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DRAVET ENGAGE. Parent caregivers of children with Dravet syndrome: Perspectives, needs, and opportunities for clinical research

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ABSTRACT

Dravet syndrome (DS) is an intractable developmental and epileptic encephalopathy significantly impacting affected children and their families. A novel, one-time, adeno-associated virus (AAV)-mediated gene regulation therapy was designed to treat the underlying cause of DS, potentially improving the full spectrum of DS manifestations. To ensure the first-in-human clinical trial addresses meaningful outcomes for patients and families, we examined their perspectives, priorities, goals, and desired outcomes in the design phase through a mixed methods approach (quantitative and qualitative). We conducted a non-identifiable parent caregiver survey, shared through a patient advocacy organization (n = 36 parents; children age ≤6 years). Parents were also engaged via three group discussions (n = 10; children age 2–20 years) and optional follow-up in-depth individual interviews (n = 6). Qualitative data analysis followed an inductive interpretive process, and qualitative researchers conducted a thematic analysis with a narrative approach. Survey results revealed most children (94%) were diagnosed by age 1, with onset of seizures at mean age 6.2 months and other DS manifestations before 2 years. The most desired disease aspects to address with potential new disease-modifying therapies were severe seizures (ranked by 92% of caregivers) and communication issues (development, expressive, receptive; 72–83%). Qualitative results showed the need for trial outcomes that recognize the impact of DS on the whole family. Parents eventually hope for trials including children of all ages and were both excited about the potential positive impact of a one-time disease-modifying therapy and mindful of potential long-term implications. Participants reflected on the details and risks of a clinical trial design (e.g., sham procedures) and described the different factors that relate to their decision to participate in a trial. Their main aspirations were to stop neurodevelopmental stagnation, to reduce seizures, and to reduce the impact on their families' wellbeing. To our knowledge, this is the first study within a patient-oriented research framework that specifically explored parents' needs and perceptions regarding clinical trials of a potential disease-modifying therapy for children with a severe, developmental disease, such as DS.

1. Introduction

Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy, estimated to occur in 1:15,500 children [1]. Dravet syndrome signs typically emerge in the first year of life and are characterized by frequent prolonged seizures, status epilepticus events, significant cognitive delays, sleep abnormalities, motor impairment, and profound behavioral difficulties that resemble autism, repetitive behaviors, and attention deficit hyperactivity disorder [2–7]. Many children require 24-h care, and mortality prior to adulthood is estimated at 15–20% [2,8].

At least 85% of DS cases are caused by complete loss-of-function pathogenic variants in a single copy of the *SCN1A* gene, which encodes for the alpha subunit of the $Na_V1.1$ sodium channel, lead-

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ing to haploinsufficiency [9]. As the effects on the sodium channel appear to contribute to the encephalopathy independently of the seizures, DS is considered a channelopathy [10]. Currently approved therapies for DS are aimed at reducing the seizure burden, but they rarely lead to lasting seizure resolution and do not address the underlying pathogenesis or neurodevelopmental and behavioral manifestations of the disease [11,12].

The DS treatment landscape is progressing from symptomatic treatments to disease-modifying therapies with the potential to address the full range of disease manifestations. Some of the investigational therapies currently in development not only seek to eliminate or substantially reduce seizure burden but also prevent or halt progression of the neurodevelopmental stagnation, behavioral symptoms, and motor impairment associated with DS. Specifically, advanced therapies in or near clinical trials include an antisense oligonucleotide (STK-001, Stoke Therapeutics, Bedford, MA, USA) and a gene regulation therapy (ETX101, Encoded Therapeutics, South San Francisco, CA). Antisense oligonucleotides are designed to enhance the efficiency of an RNA processing step to increase functional *SCN1A* mRNA and $Na_V1.1$ protein expression in *SCN1A*-expressing cells via chronic intrathecal administration [13]. Gene regulation therapy uses an adeno-associated virus (AAV) vector to drive production of an engineered transcription factor (eTF^{SCN1A}) that promotes transcription of endogenous *SCN1A* and increases $Na_V1.1$ channel density specifically within the inhibitory GABAergic neurons, the primary cell type affected in DS [14]. This gene regulation therapy is delivered via a single, one-time intracerebroventricular (ICV) administration. In preclinical studies, both disease-modifying therapies extended survival and reduced seizure frequency in DS mouse models and were well-tolerated in non-human primates [13–15].

In the development of therapies for rare diseases, meaningful engagement of parent caregivers in the study design phase allows for the incorporation of their perspectives, priorities, goals, and desired outcomes [16] and ensures that study endpoints are relevant not only to physicians, regulatory authorities, and payers, but also to patients and their families. With this in mind, regulatory and health technology assessment authorities have implemented frameworks to include patient and caregiver perspectives along the lifecycle of new therapeutic products [17–19].

Parents of children with DS assume the roles of primary caregiver, advocate, and decision maker in their child's care. Given their experience living with DS, it is imperative to consult with parents. Their insights inform clinical development of a potential disease-modifying therapy and shape our understanding of what are the most meaningful aspects of their children's lives for which treatment could have the greatest impact. Here, we report the results of a quantitative survey and qualitative study with parents of children with DS to understand their experiences, perspectives, values, and preferences regarding their children's participation in clinical trials, as well as their views on the proposed design of a first-in-human trial of a novel gene regulation therapy.

2. Materials and methods

This research was conducted in two parts: a quantitative survey and qualitative discussion groups and interviews.

2.1. Quantitative survey

2.1.1. Sampling and recruitment

On behalf of Encoded Therapeutics, the Dravet Syndrome Foundation (DSF, USA) distributed an online survey between October and mid-November 2020 to parents of children under 6 years of age living with DS via the Dravet Parent & Caregiver Support Group on Facebook. Participation in the survey was voluntary, data were collected anonymously, and permission to use survey data was obtained from respondents at the beginning of the survey. Encoded personnel had no contact with survey respondents and received no identifiable information.

2.1.2. Data collection

The survey was developed to explore, from the caregiver perspective, which non-seizure aspects of DS the parents would like to see alleviated by a new potentially disease-modifying therapy. The nineteen survey questions were informed by a review of the published DS literature and similar rare disease caregiver surveys. Specific aspects of DS were selected based on published literature, assessments in the draft clinical trial protocol, and input from DSF on the relevance of topics and language used within the survey. Response categories included five-point Likert scales, rankings of lists, closed-question multiple choice, and open response.

2.1.3. Data analysis

All data were summarized descriptively. Categorical measurements were presented using counts and proportions, and continuous measurements were presented using sample statistics including mean, standard deviation (SD), median, minimum, and maximum. Select variables were presented graphically to aid interpretation of overall trends. Missing data were not imputed. Where data were missing, the remaining data were summarized with reduced denominators.

2.2. Qualitative study

2.2.1. Study design

We used a mixed-methods design within a patient-oriented research framework that entailed narrative qualitative methodology, collecting data through observations, three discussion groups, and in-depth individual interviews with parent caregivers of children with DS [20]. This research was approved by the New England Institutional Review Board.

Patient-oriented research aims to help design and conduct studies "with" patients and families rather than "for" them [21]. The process engages patients and families in the production and dissemination of scientific knowledge through close collaboration among stakeholders (e.g., caregivers, clinicians, and medical and social scientists).

2.2.2. Sampling and recruitment

Parents of children of any age with SCN1A+ DS were recruited through outreach from the DSF and Dravet Syndrome UK. Interested parents were introduced to the Encoded Patient Advocacy team (EJ) who explained the details, objectives, and ultimate goals of the research. Inclusion criteria were the ability to speak, to understand and read English, and to have experience living with and caring for a child with DS. The study included parents with and without prior clinical trial experience. One parent from each household provided consent to participate in the research and for use of their data for subsequent publication and was provided an honorarium for their participation.

For the qualitative portion of the study, we used a non-randomized, purposeful sampling strategy consistent with a qualitative approach [22,23] and published literature on experiences with DS [24–26].

2.2.3. Data collection

Parents participated in a discussion group with researchers to give their perspectives on clinical trials for children with DS and to explore their views on the trial design for a first-in-human trial of ETX101 gene therapy. Prior to the discussion group, parents

completed an online survey via Survey Monkey (separate from the DSF survey described above) exploring their experiences with diagnosis and management of DS. Participation in the survey was voluntary, data were collected anonymously, and results were presented in aggregate form for purposes of guiding the discussion groups. The survey questions were informed by a review of published literature on DS and similar rare disease caregiver surveys. Response options included four- and five-point Likert scales, rankings of lists, closed-question multiple choice, and open response.

The discussion groups took place via an online meeting platform. At the start of the meeting, a potential clinical trial design and procedures were presented and explained to the parents (Supplemental Fig. 1). The proposed blinding and sham procedures of the trial would require that trial participants be randomly allocated to the gene therapy arm or to the delayed gene therapy control group. Children in both groups would be put under general anesthesia. The gene therapy group would receive the investigational gene therapy product (administered by ICV injection through a burr hole in the skull), while the control group would undergo a sham procedure consisting of a partial thickness burr hole in the skull, with no injection. If the gene therapy demonstrated acceptable safety after four months of follow-up, children in the delayed-gene therapy control group would receive the investigational gene therapy.

Parents and researchers were then separated into three breakout rooms for discussion (n = 3–4 parents per room). Discussions were audio recorded, and observations were conducted during the breakout sessions by two expert qualitative researchers and social scientists (CJP and NK). A semi-structured guide with guiding prompts and questions was employed to facilitate discussions and elicit parents' views [24–31]. Parents willing to share their perspectives in more detail in a private conversation were interviewed individually by the qualitative researchers (NK and CJP) at a later date, using a semi-structured interview guide based on preliminary interpretive analysis of the discussion group observations and data. Interviews took place over the phone or using an online meeting platform with both interviewer and interviewee in a private, quiet place to facilitate confidentiality.

For the discussion groups and interviews, digital audio-recordings were transcribed verbatim, and transcripts were reviewed for accuracy and de-identified for anonymity and confidentiality. Electronic files were encrypted and password protected, and access was restricted to the qualitative study personnel. Prior to the conversations' starting, parents gave verbal and written consent, were informed of the audio recording and were offered the opportunity to withdraw their participation at any time up until the analysis began.

2.2.4. Data analysis

In keeping with qualitative methodology, data analysis followed an inductive interpretive process, and thematic analysis with a narrative approach was performed [32]. This analysis entailed familiarization with the data from the discussion groups and interviews, coding subsets of transcripts in a concurrent and iterative process, organization of the codes, thematic development and discussion, hierarchical organization of the themes, definition of themes, and interpretation and contextualization of the identified themes [33]. Pamphilon's zoom-in-out technique [34] and writing throughout the analytical process were used as analytical devices to engage in a value-adding analysis [35].

3. Results

3.1. Quantitative survey

Thirty-six parents of children living with DS responded to the caregiver survey distributed by DSF via the Dravet Parent & Caregiver Support Group on Facebook; 34 of these parents had a child with a confirmed *SCN1A* mutation by genetic testing. As shown in Table 1, 11 children were ≤2 years old, 14 children were 3–4 years, and 11 children were 5–6 years old. Most children (94%) were diagnosed with DS by 1 year of age. Severe seizures were reported by nearly all parents (94%) as an early symptom (mean 6.2 months). First onset for other aspects of DS was reported at a mean 1–2 years old and included delays in communication development (89%) and expressive communication (83%), as well as problems with executive function (72%), sleep (78%), motor function (53–69%), and social (50%) and emotional (47%) behavior (Fig. 1). One-third of parents reported difficulties with eating or feeding. While 56% of respondents overall reported behavioral problems at mean onset at 2 years 3 months, the frequency increased with age (27.3% for children ≤2 years old; 64.3% for children 3–4 years; 72.7% for children 5–6 years old).

Proportions of children who experienced various manifestations of DS in the last six months are displayed by age group in Table 2. While executive function is challenging to assess in infants, issues with executive function were more frequently

Table 1
Characteristics of survey respondents.

	Children ≤2 years (N = 11)	Children 3–4 years (N = 14)	Children 5–6 years (N = 11)	Total (N = 36)
Caregiver is the child's birth parent, n (%)	11 (100)	14 (100)	11 (100)	36 (100)
Caregiver's age, n (%)				
21–29 years	3 (27.3)	1 (7.1)	1 (9.1)	5 (13.9)
30–39 years	7 (63.6)	10 (71.4)	5 (45.5)	22 (61.1)
40–49 years	1 (9.1)	3 (21.4)	5 (45.5)	9 (25.0)
Child's age, n (%)				
<1 year	2 (18.2%)	–	–	2 (5.6%)
1 year	2 (18.2%)	–	–	2 (5.6%)
2 years	7 (63.6%)	–	–	7 (19.4%)
3 years	–	4 (28.6%)	–	4 (11.1%)
4 years	–	10 (71.4%)	–	10 (27.8%)
5 years	–	–	8 (72.7%)	8 (22.2%)
6 years	–	–	3 (27.3%)	3 (8.3%)
Confirmed *SCN1A* + Dravet syndrome diagnosis, n (%)	10 (90.9)	13 (92.9)	11 (100)	34 (94.4)
Child's age at diagnosis, n (%)				
<1 years	9 (90.0%)	5 (38.5%)	4 (36.4%)	18 (52.9%)
1 years	1 (10.0%)	6 (46.2%)	7 (63.6%)	14 (41.2%)
2 years	0	2 (15.4%)	0	2 (5.9%)

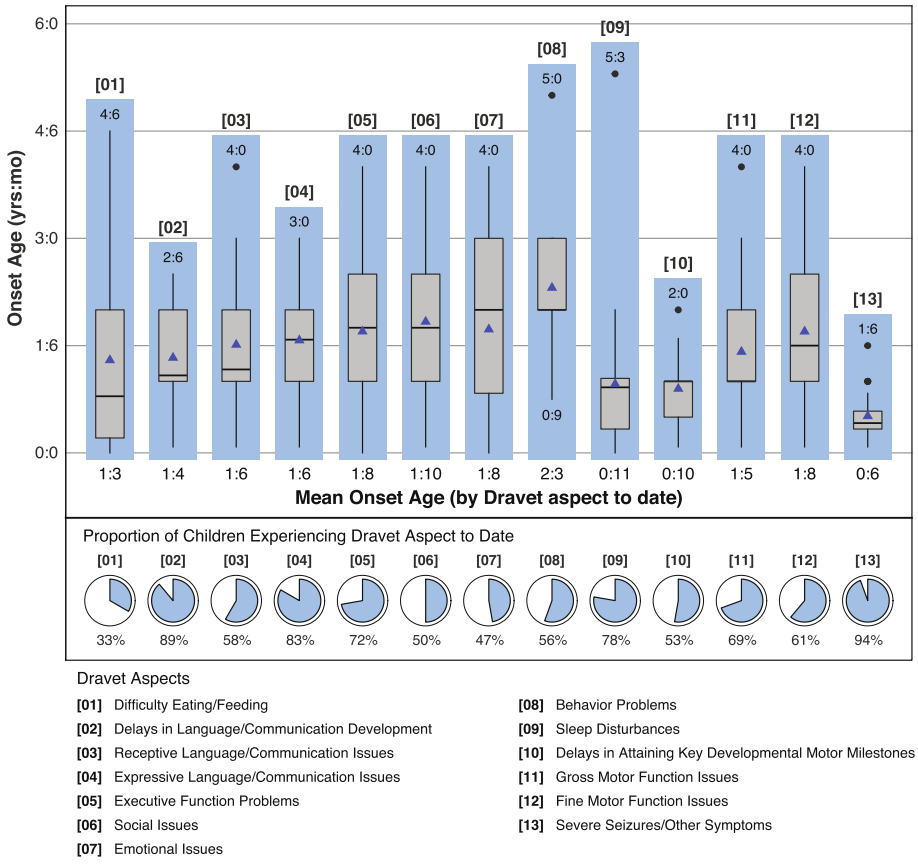

Fig. 1. Onset age and proportion of children experiencing aspects of Dravet syndrome to date. Boxplots in the upper panel display the spread of the onset age for each aspect reported by respondents whose children have experienced the aspect to date (pie charts in the mid panel). The blue triangles in the boxplots pinpoint the mean onset age and are marked at the bottom of each boxplot for clarity (age in years: months). The maximum age is marked at the top of each boxplot. The reference for Dravet aspects [1] to [13] is located in the lower panel.

Table 2
Proportion of children experiencing aspects of Dravet syndrome in the last six months.

Dravet Aspect		Children ≤2 years ($N = 11$)	Children 3–4 years ($N = 14$)	Children 5–6 years ($N = 11$)
[01]	Difficulty Eating/Feeding	1 (9.1%)	5 (35.7%)	3 (27.3%)
[02]	Delays in Language/Communication Development	8 (72.7%)	9 (64.3%)	11 (100%)
[03]	Receptive Language/Communication Issues	4 (36.4%)	3 (21.4%)	10 (90.9%)
[04]	Expressive Language/Communication Issues	6 (54.5%)	12 (85.7%)	11 (100%)
[05]	Executive Function Problems	4 (36.4%)	10 (71.4%)	10 (90.9%)
[06]	Social Issues	1 (9.1%)	5 (35.7%)	10 (90.9%)
[07]	Emotional Issues	2 (18.2%)	5 (35.7%)	6 (54.5%)
[08]	Behavior Problems	4 (36.4%)	8 (57.1%)	5 (45.5%)
[09]	Sleep Disturbances	7 (63.6%)	6 (42.9%)	9 (81.8%)
[10]	Delayed Attainment of Key Developmental Motor Milestones	7 (63.6%)	4 (28.6%)	7 (63.6%)
[11]	Gross Motor Function Issues	7 (63.6%)	9 (64.3%)	8 (72.7%)
[12]	Fine Motor Function Issues	4 (36.4%)	11 (78.6%)	10 (90.9%)
[13]	Severe Seizures/Other Symptoms	8 (72.7%)	6 (42.9%)	6 (54.5%)

Numbers are count (proportions) of children experiencing a given Dravet aspect in the last 6 months.

reported by the parents in older children, along with expressive language, social, emotional, and motor function. Delays in communication development and receptive language were nearly ubiquitous in children 5–6 years old. Over 90% of 5–6-year-old children had delays in communication development or problems with expressive language, receptive language, executive function, social function, and fine motor function. Sleep disturbances such as difficulties with falling or staying asleep, or reduction in sleep quality, were reported in 82% of children 5–6 years old and approximately half of them had emotional issues, severe seizures, and behavior problems. Difficulty eating or feeding was reported in about one quarter of children 5–6 years of age.

Parents were asked to select all manifestations of DS that they would like to see alleviated by a new therapy and to rank them in order of importance (Fig. 2). While there was no restriction on the number of aspects parents could select to be addressed by a new therapy, they did not select all options listed on the survey question. Severe seizures was selected most frequently followed

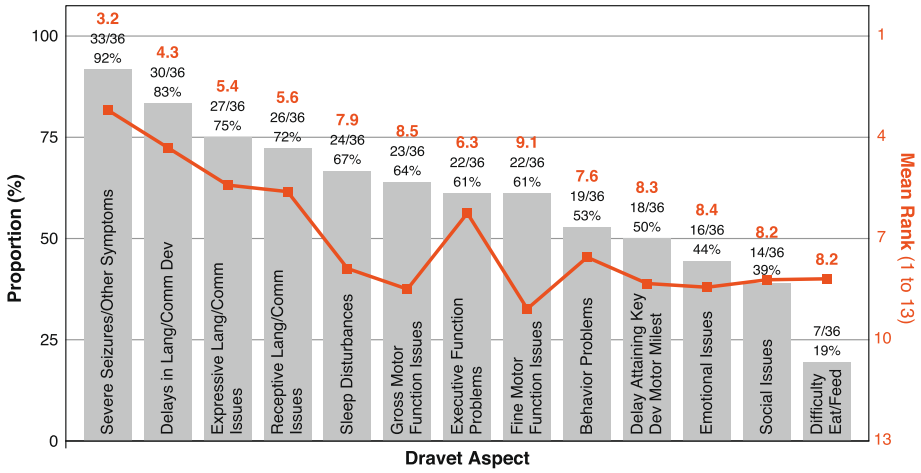

Fig. 2. Proportion of survey respondents wanting to see specific aspects of Dravet syndrome alleviated by a new therapy and importance rank. Proportions are visualized as vertical bars along the *X*-axis and marked at the top of each bar. The mean rank assigned to each Dravet aspect is superimposed as an orange point and connected across all 14 Dravet aspects. The ranks were assigned by the parent caregivers based on a Likert-scale ranging from 1 (most important) to 13 (least important) and are displayed directly above the proportions in orange text.

by communication issues, sleep, and gross and fine motor function. Emotional and social function, and difficulty eating/feeding were selected the least. There was good correlation between the proportion of parents who selected a given manifestation to be alleviated and how they ranked it in relative importance (Fig. 2). However, ranking on importance could also be attributed to the proportion of children experiencing those aspects of Dravet; for example, while only 19% of parents indicated that difficulty eating and feeding should be addressed by a new therapy, with a relative score of 8.2 on a scale of 0 (most important) to 13 (least important) (Fig. 2), only 33.3% of the children reported here had yet experienced this problem (Fig. 1). As such, parents who have not yet experienced certain DS manifestations, may not fully realize their impact.

3.2. Qualitative study

A total of 10 parents (8 female, 2 male) representing 10 children (4 female, 6 male) with SCN1A+ DS participated in discussion groups: 6 from the United States, 3 from the United Kingdom, and one from Spain. Their children ranged in age from 2 to 20 years (mean: 8 years 7 months; median: 5 years 9 months). Six of the 10 parents (5 female, 1 male) agreed to a follow-up, in-depth interview (children: 2 female, 4 male).

In their narratives, parents shared their perspectives on the design of the proposed first-in-human trial and reflected on how their experiences, social context, and expectations shape their decision-making process to enroll a child with DS in a clinical trial. The interpretive results are organized into four themes described below.

3.2.1. Enrolling a child in a clinical trial: expectations and valued outcomes

Parents reflected on their hopes and expectations for clinical research and grounded these in their motivations to enroll their child in a trial of a novel gene therapy. They emphasized the need to incorporate research outcomes that recognize the impact of DS in the lives of not only the affected children but also their siblings, parents, grandparents, and extended family.

When considering a clinical trial for their child, parents' main hope was to stop disease progression, along with seizure reduction. They were most often focused on "not losing what they already have" (e.g., stable DS manifestations, sense of control in their family lives, or knowledge about how to manage current symptoms), and the impact and meaning they ascribed to their present situation affected how they valued trials of potential new treatments.

Parents emphasized that the impact of DS goes far beyond seizures (Table 3). Their hopes for a new therapy were to reduce the number and/or intensity of seizures, while also addressing other manifestations of DS to have a positive impact on the family's well-being and quality of life. Importantly, they described how their experiences are often not reflected in clinical trial endpoints, including aspects related to their child's development and the wellbeing of their families (e.g., caregiver fatigue, parents' sleep time, impacts on social and family time, changes in professional situation and expectations for parents, and siblings' care and well-being). They noted that important indicators of the social, mental, and physical health of parents and families in the context of a severe neurological childhood disease are too often overlooked in clinical research. Parents highlighted the importance of offering balanced educational resources to siblings for them to understand DS more clearly and to acknowledge the impact that DS can have on their lives while reassuring them they can live a fulfilling life. Selected quotes on parents' perspectives and expectations, and what matters most to them are highlighted in Table 3.

3.2.2. Is the trial right for my child? Perspectives on age-related inclusion criteria

The age inclusion criterion (6 months to 5 years of age) of the proposed clinical trial was discussed in detail, including how this criterion may affect enrollment. While parents expressed hopes for clinical trials suitable for all children, they understood that disease-modifying therapies may derive the most benefit for younger children who have not yet experienced onset of neurodevelopmental delay typical of DS. Some parents of older children speculated that families with younger children may not have fully experienced the social, emotional, and physical hardships of the disease and may harbor hopes that their child will not progress and develop severe or fatal symptoms (Table 3). This may influence the preparedness of parents with younger children to assess the potential risks and benefits of a new therapy that could prevent disease progression, before these parents have experienced the full spectrum of DS manifestations and the impact these will have on their family. While parents of older children expressed some hesitancy that entering a clinical trial could lead to loss of the long-sought care equilibrium their families had established, they explained that "knowing what they know now" about what lies

Table 3
Overview of themes identified, subcategories, and pertinent quotes from the qualitative study.

Theme	Subcategory	Quote
Enrolling my child in a clinical trial	Expectations for patients 6 years of age and older	"I think parents, especially early on, are just really holding on to that hope (that their child will be cognitively on track). Or maybe their child will still outgrow this, even though we, we know that's not true. So, I think maybe those at the very early stages of diagnosis if they are not willing to accept what lays in the future and or perhaps don't have the education behind that, might be a little more hesitant. But I think anyone who has a child, who just really understands that this is the course of the disease will be anxious in those early days to get their child enrolled in hopes of being able to prevent this neural progression." "A few years ago, researchers focused on seizures, not in the holistic approach to Dravet syndrome. Dravet is much more than a type of epilepsy. I think, and other families agree with this too, in the end, when your child is older, it does not matter if your child has one or two crises. But what matters is the intellectual abilities, the developmental issues, if they speak, and eat. We don't have to focus on the number of seizures, this is what will positively impact the whole family, parents and siblings".
	Valued outcomes	"Going out and doing things as a family or socializing is very difficult because you never know what the behavior is going to look like. It's a big issue for our families because the sleep impacts seizure control quite frequently [...], parents are being impacted by the lack of sleep as they monitor the child and kind of give that 24 hours round the clock care. [...] (Researchers need to start) thinking about those other issues, especially because seizures are such an easy endpoint." "Our children have horrible, horrible quality of life overall. So, any improvement you can offer not only benefits them, but it really benefits us as caregivers because they are such a heavy burden on our families." "Siblings need to be offered more than information, let's say what Dravet syndrome is and how it can impact everyone. We try our best for our child not to have any type of carer role because we want them to have the best life that they can have, too. And it's about trying to get them reassured but at the same time being honest. And I don't know if there's a specific resource there that could offer this." "It would be amazing to hear my daughter's voice express preference, needs, wants. It would remove frustration barriers and learning barriers and help her live an independent life." "For me, if I could, if my child were to get this treatment, I would hope for my child to re-acquire language, be able to speak to me once again, be able to express pain, joy at what they want, opinions. That would be the best outcome for me, because with voice, then they can self-advocate. And when you can self-advocate, nothing gets in your way."
Is the trial right for my child?	Age-related inclusion criteria	"The therapy aims to change the natural history, so the sooner the better, then the impact will be higher from the medical point of view. But this is something that needs to be explained so people understand." "I can understand why you want to do it with the younger children [...] because [...] they are the ones who have not experienced yet all the manifestations that come with Dravet syndrome. And therefore, you can have such an influence on their lives." "I suppose for me in some ways I can understand that (trial including young children only). I think because children develop so much in the early years and they make so much progress in their early years. I think maybe in some ways it would be easier to be able to see the difference in children who are younger, I suppose, for me to say it's not what I want to hear, but at the same time, I totally understand it. But I do think that it would be good to test out with older children. [...] I think that as you roll out, there should be an explanation to those parents that might not understand the process." "For me, my daughter being a teen, we're not really thinking that she's going to be participating in the trial anytime soon [...] (but) is there a chance that our older kids who have been suffering for a very long time, living abbreviated lives (could) have a fuller more richer life?" "All the families that I speak to when they are newly diagnosed, when their children are younger, they all say, "my kid is doing really well". And you are like "they are not", but I can't say that to them. [...] You know, everyone is in denial. I was that parent too, but I did not know what I was dealing with. Because people were telling me "oh, everyone develops differently", on the whole, they don't. [...] They think their child is doing fine. [...] That's my worry for the younger kids, it's acknowledging that your child is going to be really bad. And you have to intervene now but if you are in denial that your child's okay, it's unlikely that they will want to start injecting some drug into their brain because they think they are ok." "The younger ones, the parents are not going to have the older vein experience, so they are going to be more timid (to participate in a trial) [...] So, it is unreasonable to expect a parent of one-year-old to be willing to do this, but very reasonable to expect a two and a half to three-year-old parent to be willing to do it."
First-in-human clinical trial design	Sham procedure – younger children	"The fact that you could go through all of this and then have a sham procedure done and have to go back and do it again would be concerning. I understand the reasoning for it, but as a parent, it's not ideal. I think people would maybe be more willing to participate if they knew they were going to actually be given the medication upfront. It's not ideal, but none of this is ideal. For me, having an injection in the brain... If I knew it was safe or if I knew that it had been safe previously, you know, I wouldn't be as completely opposed to it.
	Sham procedure – older children	"My thought is that it sucks, but... it's the less of two evils. I mean, I don't care about this kind of stuff at all in the sense that I don't want them to follow the natural history. So, if anything that we can do stops that, I'm more than willing to take the chance or the risk." "I see it as just a necessary step to getting a drug fit, a drug that is gonna work. I think at this point in time, as parents we are desperate for something that's going to not just control seizures but help overall with daily living and things like that. So, in the long run, tiny incision and hole is nothing compared to what we go through on a daily basis." "Our children are all very used to unfortunately undergoing lots of different treatments, including general anesthesia. And so, whilst it's not ideal to have to undergo anesthesia this is not something that would prevent me certainly from taking part in the trial."

Table 3 (*continued*)

Theme	Subcategory	Quote
	Crossover duration	"I think when you enter a trial of this nature, you have to accept that being part of that trial doesn't guarantee you the treatment at the first phase, but it does guarantee is at the treatment at some point. And I think those decisions are out of your hands. If you're not happy with this then you just wouldn't take part at all. I think it's fair for all families, we all think it wouldn't be ideal, but we accept that this is the way that clinical studies run…" "I think six months to a year is unrealistic. When you've got a medically fragile child in six months to a year, literally, it can mean life and death. I would not sign up for a double-blind that was gonna take off. I just couldn't emotionally handle that. We have enough emotional burden as it is, just dealing with everyday things I couldn't emotionally handle six months through a year of an unknown. I would not be able to handle it and be able to function normally." "I suppose it's a chance that you take. I think four months is not a long period of time. And when it comes to children with Dravet syndrome, your life is very much a pain. It's a bit like a roller coaster, because there's always the unexpected. So, I am so afraid…I think that is much more manageable than looking at a year down the line. I think four months is a really good length of time."
	Sham group, seen benefit	"Actually, if you wait the 4 months, and you are in the control group, then you get to see if it is okay and if the therapy is safe as well. I mean, maybe I want the sham."
Gene therapy	Remains in the body forever	"I see more benefits than potential risks. It's true that I'm a positive person when it comes to risk assessment. I see more potential benefits than risks" "I don't think it [gene therapy]'s risky, it's happened, it's been done in many other diseases successfully. I definitely think that's the way that medicine is moving – has moved – I think we're there. I think it's necessary…because you've got diseases like Dravet syndrome that are so impactful on people's lives that…literally, the only way is a cure…and that's via gene therapy. So, I find it incredibly exciting and hopeful and necessary. Yes, it has its risk factors, and I have my own personal insecurities, but would that prevent me if I knew…I don't know. All I'm kind of saying is that I'm not sure I'd want to go first." "You know, it's not something that you want to think about, it's much easier to give your child the medication that you can just take away. My concern would be if something goes wrong with it or it's not a positive effect, is this now permanent?" "There is a positive and negative. The fact that it could only be one-time therapy, sounds like a great idea."

ahead, they would be willing to enroll their child at a younger age in a trial of a therapy that may slow the cognitive, behavioral, and developmental aspects of DS.

Exclusion of older children from clinical trials was controversial for two reasons. First, parents were concerned that their own children would be excluded from a potential disease-modifying therapy and the best opportunity for improvement. Second, they explained their hope that disease-modifying therapies may still stabilize older children for whom the majority of developmental, behavioral, and cognitive delay has already occurred. They understood that developmental problems may not be fully reversible but considered that stabilization along with a seizure reduction would be an enormous benefit to their family's wellbeing. For this reason, they would like to see clinical trials designed to include older children.

3.2.3. Views on a first-in-human gene therapy clinical trial design

Parents shared their views on the design of a clinical trial for a novel gene regulation therapy, specifically the ICV route of administration, the trial randomization, and the blinding of treatment by using a sham procedure. Parents' perspectives and factors that would affect their decision to participate were influenced by their children's history and experiences with DS, as well as prior treatments utilized.

The interpretive analysis showed that differences in parents' perspectives about benefits and risks of gene therapy administration, randomization, and blinding via sham procedures were strongly connected with their children's age. Parents of younger children, who have been navigating the diagnosis and the healthcare system for less time expressed greater concerns, including perceived risks related to the ICV route of administration and the possibility of having this procedure twice (once as the initial control group sham procedure and again for the delayed gene therapy administration), and the fact that gene therapy cannot be "taken away." In Table 3, the caregiver of a young child explains how the administration and sham procedures could influence their decision to enroll their child in a trial. Parents of older children, who have more experience participating in clinical research and have endured a longer journey with DS, were less worried about the sham procedure and the ICV route of administration. These parents have had such difficult and painful experiences living with DS that they have a heightened tolerance for medical procedures; thus, they perceived a potential injection into the brain ventricles as low risk compared with what their children and family had already endured, particularly in the context of potential beneficial treatment effects (i.e., "Making a hole is nothing compared to what we already live with"). Ultimately, the fact that this is a potential one-time therapy was considered positive and reduced concerns about the ICV administration.

Parents were comfortable with the potential randomization process and the proposed waiting period between study arm assignments and unblinding. After four months from the first procedure, they would know whether their child had received control or investigational treatment, and children in the control arm would receive the investigational gene therapy. Parents considered this waiting period of four months suitable and tolerable, without exacerbating disease burden; six months or longer would be undesirable (see quotes in Table 3). Those with previous experience with clinical research also considered that being randomized to the control arm enabled observation of preliminary safety in the gene therapy arm, so that potential adjustments are more likely to have occurred by the time their child receives the investigational product. The sham-controlled design and waiting time also gave parents an elevated sense of safety to participate.

3.2.4. Gene therapy: "it stays in your body forever"

Parents' narratives around a newly developed gene therapy centered on the potential that the therapy could stay in their child's body forever. This was characterized as presenting both benefits and limitations. On the one hand, they valued the possibility of a single administration transformative therapy that might provide durable seizure reduction and help younger children avoid every-

thing that the older patients have had to endure. On the other hand, they were concerned about the permanence of an investigational therapy with unproven safety that could result in exclusion from future trials of other therapies using the same vector. This risk–benefit assessment of gene therapy clinical trial participation is highly individual.

4. Discussion

As a severe developmental and epileptic encephalopathy, DS has a significant impact on the lives of affected children and their families. While approved therapies for DS provide some benefit in managing seizures [6], advanced therapies that target the underlying channelopathy are needed to address the full spectrum of disease manifestations [7,26,31]. To our knowledge, this is the first study within a patient-oriented research framework that specifically explores parents' needs and perceptions regarding clinical trials of a potentially disease-modifying therapy for children with a severe, developmental disease, such as DS.

Here, consistent with previous studies, parents of children with DS reported numerous aspects of the disease that severely impact both their child's and their other family members' lives beyond seizures [7,26,31]. In both the quantitative and qualitative portions of our study, they described the medical, social, and emotional burden the entire family experiences and the profound need for a therapy that alleviates this.

Nearly all parents in this study reported that their child has experienced delays in communication development and expressive language, while sleep disturbances and problems with executive functioning were also very common. Apart from behavioral problems (reported in 56% of patients at a mean of 2 years and 3 months), the onset was before 2 years of age for all manifestations. This is younger than is typically reported in the literature [2,36], which may indicate recall or selection bias. It is possible that parents of children with more severe disease manifestations are more likely to participate in surveys seeking to understand clinical trials of new therapies. This bias must be considered when extrapolating the feedback to a broader population. Alternatively, it is also possible that parents are detecting subtle aspects of their child's ability to interact more quickly than physicians focusing on seizure control, which reinforces the importance of obtaining feedback from both clinicians and families when trying to understand fully disease characteristics and burden. In children with DS, progression of cognitive development stagnates but does not typically regress. Longitudinal studies of intellectual development suggest that developmental/intelligence quotient (DQ/IQ) decreases over time [37]. In a study of 26 children with DS, the mean DQ declined 33 points (range: 6–77) from the first assessment at 12 months to the second assessment at 60 months [38]. In another study of 15 children with DS, DQ/IQ significantly decreased with age ($r = -0.53$, $P < .001$), from normal before 2 years (mean 80, range 64–105) to low after 3 years (mean 48, range 30–69). In this study, raw (not age-adjusted) DQ sub-scores increased with age during the first decade but not at the expected rate, so while regression was not observed, the gap between age-matched peers widened and could be perceived as worsening development [39].

The onset and frequency of reported DS symptoms were more variable at younger compared with older ages. All children 5–6 years of age experienced delays in general communication ability and expressive language, while 91% had impaired receptive language, fine motor, and/or social skills. These challenges affected children's functioning across a broad range of domains including communication, motor, behavior, social, and emotional. The devastating impact of DS extended throughout the child's family unit, encompassing siblings and parents as well. Parents' enthusiasm for a one-time disease-modifying treatment that may improve the full spectrum of DS manifestations could reflect their recognition that such treatment would influence the wellbeing of their entire family.

During the qualitative study, parents expressed that their primary motivation for considering new therapies was to stop disease progression. Despite newly approved therapies, seizure reduction remains the single most important outcome and unmet need (92% of parents). Interestingly, we identified a proportion of parents who believe that early reduction of seizures and polypharmacy would prevent the onset of other DS manifestations (Supplemental Table 1). Currently, there is no evidence to suggest that seizure reduction alone, without correction of the underlying channelopathy, can fully prevent or halt the accumulated developmental, motor, and cognitive impacts of DS [10,40]. Nonetheless, this highlights the need for further research and family education on this topic.

The high priority that parents place on communication highlights its essential role in functioning and connectedness. The ability to communicate creates the foundation for accessing needs and wants and sharing life experiences. One parent stated that language reacquisition following a new treatment would allow their child to express feelings, opinions, and self-advocate again and "when you can self-advocate, nothing gets in your way." One of the most salient findings from parent participation in this study is the recognition that communication ability is a critical endpoint for any clinical trial investigating the efficacy of a disease-modifying therapy for DS.

That parents expressed how clinical trial endpoints rarely explore how families are impacted by a disease is important for researchers to address. These outcomes are important indicators of how a potential treatment is indirectly affecting the social, mental, and physical health of parents. While not a strict measure of efficacy, such information is important for assessment of product value, and, thus, is of critical importance for supporting access to approved therapies. Parents described how they try to ensure siblings do not take up the duties of a caregiver; however, they acknowledged the impact DS has on the entire family and how resources need to be provided to educate and manage siblings' expectations. The nuanced way in which caregivers and families value health and wellbeing must be considered in order to select meaningful outcomes that can validate the usefulness of a novel therapeutic intervention beyond the clinical trial setting.

Clinical development of gene therapies aiming to address complex neurological systems in a cell-selective manner is necessarily complex. Rigorous pre-clinical studies in small and large animal models are conducted to determine efficacy and ensure safety without off-target effects. Clinical trials are discussed at length with regulatory authorities and clinical experts. However, in diseases with broad functional impacts, like DS, it is of utmost importance to ensure potentially transformative therapies address what is most meaningful to patients and families, and that clinical trials are thoughtfully designed to not pose an undue burden to their participation. To this end, parents generally understood and agreed with the proposed clinical trial design and rationale for a potentially disease-modifying, single administration gene regulation therapy: starting at age 6 months to 5 years, the ICV administration for broad distribution in the brain, and a sham control procedure to ensure the rigorous assessment of safety and efficacy.

Parents in our study understood the concept of "time is brain." Treating children at an early age with a potentially disease-modifying therapy may not only control seizures but also alter epileptogenesis, thus preventing the epileptic encephalopathy component of DS. Furthermore, by correcting the underlying channelopathy, early treatment offers the potential to attenuate the developmental encephalopathy. Treating children during the criti-

cal period of brain development when there is enhanced neuroplasticity may potentially yield the most meaningful clinical outcomes [41]. The benefits of intervening early with a disease-modifying gene therapy have been illustrated by the unprecedented clinical success of onasemnogene abeparvovec-xioi (AAV9-mediated gene replacement therapy) in spinal muscular atrophy (SMA), where treatment before 1 year of age prevented disease onset [42–46] and an earlier age of treatment initiation was associated with better outcomes [47]. The potential benefits of early intervention in developmental and epileptic encephalopathies (DEEs) are best evidenced by studies of infantile spasms where treatment at early stages of the disease was associated with improved long-term seizure control and cognitive outcomes [48,49].

Parents accepted a single ICV injection of gene therapy to optimize therapy distribution and give their child the best chance of a meaningful improvement. ICV drug administration is a well-established method for delivery of treatment to the cerebroventricular system [50] and has been used worldwide for decades to treat children and adults with a broad range of CNS disorders [51]. Implanted ICV devices often remain in place indefinitely for chronic therapy [52] with very low incidence of complications, such as bleeding or infection [53–55]; based on discussions with neurosurgical experts, the risks of a single, small volume ICV administration of gene therapy are expected to be lower still. While parents expressed concern about the surgical procedure, particularly for children in the delayed-therapy control arm, the majority considered this to be preferable to living with DS.

Concurrent control designs and randomization are typically required by regulatory agencies in order to identify and control for unknown variables that could alter outcomes independently of the study intervention [56,57]. Parents understood the need for scientific rigor and considered the delayed-therapy control acceptable (“it’s the less of two evils”), provided investigational therapy is guaranteed in a contemporary timeframe (i.e., 4 months following randomization). However, given precedent with other DS trials [58], some parents questioned if external or historical controls could be used in an open-label study design. An open-label design would allow collection of preliminary safety and efficacy data to inform the risk:benefit assessment for patients and caregivers. However, while such datasets provide important initial supporting information, they may not be sufficient for regulatory agencies to determine efficacy, and high-quality data from well-controlled studies are still requested for approval of investigational products [59–61]. If asking patients and families to take on the risks and burdens of an investigational gene therapy clinical trial, using a scientifically rigorous design that provides a clear answer to the study question is usually considered more respectful of participants.

When assessing potential risks of participating in a gene therapy clinical trial, parents of older children perceived that they assessed risk differently than those with younger children who have not yet experienced the increased DS burden that comes with age. However, they also counseled that, with the hindsight they now have, they would be even more willing to enroll their young child in a clinical trial; thus, it will be vitally important to continue educating and helping parents of young children to understand fully the expected course of DS and manifestations yet to emerge so that they are equipped to determine whether a clinical trial of an investigational disease-modifying therapy is the right decision for their child and family.

For the older children, a longer experience living with DS meant the parents highly valued stability in their child’s condition. They would only consider the potential disruption to their lives and routine posed by a clinical trial if there was possibility of significant benefit. Nonetheless, they also emphasized that seizure freedom, even in the absence of cognitive or developmental improvement, would represent a considerable improvement to their lives. This is supported by data from Dravet and other DEEs, which demonstrate that seizure severity is associated with reduced quality of life in children with refractory seizures [62]. Importantly, the spectrum of disease manifestations that significantly impact quality of life of the affected child and the family are attributed not only to seizure burden but also the underlying sodium channelopathy [10].

These perspectives suggest that there may be an optimal initial window for consideration of inclusion of children with severe DEEs in clinical trials. In the case of DS, some of the participants speculated in our study that parents of children between 2 and 4 years of age may have begun to accept the outlook for their child, while still having opportunity to prevent the full spectrum of manifestations. Understanding this window will be important for future clinical trials of disease-modifying therapies for DS and other DEEs. It is important to consider that this potential initial window may evolve over time based on cumulative evidence of efficacy of disease-modifying therapies.

Parents were both excited about the potential positive impact of a one-time disease-modifying therapy and cautious of the potential long-term implications. While clinical experience with AAV-mediated gene therapy is increasing, with nearly 150 clinical trials approved by regulatory agencies from different countries – 94 of which have been completed and 51 for which the efficacy endpoint was reached [63] – data on long-term effects are still relatively few. More so than ever, the informed consent process for trials of such therapies must provide education with clear, balanced information that enables parents to make well-informed decisions. It is important to recognize the fear and tensions parents face when making such decisions, especially in the context of a progressive disease such as DS. Clinical investigators must allot ample time to speak with parents, explain and answer questions, have robust discussions about the known and unknown risks and benefits of gene therapy, and discuss long-term commitments involved with follow-up studies required by regulatory agencies.

The parent caregiver perspectives gleaned from this study were used to inform and adapt the clinical trial design to include a Part 1, open-label, dose-escalation study to address caregivers’ concerns regarding the safety of ETX101, an investigational AAV-mediated gene regulation therapy for DS. This treatment approach has the potential to address the full range of DS manifestations by targeting the underlying genetic cause of the disorder. The forthcoming clinical trial is a Phase 1/2, two-part, multicenter study to evaluate the effects of a one-time ICV administration of ETX101 on cognitive development, behavior, movement, communication skills, seizure frequency, and sleep patterns of young children living with DS. Based on the insights gathered in this research, additional support will be provided to study participants to help ensure the wellbeing of patients and families from initial engagement through the duration of their participation in the trial. These services include electronic informed consent, support for family travel logistics and expenses, a study visit schedule to minimize in-person clinic visits wherever possible and biological sample collection. Investigators will be encouraged to allow adequate time for caregivers to understand and consider participation in the gene therapy trial. To facilitate a more fully informed consent, caregivers will be provided with educational materials, in addition to the informed consent form itself, to describe the gene therapy trial design in more detail, the mechanism of action of ETX101, and their expected commitment to the study.

5. Limitations

The limitations of our studies include the relatively small number of families interviewed, the parents in the qualitative study

represent just three countries with a predominance of US parents, and the anonymous nature of the online quantitative survey. While our study identified important considerations for trial design and meaningful trial outcomes, further research is needed to understand fully the impact, concerns, and perspectives of families living with DS participating in clinical trials. Because only one parent from each family participated, 80% of whom were mothers, there is a possibility of implicit gender bias, whereby the opinions may not reflect the perspectives of different genders and parental roles. There is also potential for selection bias, whereby parents who were willing to participate in this study may be inherently more interested in having their children participate in clinical research or in learning about upcoming therapies and expressing their opinions future clinical trials.

6. Conclusions

Parents reported numerous unmet needs for their children living with DS and were excited about the prospect of a one-time gene regulation therapy that might address the full spectrum of DS manifestations. Their perspectives and values regarding the risks and benefits factored in their child's age, cumulative experience with DS, existing disease burden, and the overall impact of DS on family wellbeing. This study, in addition to biomedical health outcomes, highlights that parents and families value health and wellbeing outcomes in different and more nuanced ways than clinicians and scientists. Collaboration between multiple stakeholders from different backgrounds and experiences, such as the one described here, to discuss the design and administration of clinical trials in children with severe neurodevelopmental disorders is critical for ensuring that trial outcomes address the needs of patients, families, clinicians, and researchers.

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Competing interests

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Appendix A. Supplementary data

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References

[1] Symonds JD, Zuberi SM, Stewart K, McLellan A, O'Regan M, MacLeod S, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. Brain 2019;142: 2303-2318.
[2] Gataullina S, Dulac O. From genotype to phenotype in Dravet disease. Seizure 2017;44:58–64.
[3] Cetica V, Chiari S, Mei D, Parrini E, Grisotto L, Marini C, et al. Clinical and genetic factors predicting Dravet syndrome in infants with SCN1A mutations. Neurology 2017;88:1037–44.
[4] de Lange IM, Gunning B, Sonsma ACM, van Gemert L, van Kempen M, Verbeek NE, et al. Outcomes and comorbidities of SCN1A-related seizure disorders. Epilepsy Behav 2019;90:252–9.
[5] Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain 2012;135:2329–36.
[6] Wirrell EC, Laux L, Donner E, Jette N, Knupp K, Meskis MA, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American Consensus Panel. Pediatr Neurol 2017;68:18–34.e3.
[7] Villas N, Meskis MA, Goodliffe S. Dravet syndrome: Characteristics, comorbidities, and caregiver concerns. Epilepsy Behav 2017;74:81–6.
[8] Skluzacek JV, Watts KP, Parsy O, Wical B, Camfield P. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. Epilepsia 2011;52(Suppl 2):95–101.
[9] Wu YW, Sullivan J, McDaniel SS, Meisler MH, Walsh EM, Li SX, et al. Incidence of Dravet syndrome in a US population. Pediatrics 2015;136:e1310–5.
[10] Brunklaus A, Zuberi SM. Dravet syndrome–from epileptic encephalopathy to channelopathy. Epilepsia 2014;55:979–84.
[11] Aras LM, Isla J, Mingorance-Le Meur A. The European patient with Dravet syndrome: results from a parent-reported survey on antiepileptic drug use in the European population with Dravet syndrome. Epilepsy Behav 2015;44:104–9.
[12] Lagae L, Brambilla I, Mingorance A, Gibson E, Battersby A. Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. Dev Med Child Neurol 2018;60:63–72.
[13] Han Z, Chen C, Christiansen A, Ji S, Lin Q, Anumonwo C, et al. Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of Dravet syndrome. Sci Transl Med 2020;12: eaaz6100.
[14] Belle A, Lin W, McLaughlin J, Li G, Lucey G, Soe M, et al. ETX101, a GABAergic interneuron selective AAV-mediated gene therapy for the treatment of SCN1A + Dravet syndrome: biodistribution and safety in non-human primates [abstract 391]. In: American Epilepsy Society AES2020 Virtual Meeting; 2020.
[15] Young AN, Tanenhaus A, Chen M, McLaughlin J, Belle A, Li J, et al. A GABA-Selective AAV vector-based approach to up-regulate endogenous scn1a expression reverses key phenotypes in a mouse model of Dravet Syndrome. In: American Society of Gene & Cell Therapy Annual Meeting. Washington DC; 2019.
[16] Allard J, Ballesteros F, Anthony SJ, Dumez V, Hartell D, Knoll G, et al. What does patient engagement mean for Canadian National Transplant Research Program Researchers? Res Involv Engagem 2018;4:13.
[17] Perfetto EM, Burke L, Oehrlein EM, Epstein RS. Patient-focused drug development: A new direction for collaboration. Med Care 2015;53:9–17.
[18] Chalasani M, Vaidya P, Mullin T. Enhancing the incorporation of the patient's voice in drug development and evaluation. Res Involv Engagem 2018;4:10.
[19] Janssens R, Huys I, van Overbeeke E, Whichello C, Harding S, Kübler J, et al. Opportunities and challenges for the inclusion of patient preferences in the medical product life cycle: a systematic review. BMC Med Inform Decis Mak 2019;19:189.
[20] Guidance for Industry. Patient-focused drug development: Collecting comprehensive and representative input. US Food and Drug Administration, June 2020. https://www.fda.gov/media/139088/download.
[21] Strategy for Patient-Oriented Research. Patient engagement framework Accessed: December 15, 2020. In https://cihr-irsc.gc.ca/e/documents/spor_framework-en.pdf, ; 2019.
[22] Morse JM. Strategies for sampling. In: Morse JM, editor. Qualitative nursing research: A contemporary dialogue. Newbury Park, Ca: Sage; 1991. p. 127–45.

[23] Glaser BG. Theoretical sensitivity. Mill Valley, CA: Sociology Press; 1978.
[24] Nolan KJ, Camfield CS, Camfield PR. Coping with Dravet syndrome: parental experiences with a catastrophic epilepsy. Dev Med Child Neurol 2006;48:761–75.
[25] Nolan K, Camfield CS, Camfield PR. Coping with a child with Dravet syndrome: insights from families. J Child Neurol 2008;23:690–4.
[26] Camfield P, Camfield C, Nolan K. Helping families cope with the severe stress of Dravet Syndrome. Can J Neurol Sci 2016;43(Suppl 3):S9–S12.
[27] Berg AT, Kaiser K, Dixon-Salazar T, Elliot A, McNamara N, Meskis MA, et al. Seizure burden in severe early-life epilepsy: Perspectives from parents. Epilepsia Open 2019;4:293–301.
[28] Jensen MP, Brunklaus A, Dorris L, Zuberi SM, Knupp KG, Galer BS, et al. The humanistic and economic burden of Dravet syndrome on caregivers and families: Implications for future research. Epilepsy Behav 2017;70:104–9.
[29] Nabbout R, Auvin S, Chiron C, Irwin J, Mistry A, Bonner N, et al. Development and content validation of a preliminary core set of patient- and caregiver-relevant outcomes for inclusion in a potential composite endpoint for Dravet Syndrome. Epilepsy Behav 2018;78:232–42.
[30] Black AP, Baker M. The impact of parent advocacy groups, the Internet, and social networking on rare diseases: the IDEA League and IDEA League United Kingdom example. Epilepsia 2011;52(Suppl 2):102–4.
[31] Nabbout R, Auvin S, Chiron C, Thiele E, Cross H, Scheffer IE, et al. Perception of impact of Dravet syndrome on children and caregivers in multiple countries: looking beyond seizures. Dev Med Child Neurol 2019;61(10):1229–36.
[32] Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77–101.
[33] Butler-Kisber L. Qualitative inquiry: thematic, narrative and arts-informed perspectives. first edition. Los Angeles, CA: Sage Publications, Ltd.; 2010.
[34] Pamphilon B. The zoom model: A dynamic framework for the analysis of life histories. Qual Inq 1999;5(3):393–410.
[35] Eakin JM, Gladstone B. "Value-adding" analysis: doing more with qualitative data. Int J Qual Methods 2020;19: 10.1177/1609406920949333.
[36] Ceulemans B. Overall management of patients with Dravet syndrome. Dev Med Child Neurol 2011;53(Suppl 2):19–23.
[37] Jansson JS, Hallböök T, Reilly C. Intellectual functioning and behavior in Dravet syndrome: A systematic review. Epilepsy Behav 2020;108:107079.
[38] Ragona F, Granata T, Dalla Bernardina B, Offredi F, Darra F, Battaglia D, et al. Cognitive development in Dravet syndrome: a retrospective, multicenter study of 26 patients. Epilepsia 2011;52: 386-92.
[39] Nabbout R, Chemaly N, Chipaux M, Barcia G, Bouis C, Dubouch C, et al. Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy. Orphanet J Rare Dis 2013;8:176.
[40] Catarino CB, Liu JYW, Liagkouras I, Gibbons VS, Labrum RW, Ellis R, et al. Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology. Brain 2011;134:2982–3010.
[41] Ismail FY, Fatemi A, Johnston MV. Cerebral plasticity: Windows of opportunity in the developing brain. Eur J Paediatr Neurol 2017;21:23–48.
[42] Al-Zaidy SA, Mendell JR. From clinical trials to clinical practice: practical considerations for gene replacement therapy in SMA type 1. Pediatr Neurol 2019;100:3–11.
[43] Foust KD, Wang X, McGovern VL, Braun L, Bevan AK, Haidet AM, et al. Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN. Nat Biotechnol 2010;28:271–4.
[44] Robbins KL, Glascock JJ, Osman EY, Miller MR, Lorson CL. Defining the therapeutic window in a severe animal model of spinal muscular atrophy. Hum Mol Genet 2014;23:4559–68.
[45] Mendell JR, Shell R, Lehman R, al e. Gene-replacement therapy in spinal muscular atrophy type 1: Long-term follow-up from the Onsemnogene Abeparvovec-xioi Phase 1/2a Clinical Trial. In: 2019 Cure SMA Annual Conference. Anaheim, CA; 2019.
[46] Waldrop MA, Karingada C, Storey MA, Powers B, Iammarino MA, Miller NF, et al. Gene therapy for spinal muscular atrophy: safety and early outcomes. Pediatrics 2020;146;e20200729.
[47] Kong L, Valdivia DO, Simon CM, Hassinan CW, Delestrée N, Ramos DM, et al. Impaired prenatal motor axon development necessitates early therapeutic intervention in severe SMA. Sci Transl Med 2021;13:eabb6871.
[48] Nariai H, Duberstein S, Shinnar S. Treatment of epileptic encephalopathies: current state of the art. J Child Neurol 2018;33(1):41–54.
[49] Kivity S, Lerman P, Ariel R, Danziger Y, Mimouni M, Shinnar S. Long-term cognitive outcomes of a cohort of children with cryptogenic infantile spasms treated with high-dose adrenocorticotropic hormone. Epilepsia 2004;45:255–62.
[50] Cohen-Pfeffer JL, Gururangan S, Lester T, Lim DA, Shaywitz AJ, Westphal M, et al. Intracerebroventricular delivery as a safe, long-term route of drug administration. Pediatr Neurol 2017;67:23–35.
[51] Slavc I, Cohen-Pfeffer JL, Gururangan S, Krauser J, Lim DA, Maldaun M, et al. Best practices for the use of intracerebroventricular drug delivery devices. Mol Genet Metab 2018;124:184–8.
[52] Brineura (cerliponase alfa) US prescribing information. BioMarin Pharmaceutical Inc.: Novato, CA; 2017. https://www.brineura.com/wp-content/themes/jupiter-child/assets/pdfs/resources/Brineura-Prescribing-Information.pdf.
[53] Peyrl A, Chocholous M, Azizi AA, Czech T, Dorfer C, Mitteregger D, et al. Safety of Ommaya reservoirs in children with brain tumors: a 20-year experience with 5472 intraventricular drug administrations in 98 patients. J Neurooncol 2014;120:139–45.
[54] Slavc I, Schuller E, Falger J, Gunes M, Pillwein K, Czech T, et al. Feasibility of long-term intraventricular therapy with mafosfamide (n = 26) and etoposide (n = 11): experience in 26 children with disseminated malignant brain tumors. J Neurooncol 2003;64:239–47.
[55] Kramer K, Smith M, Souweidane MM. Safety profile of long-term intraventricular access devices in pediatric patients receiving radioimmunotherapy for central nervous system malignancies. Pediatr Blood Cancer 2014;61:1590–2.
[56] United States Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. Guidance for Industry. Providing clinical evidence of effectiveness for human drugs and biological products. 1998. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf.
[57] Katz R. FDA: evidentiary standards for drug development and approval. NeuroRx 2004;1:307–16.
[58] Laux L, Brathwaite C, Wyant N, Avendano J, B. T. Abst. 344. Safety and pharmacokinetics of antisense oligonucleotide STK-001 in children and adolescents with Dravet syndrome: single and multiple ascending dose design for the open-label phase 1/2a MONARCH study. In: American Epilepsy Society (AES) 2020 Virtual Annual Meeting 2020.
[59] Guidance for Industry. E10 choice of control group and related issues in clinical trials. US Food and Drug Administration, May 2001. https://www.fda.gov/media/71349/download.
[60] Guidance for Industry. Rare diseases: common issues in drug development. US Food and Drug Administration. January 2019. https://www.fda.gov/media/119757/download.
[61] Draft Guidance for Industry. Human gene therapy for neurodegenerative diseases. US Food and Drug Administration, January 2021. https://www.fda.gov/media/144886/download.
[62] Brunklaus A, Dorris L, Zuberi SM. Comorbidities and predictors of health-related quality of life in Dravet syndrome. Epilepsia 2011;52:1476–82.
[63] Kuzmin DA, Shutova MV, Johnston NR, Smith OP, Fedorin VV, Kukushkin YS, et al. The clinical landscape for AAV gene therapies. Nat Rev Drug Discov 2021;20:173–4.