorders	• OCD ○ "OCD is a global impact on [my son's] life" ○ Bad day: "When his OCD takes over what he does." • ADHD • "Both children have ADHD, hard for them to stay in one place"
Social	Interactions	• Decreased interaction with peers ○ "He gets nowhere in social settings at times." ○ "She can't follow games and conversation as quickly" ○ "She doesn't get invited to things like the other kids" ○ "Doesn't know how to play as the other kids" ○ "Doesn't understand that she is different from anybody else" ○ "Need 30 more seconds to deliver a response (especially a motor response)" • Negative interaction with peers ○ "He'll put a complete stranger's hood up. He would physically move a person if they're on the swing he wants to go on." ○ "Evelyn misses a lot of social cues. Personal space. She takes other people's food." ○ "kids mimic her" • School/work ○ "She gets picked on in school" ○ ADHD "Affects school" ○ "A bad day is when [my child] didn't do good at work." • Awareness of social challenges (one child's experience) ○ "Emotional intelligence is quite high" ○ "She understands that she doesn't get invited" ○ "She wants to interact so badly with other children" • What happens on a good day? ○ "To see [my child] interact with people" ○ "To see him engage with something. Something that he's capable of joining in whether physically or socially" ○ "When she gets invited to play on the playground" ○ "When [my child] uses Proloquo2go to make a funny comment" (Good day)
	Lack of independence	• "She knows her parents have to go with her" • "Needs supervision" • "Doesn't feed herself yet"
	Communication	"She talks some, not great, but she can communicate."

(continued)

Table 1. (continued)

Broad Category	Code/Theme	Supporting Quotes
Family impact	Caregiver burden	• "Keeping an eye on them is essential because they'll wander off" • "It kind of took over my whole life. We have therapy five days a week. Everything on the weekend is special needs programming." • "Constant therapy, extra attentive to where you go and who you're around" • "Took a year off work to provide care for her (wouldn't take her to a daycare even if that was possible)" • "Takes over your life with therapy and appointments. I'm not working anymore, not an option for me anymore." • "I homeschool her, we don't have great options out here. It's a 24/7 job." • "We can't leave her with just anyone."
	Isolation	• "Families feel so isolated, it's such a bad feeling. Other diseases have groups and local chapters. With a rare disease, you just don't have that. You have to educate everyone (teachers, medical team). You never feel you're in a place where someone is offering support."
	Impact on relationships	• Family ○ "Limits what we (husband and I) can do" ○ "Definitely affects marriage." • Friends ○ "Makes my life different in terms of friends, even the ones with children." ○ "Friendships are definitely affected. I can't be around friends who complain a lot about their typical children, I just can't handle it." ○ "Other friendships have gotten deeper because of it, some friends have really stepped up."
	Coping	• Cognitive coping ○ "I've gotten used to certain behaviors, I don't hear even hear Jack's humming noise anymore." ○ "It changes how you view things." ○ "We have no regrets. It's hard to talk about. It's life altering, I can't imagine life any other way." • Behavioral coping ○ "We as a family have modified our behavior to make their lives easier and our lives easier. I know now not to bring them into certain situations. I can't bring them to certain social settings which has had an impact on our life." ○ Advocacy ▪ "We started the association, wholeheartedly jumped into this. It's made us who we are." ▪ "The best news you can give a family is that they're not alone."

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder; SSADHD, succinic semialdehyde dehydrogenase deficiency.

stated that seizures appeared primarily after puberty in female patients with SSADHD (Table 1).

Cognitive/Intellectual Function

Study participants discussed the impact of SSADHD on cognitive and intellectual function in their children. Several participants described delays in reaching developmental milestones; 2 parents addressed delays in toilet training and one addressed delays in walking. One parent discussed issues with processing speed as well as apraxia, which impeded school performance (Table 1). Another participant mentioned that their child "intellectually . . . can't keep up with the other kids" and "needs more processing time."

Psychological/Behavioral Function

Participants also discussed psychological and behavioral issues in their children with SSADHD. Many of these issues became more evident as patients grew older. Three participants described frequent defiance and opposition to authority, often related to the patient's overall mood. Neuropsychiatric manifestations, such as obsessive-compulsive disorder and attention-deficit/hyperactivity disorder were also discussed among 2 parents of older children with SSADHD (Table 1).

Social Function

Social function in individuals with SSADHD was another topic discussed among participants during the focus group. Three

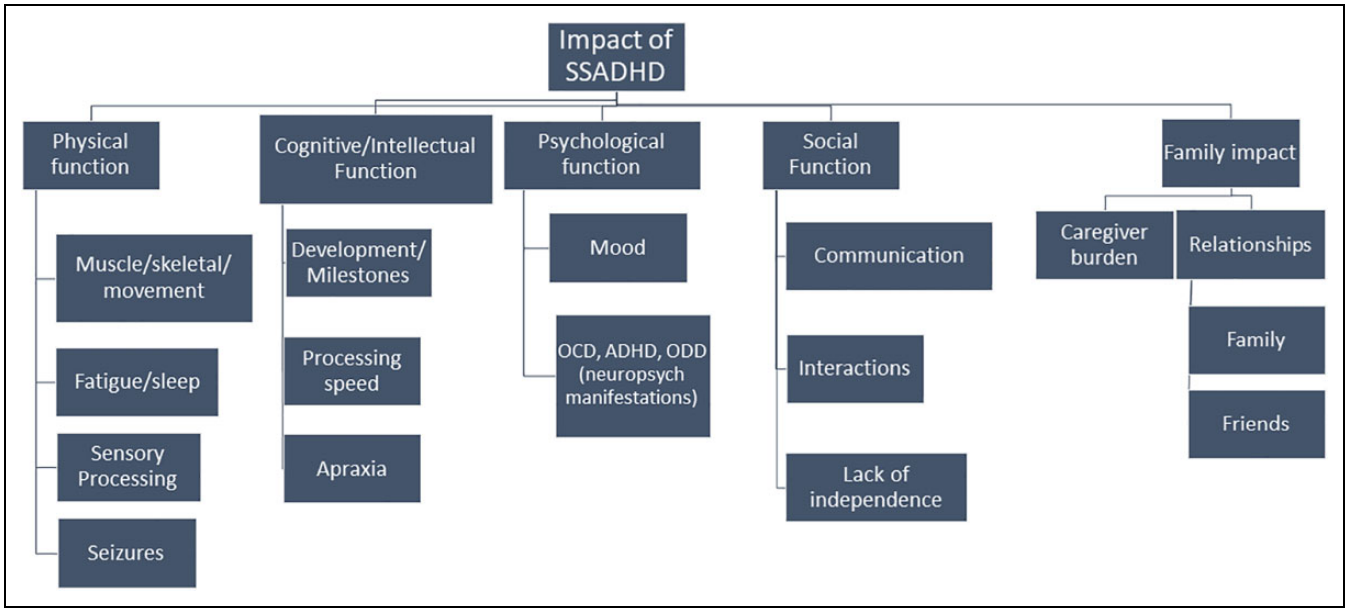

Figure 1. QOL framework for SSADHD. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder; ODD, oppositional-defiant disorder; QOL, quality of life; SSADHD, succinic semialdehyde dehydrogenase deficiency.

participants described overall decreased or generally negative interactions between their children with SSADHD and their peers. This included inappropriate behaviors from children with SSADHD, peers mimicking and mocking behaviors in patients, and patients often not being included or invited to participate in activities with peers. Concerns from these participants were that their child "gets nowhere in social settings at times" or "Doesn't know how to play as the other kids" (Table 1). Two participants also identified the overall lack of independence of their child as a limiting factor to social interactions (Table 1).

Family Impact

Participants discussed the overall impact of SSADHD on the nuclear family, beyond the sole impact of the disease on the patient. Three participants described the considerable burden that they felt with the multitude of tasks required in being the family caregiver of a patient (or patients) with SSADHD. One participant stated that being a caregiver "takes over your life with therapy and appointments" and had to stop working as a result (Table 1). Two parents described feeling isolated from friends and family members due to their responsibilities, their differences in family experiences and a perceived lack of understanding from others (Table 1). Nevertheless, most participants also discussed various coping strategies to help manage their experience as the caregiver of an individual with SSADHD (Table 1).

Discussion

We report an initial summary of themes that may inform the development of a quality-of-life survey relevant to the experience of SSADHD, using input from family caregivers. SSADHD presents with broad clinical heterogeneity,[10] which poses challenges in the development of meaningful clinical outcomes in therapeutic trials.[11] Considering this challenge and the recent Food and Drug Administration guidance to better incorporate patient voices in clinical trials for both common and rare disorders,[2,3] a clinical outcome assessment such as a quality-of-life survey tool may be an appropriate clinical endpoint to understand the overall impact of SSADHD and determine the effectiveness of available and future therapeutics. Our preliminary data with family caregivers of patients suggest that several concepts of interest, including motor coordination issues, seizures and related neuropsychiatric morbidity, align with the published literature that describes the broader phenotype of SSADHD.[1,10,12] However, certain concepts, such as the social impact of SSADHD, are not as well characterized in the literature and potentially warrant further investigation. Patient-reported outcomes that include social functioning domains have demonstrated poorer results in patients with neuropsychiatric disorders,[13,14] suggesting that a social functioning domain may be valid as part of a quality-of-life construct for SSADHD.

Our focus group interview also revealed that SSADHD has a significant impact on the nuclear family. Although the Food and Drug Administration recommends that outcome measures in clinical trials be solely based on the patient, the knowledge of the impact of the disease on the nuclear family is highly relevant to the success of such trials, for improvement of the quality of life of the caregivers is key to compliance to treatment and thus to treatment effectiveness. Further, the coping mechanisms described by families may be useful in the identification of new resources and tools to improve family caregiver experience in the management of SSADHD, which may translate to better management of the patients' quality of life.

Limitations and Future Directions

This study revealed concepts and subdomains that validate their use in a future quality-of-life survey instrument for SSADHD, but it is only the first step in the development of such a survey instrument. The focus group represented only 7 patients, a limitation of our approach. However, considering that SSADHD is an ultra-rare disorder with 200 to 400 patients worldwide, data collected from 7 patients may provide a reasonable account of the overall SSADHD population as a first step. Future studies with more participants from diverse backgrounds will ensure that concepts identified in this study are valid across demographic variables and disease presentations.

Both demonstration of concept saturation and cognitive interviewing are important steps to ensure content validity, respondent comprehensibility of survey items, and accurate reflection of the patient experience in quality-of-life surveys.[2,3] Hence, our study will need to be followed up by additional and more targeted focus groups to achieve concept saturation, where no new concepts related to quality of life are introduced by the participants. Only then, will data collection be deemed sufficient to draft a quality-of-life survey. Once this is accomplished, cognitive interviewing of SSADHD caregivers will be conducted to determine whether the target population understands the question items as intended by the authors, or if further modifications are needed.

As this was a preliminary study, the focus group was not recorded, and therefore certain themes related to changes in tone or gesture during the focus group may have not been captured in the notes of the moderators. Future focus groups to assess for concept saturation will be recorded to capture all aspects of the discussions, including the more implicit indications.

Conclusion

We have developed the foundation of a meaningful clinical outcome tool for SSADHD patients and their families. Subsequent progress in this initiative will augment studies related to the natural history characterization and further clinical trials in SSADHD.

Acknowledgments

The authors would like to thank the SSADH Association and Speragen, Inc for their valuable guidance in the execution of this study, and Melisa J. Lopez for her assistance in preparing the manuscript for publication.

Author Contributions

MB (bosem@montclair.edu) made a substantial contribution to the conception and design of this work, acquisition, analysis and interpretation of data, and in drafting and revising the manuscript for content. JBR made a substantial contribution in the acquisition, analysis, and interpretation of data, and participated in drafting and revising the manuscript for content. KMG made a substantial contribution in the acquisition, analysis, and interpretation of data, and participated in drafting and revising the manuscript for content. WBR made a substantial contribution in the acquisition, analysis, and interpretation of data. HMM made a substantial contribution in the acquisition, analysis, and interpretation of data. AM made a substantial contribution in the acquisition, analysis, and interpretation of data. CAH made a substantial contribution in the acquisition, analysis, and interpretation of data. MLD made a substantial contribution in the acquisition, analysis, and interpretation of data, and participated in drafting and revising the manuscript for content. PLP made a substantial contribution in the acquisition, analysis, and interpretation of data.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by a Training and Career Development Award to MB (10 U54 DK 83916) from the Rare Disease Clinical Research Network, and the Sterol and Isoprenoid Research Consortium to WBR (U54 HD061939) of the National Center for Advancing Translational Sciences and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and NIH.

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Supplemental Material

Supplemental material for this article is available online

Ethical Approval

Approval for the study was granted by the Montclair State University Institutional Review Board (IRB-FY20-21-2241). All participants provided written consent for the study.

References

1. Pearl PL, Wiwattanadittakul N, Roullet J-B, Gibson KM. Succinic Semialdehyde Dehydrogenase Deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews®*. University of Washington, Seattle; 1993. www.ncbi.nlm.nih.gov/books/NBK1195.
2. US Department of Health and Human Services, Food and Drug Administration. Guidance for industry-patient-reported outcome measures: Use in medical product development to support labeling claims.
3. Benjamin K, Vernon MK, Patrick DL, Perfetto E, Nestler-Parr S, Burke L. Patient-reported outcome and observer-reported outcome assessment in rare disease clinical trials: An ISPOR COA Emerging Good Practices Task Force report. *Value Health*. 2017; 20(7):838-855. doi:10.1016/j.jval.2017.05.015.
4. Hsieh R-L, Hsueh Y-M, Huang H-Y, Lin M-I, Tseng W-C, Lee W-C. Quality of life and impact of children with unclassified developmental delays: quality of life of developmental delays. *J Paediatr Child Health*. 2013;49(2): E116-E121. doi:10.1111/jpc.12081.

5. Austin JK, Smith MS, Risinger MW, McNelis AM. Childhood epilepsy and asthma: comparison of quality of life. *Epilepsia*. 1994;35(3):608-615. doi:10.1111/j.1528-1157.1994.tb02481.x.
6. Jarasvaraparn C, Zlomke K, Vann NC, Wang B, Crissinger KD, Gremse DA. The relationship between sleep disturbance, quality of life and psychosocial functioning in pediatric patients with inflammatory bowel disease. *Ann Gastroenterol Dig Disord*. 2018;1(1):9-25.
7. Elo S, Kyngäs H. The qualitative content analysis process. *J Adv Nurs*. 2008;62(1):107-115. doi:10.1111/j.1365-2648.2007.04569.x.
8. Patton MQ. *Qualitative Evaluation and Research Methods*. 2nd ed. Sage; 1990.
9. Lincoln YS, Guba EG. But is it rigorous? Trustworthiness and authenticity in naturalistic evaluation. *New Directions for Program Evaluation*. 1986;1986(30):73-84. doi:10.1002/ev.1427.
10. Malaspina P, Roullet J-B, Pearl PL, Ainslie GR, Vogel KR, Gibson KM. Succinic semialdehyde dehydrogenase deficiency (SSADHD): pathophysiological complexity and multifactorial trait associations in a rare monogenic disorder of GABA metabolism. *Neurochem Int*. 2016;99:72-84. doi:10.1016/j.neuint.2016.06.009.
11. Vogel KR, Ainslie GR, Walters DC, et al. Succinic semialdehyde dehydrogenase deficiency, a disorder of GABA metabolism: an update on pharmacological and enzyme-replacement therapeutic strategies. *J Inherit Metab Dis*. 2018;41(4):699-708. doi:10.1007/s10545-018-0153-8.
12. Pearl PL, Gibson KM, Cortez MA, et al. Succinic semialdehyde dehydrogenase deficiency: lessons from mice and men. *J Inherit Metab Dis*. 2009;32(3):343-352. doi:10.1007/s10545-009-1034-y.
13. Subramaniam M, Soh P, Ong C, et al. Patient-reported outcomes in obsessive-compulsive disorder. *Dialogues Clin Neurosci*. 2014;16(2):239-254.
14. Handisides JC, Hollenbeck-Pringle D, Uzark K, et al. Health-related quality of life in children and young adults with Marfan syndrome. *J Pediatr*. 2019;204:250-255.e1. doi:10.1016/j.jpeds.2018.08.061.