Journal of Patient Experience
Volume 8: 1-14
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DOI: 10.1177/23743735211039319
journals.sagepub.com/home/jpx
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Family Perspectives on Clinical Research for Pediatric Multiple Sclerosis: Enhancing Equity

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Abstract

Pediatric new drug trials are federally mandated, but family perspectives in multiple sclerosis (MS) research are limited. Due to MS chronicity and long-term medical system involvement, we obtained family views on research priorities and optimized methods for future studies. Focus groups were convened with families impacted by pediatric-onset MS. Recruitment included those followed by the Network of Pediatric MS Centers, geographically disparate locations, and centers' voluntary election. Study questions included: healthcare experiences, clinical trials perspectives, cognitive/psychosocial/educational outcomes, disease course and disability accrual. All subjects supported future clinical studies. Patients highlighted contribution to knowledge base but were wary of experimental medication and disease-course impeding activities. Parents underscored medication delivery modalities, side-effects, and limiting children's discomfort. All wanted study relevance made explicit. Suggested future study design elements included: providing compensation, limiting assumptions regarding outcome linkages, understanding study-related psychological impacts, and reducing participation burdens. Rare disease research can assist general medicine diagnosis and referral. Variable study designs and explicit rationale may augment participation. Closing the pediatric research gap requires family engagement in the research process.

Keywords

clinician–patient relationship, patient engagement, patient perspectives/narratives, pediatrics, qualitative methods

Introduction

Pediatric therapeutic drug trials are now mandated in the United States, Europe, Canada, and Japan (1). This represents a shift, once deterring children from research exposure, to better understanding and safeguarding them through research. These policy changes have slowly evolved. Still, research is lagging (1) despite documented benefits of pediatric medication trials. The discrepancy between pediatric versus adult clinical research is more than ten-fold (2). Examples include oncological diseases where the median lag time from first in adult to first in child trial is 6.5 years (3) and infectious diseases which often affect children disproportionately (4). Hesitancy to conduct pediatric clinical research may be based on mandates (5) designating children as vulnerable and intensifying scrutiny to minimize risk. Although created to increase child protections, regulations

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created avoidance of pediatric clinical trials regarding liability and approval concerns (6). Other challenges to pediatric clinical research may be limited guidelines and infrastructure within individual disease tracts, rarity of pediatric illnesses (7) resulting in small study cohorts (8), and inadequate understanding of enlisting and engaging parents and children. Therefore, despite directives to involve pediatric patients in research discussions (9), little has been done to obtain patient and family perspectives. At best, parents are considered proxies for children.

Policies to enhance equity to and quality of clinical research for pediatric populations are insufficient. The Federal Drug Administration (FDA) criterion for pediatric involvement in clinical studies is, "To achieve an important pediatric public health need" (10). Persistent gaps need to be addressed to accelerate equitable access to evidence-based therapies in children, particularly those with rare diseases and from underserved populations.

Multiple sclerosis (MS) is a demyelinating and degenerative disease of the central nervous system. Nearly 5% of all MS patients have childhood onset, and that may be increasing (11–13). Yet many of the most efficacious, approved therapies in adult clinical trials are inappropriate (14), or yet to be formally evaluated for pediatric use (8). The first adult MS treatments were FDA approved in 1993, while the first treatment for the pediatric MS was FDA approved in 2018 (15), over 25 years later. Pediatric-onset MS (POMS) warrants a better understanding of patient medication trajectories particularly because the disease course and demographics differ from adult-onset MS (16–18). Specifically, POMS have higher relapse rates than adult-onset MS, yet a significant therapeutic gap exists. There are over 15 therapies approved for adult-onset MS, but only one approved for POMS, largely due to absence or delays in conducting pediatric trials (15). Similar gaps remain with pediatric epilepsy, oncology, and rheumatological conditions, predominantly resulting from limited stakeholder input (8,19,20). POMS work may inform these conditions. Because of POMS chronicity and extended medical system encounters, stakeholder input into treatment and research is critical to overcoming participation barriers and optimizing study design and outcomes.

The primary hypothesis of this study was that patients and families living with POMS can provide unique insights into their priorities regarding clinical research studies and perceived barriers to participation in research and interventional therapeutic studies. This study aimed to engage families and patients impacted by POMS to better understand how disease experience influences research participation interests, concerns, and priorities and meaningful engagement in future studies. Our exploration demonstrates the utility and importance of participant input on clinical research in diverse pediatric medical populations. Studies exploring familial and patient views on clinical research are limited (21–24). Qualitative methods clarify participant interpretation and give them voice (25). Focus groups assist with generating new ideas (26), capturing broad population-based information, and encouraging participants' discourse (27). The study described can also be a model for developing patient-informed research studies and clinical trials in other rare pediatric diseases.

Methods

Utilizing criterion purposive sampling (28) to identify and select information-laden cases, we convened focus groups in three United States cities. The infrastructure and patient base of the Network of Pediatric MS Centers (NPMSC) facilitated subject recruitment based on eligibility and demographic factors. Study criteria included: parents of children with POMS, young adults (age 18-40 years) diagnosed with POMS, currently followed in NPMSC, geographically disparate locations including higher concentrations of Spanish speaking, and voluntary election by network centers. IRB approval was received for the lead agency and pediatric MS centers. Written informed consent was obtained for subjects. The rationale for using parents and young adult patients was to select two groups that had the most insight regarding the longitudinal POMS clinical experience.

A focus group guide examined several areas of POMS treatment research including: experience with healthcare system/clinicians since POMS diagnosis, POMS medication experience, previous clinical research and/or medication clinical trials participation, POMS causal/contributing factors, cognitive and psychosocial effects of POMS, disease course and disability accrual, other participant-identified research topics, and motivators and barriers to research participation (Table 1). The focus group guide was developed with input from multidisciplinary providers working with POMS patients and families (eg, neurologists, psychologists, neuropsychologists, and nurses). Specific consultation was sought from an expert in qualitative research design and analysis. The preeminent focus group text by Krueger and Casey (27) informed the flow and sequencing of questions, as well as the duration and composition of the focus groups.

Research was conducted over a six month period and led by a multidisciplinary team consisting of two pediatric psychologists, one PhD expert in qualitative methods, and one pediatric MS-specialized neurologist (study PI) who observed and fielded clinically-oriented questions. Some team members were bilingual to engage Spanish-speaking participants. Each 90-minute session was assigned a lead moderator, note taker, and observer. Sessions were audio-recorded and transcribed verbatim using professional transcription services. This study format adhered to a conventional qualitative design for medical settings and systems (29–31) and team-based analysis approaches (32,33).

Through team-based analysis, researchers (TC, EO, LM, KC) developed, reviewed, and revised, by consensus, an a priori codebook with detailed definitions and explicit directions for use (32,33). The codes were derived from the key categories of the focus group guide. Data were entered and

Table 1. Focus Group Guide.

A. Health care experiences: (10 min)	
We would like to start with some basic introductions followed by a discussion of your (child and family's) experience since you were/your child was diagnosed with MS.	
1. *Go around room and ask each person to state name, age/child's age and age at diagnosis.*	
2. Tell us about some of the best experiences you have had with health care since your/child's MS diagnosis. • What made them good?	• *Convenient scheduling* • *Clinician returns calls quickly* • *Understand doctor's explanations/ treatment plan*
3. Tell us about some of the worst experiences you have had with health care since your/child's MS diagnosis. • What made those experiences not so good?	• *Too many hours at hospital* • *Too many different locations* • *Don't understand diagnosis or treatment plan, etc*
B. Medication experience: (15 min)	
We'd like to talk next about your experience with medicine to treat your/your child's MS.	
4. Please describe what medications you/your child take and how you take them?	• *Frequency, dose, with meals, etc* • *Who gives the medicine, you, your child, someone else?*
4a. This could include medications you/your child currently take or medications you/your child have taken in the past.	• *Describe what happens when it's time to take your/your child's medication? Prompts: what happens first, then what…*
5. Who remembers about taking the medicine and reminds you/your child?	
6. What challenges, if any, have you/your child had with taking medicine for MS?	• *Side effects* • *No effects* • *Seemed to work for a while then not* • *Did not seem to work at all, etc*
7. What would tell you, (your child) or your doctor that an MS medicine is/is not working well? *What would you look for or see to know it is/is not working?*	• *Stopping relapses/attacks* • *Improved attention, physical function* • *Less fatigue*
8. Often times, people don't take their medications exactly as prescribed or suggested by their doctor. What have been reasons for not giving/taking the medicine or for not taking it as you were told?	• *Easier for child/ avoids arguments* • *Child refuse* • *Side effects* • *Cost* • *Hard to remember* • *Complicated to administer* • *Don't understand instructions—language/literacy*
9. What helps you/your child to take the medicine as you were told?	• *Alarms/ calendars* • *VNA support* • *Having someone else give the medication* • *Frequency—either more or less often* • *Payment assistance*
C. Clinical trials: (20-25 min)	
Next we want to talk about clinical trials or research studies of medications in pediatric MS. Although children and adolescents with MS often take MS medicines, everything that we know about these medications, including how much to give, what side effects might occur, and how well the medicine will work, comes from research on adults. There have been no studies (also called clinical trials) of these medicines in children and teens. But recently, laws have changed requiring that new medicines for MS be tested in children, as well as adults.	
10. We would like to hear about anyone's experiences participating in clinical trials and about what you think about the idea of testing MS medicines with children and teens?	• *Good idea* • *Concerns/worried about time involved*
11. If an MS medicine could do one thing for your child/you, what would be the most important thing it should do?	
12. We wonder what you think of the idea of measuring the number of attacks (also called relapses, exacerbations or flare ups) as a way of telling if the medicine you/your child is taking for MS is working well?	• *Good way of testing?* • *Not good—for example, because might not have had attacks during study anyway* • *Too anxiety provoking?*
12a. How do you know if you/your child is having an MS attack?	• *Feeling tired* • *Vision changes* • *Weakness* • *Not wanting to go to school/work*
13. One way that is used to study if a medicine works well is to give some people the real medicine, and give other people something that looks like the medicine and is given the same way at the same times, but has no medicine in it (that is called a placebo). Participants are not told whether or not they are getting the real medicine.	
13a. What do you think of using a placebo in studies of MS medicines in children and teens?	

(continued)

Table 1. (continued)

13b. What factors would you need to consider in deciding whether to participate/let your child participate in a drug trial where you/ your child might get a placebo?	• *If you/your child knew you would get the real medicine at some point?* • *If children who had an attack or relapse on the placebo were taken off the placebo and put on the real medicine?*
13c. Sometimes trials can compare 2 different medicines. So no one has to take a placebo. Some people take one medicine and another group takes a different medicine and the two groups are compared. What do you think of that kind of study?	
14. Some MS medicines are given as injections (shots under the skin), and other MS medicines are taken as pills. In order to study these medicines in children and teens, it might be necessary to ask children to take both injections and pills. One would be the actual medicine and the other would be a placebo but every child would be getting an active medicine. No one would get a placebo.	
14a. What do you think of that kind of study?	
14b. What factors would you need to consider in deciding whether to participate/allow your child to participate in a study where you/he might take both shots injections and pills?	
15. What factors would you need to consider in deciding whether to participate/have your child participate in a study of new medicines if it required that they come to see the doctor more often?	
15a. What is the frequency of clinic visits you would feel comfortable with?	• *Every month, three months, six months* • *Over six months, one year, several years*
16. Clinical trials of new medicines often also involve things like filling out questionnaires or forms, having bloodwork, MRI's, or other tests for memory, concentration, reading, etc).	
16a. What other factors (from these or others we may not have thought of) would you consider when deciding whether to enroll/ your child in a clinical trial of a medication?	• *Who completes questionnaires (you, your child, doctors, nurse)* • *Number of questionnaires/time it takes to fill out questionnaires 10 min or less, 30 min or less, 1 h, several hours* • *Questions asked on the questionnaires* • *Length of study visit 30 min, hour, half a day, day)* • *If study visit is part of regular/routine visit or not* • *Number of other tests necessary (eg, blood draws, MRI, cognitive testing)* • *Frequency of other tests necessary (eg, blood draws, MRI, cognitive testing) Once a month? Once every 3 months? Once every 6 months?*
17. Some studies might follow children who have tried new MS medications when they become adults to monitor long-term safety.	
17a. What do you think is the best way to do this?	
17b. How should we go about contacting them to ask about side effects, other conditions/diseases and generally how they are doing?	• Phone, email, text, in what language, etc
18. We are very interested in hearing all of your thoughts and ideas about testing new MS medicines in children and teens. What other ideas do you have about studies of MS medicines in children and teens?	
Break—End of Part 1 (5 min)	
D. Genetic risk for MS (5 min) We are also very interested in finding out your views on research that explores what causes pediatric multiple sclerosis. One type of study explores what is called genetic risk for MS. Genetic risk means if a parent has a particular gene that they pass to their children then their children will be more likely to get MS. These studies involve bloodwork looking for genes shared between family members (eg, parents and children or siblings) that might put a person at risk for getting pediatric MS.	
19. What do you think of the idea of conducting research studies to look for genes that may cause pediatric MS?	
20. What factors would you need to consider in deciding whether or not to participate/have your child participate in research on genetic risk for MS?	• *Completing questionnaires about your family history and ancestry?* • *You/ your child or other family members donating blood for genetic analysis?* • *Whether or not research might lead to a way to prevent or treat MS?*
21. Genetic studies may require analyzing your/your child's entire genetic make-up (also called DNA). There is a chance that genes would be found for other diseases. How do you feel about this?	
E. Environmental risk factors (5 min) There is some evidence that exposure to certain infections or things in the environment (like pollution or a lack of vitamin D in sunlight) may be partially responsible for causing pediatric MS. We are interested in finding out your views on research that would study possible environmental risk factors for pediatric MS.	
22. What do you think of research studies to look for environmental risk factors that may cause pediatric MS or worsen it?	
23. What factors would you need to consider when deciding whether or not to participate in research on environmental risk factors?	• *Questionnaires—how many?* • *Need for blood, urine or stool samples for labwork?* • *Frequency?* • *Whether or not research might lead to a way to prevent or treat MS?*

(continued)

Table 1. (continued)

F. Cognitive and psychosocial outcomes (5 min) Multiple sclerosis can sometimes affect a person's ability to focus, think or process information, or can affect emotions and level of energy. It may also impact how children with MS do in school. This type of research usually involves completing questionnaires and/or a battery of cognitive tests of things like attention, memory, and reading. It might also involve getting report cards or other records from schools.	
24. What do you think about conducting research on cognitive and psychosocial outcomes in pediatric MS?	
25. What factors would be important to you when deciding whether to enroll/your child in a study of the cognitive, psychological or educational effects of MS?	• Whether or not there is neuropsychological testing • Length of test battery • Where and when testing can be completed • School involvement • For questionnaires—length, whether they could be completed at home, online • Whether or not some treatment is offered
G. Disease severity (5 min) Some people with MS have a mild disease course, while others have a more severe disease course. People with a severe course may have more significant physical limitations or may have complications sooner and faster than people with a mild course. Research studies that look at physical disability in the present as well as when children with MS become adults is another area of study. These studies might include questionnaires as well as physical exams testing strength and balance.	
26. What do you think about conducting research on physical disability outcomes in pediatric MS?	
27. What factors would you need to consider in deciding whether or not to participate/have your child participate in research on the short and long-term effect of pediatric MS on physical functioning?	• *Questionnaires* • *Frequency of visits* • *Length of study—1 year, 2 years, 5 years, 10 years, >10 years* • *Part of routine visits/ care* • *Convenience—don't need to take time off from work* • *Might lead to ability to predict how you/your child will do over long term* • *Whether or not studies of disability might lead to some treatment*
H. General issues Our final set of questions are about research into pediatric MS in general.	
28. There is often a gift and/or monetary reimbursement given for participation in a research study. What do you think about this?	
28a. What type of activities should be reimbursed?	• *Parking* • *Travel to appointments* • *Your time away from work*
28b. Would the provision of a gift affect your decision to participate in a study?	• *Different for different types of studies*
29. Are there any other questions that you think that researchers should be asking about or doing research on in pediatric MS?	
30. What questions do you think are the most important to ask in pediatric MS?	• *Drug trials* • *Genetic and familial risk factors* • *Environmental risk factors* • *Cognitive, psychological and educational outcomes* • *Disease Course and physical disability* • *Other topics initiated by the group*
31. What do you think is the best way for researchers to continue to gather the opinions and input from parents/people with pediatric-onset MS?	• Meetings/focus groups • Internet-Facebook • Teleconferences • Paper surveys (eg, at medical visits or by mail)
32. Are you aware of fund-raising efforts for research in pediatric MS? If so, what do you think of fundraising efforts for research in pediatric MS?	
32a. Any suggestions to improve those?	
33. What's the best way for you and other MS patients and families to find out about future research in pediatric MS?	• Website? • Newletters? • Patients meetings? • Webinars? • Teleconferences? • Support groups? • Asking your doctor? • TV shows?

analyzed with NVivo 11 software, using thematic analysis where patterns were identified, documented, and reported (32). We organized and presented data quasi-quantitatively where code frequencies and incidence were aggregated and compared (34). The coding was overseen by one lead researcher, along with three research assistants simultaneously trained. The entire team reviewed coding results at various intervals and guided data query and reporting. The study protocol followed the Consolidated Criteria for Reporting Qualitative Healthcare Research (35).

Results

A total of 26 predominantly females participated: parents (N = 12) of youth with POMS and young adult patients (current age 18-40 years) diagnosed with POMS onset <age 18 years (N = 14), mostly unrelated to parent subjects (Table 2).

The most salient discrepant findings were between parents and young adults with little variation between locales. Findings are, therefore, presented by parent versus patient. Findings are reported below with Table 3 subsequently offering illustrative quotations by theme and cohort.

Experiences with Medical System

Both cohorts shared highlights of past medical system experiences. This provided contextual information to interpret results pertaining to future study involvement. Results are presented in terms of perceived positive and negative experiences.

There were similar views among cohorts regarding positive healthcare experiences. Each felt valued when POMS physicians were compassionate, communicative, and proactive. There were subtle discrepant views among parents and patients with negative healthcare system experiences. Parents highlighted challenges around obtaining an accurate initial diagnosis. Patients spoke in terms of the lack of MS expertise, as well as a tendency to not be taken seriously by emergency room clinicians, especially in smaller community hospitals.

Patients emphasized social factors that promoted or impeded their overall MS-related health and wellness. Social determinants of health included treatment locations, access to expert care, differential treatment, age-related discrimination, knowledge of MS within educational systems, complications of depression, transportation challenges, and medication costs.

Patients resented feeling different from peers, and noted the inability to regularly partake in sports. They were concerned that once they were diagnosed, the disease would define them. They highlighted the desire for meeting others in similar situations. They felt that their voices were validated when they worked with POMS specialists.

Parents cited some negative experiences with the healthcare system. However, they were more likely to view challenges in terms of obtaining an accurate diagnosis and determining the most manageable and least distressing treatments for their children. They also expressed concern about communication between school officials and MS clinicians.

Views on Research

Both cohorts supported future clinical research studies and elaborated on their respective considerations for involvement. Top thematic codes were derived from code frequencies among all focus groups, as well as queried comparisons among study groups. Data are presented in terms of the following overarching themes: considerations for clinical study involvement (Figures 1 and 2); views regarding studies including placebo, views regarding studies comparing two medications, and views regarding cognitive studies.

Considerations for Clinical Study Involvement

Both parents and patients highlighted circumstances that either previously had or potentially could impede or encourage participation in any type of clinical study regarding medications and/or other MS-related factors. Both cited convenience as paramount. Neither group wanted to be overburdened in terms of adding to the existing MS treatment requirements. They feared fatigue predominantly for patients. However, young adults were also concerned about time requirements for family members. Each group expressed a need for some level of compensation. Young adults stated that other incentives should be child-centric or more fun, such as using technology and games. Parents and patients saw research participation as a way to help others, limit pain and suffering, and to identify POMS causes and cures. They relished the opportunity to contribute.

Views Regarding Placebo and Two Medication Studies

Participants were asked to consider clinical trials involving either placebos or a comparison of two medications with various medication delivery modalities. Both groups expressed distinct feelings about involvement in such studies with parents citing minimizing discomfort for their children and patients highlighting a desire to resort to prior medications as needed. Both emphasized obtaining a thorough understanding of the rationale for study, processes entailed in participation, expected benefits, and potential harm.

Cohorts wanted as much information as possible on medications including those that could be used, as well as those from adult-focused clinical trials. Parents were particularly concerned about children having to switch from pill to injection, thereby potentially increasing anxiety or pain. Parents were wary of youth compliance with medication regimen. Finally, both parents and patients expressed concern about returning to an old medication if a study medication was not efficacious.

Table 2. Demographics by Focus Group Type.

Focus group by city	Sample size	No. of females	Percentage of females	Spanish speaking/Latinx	Average child age at POMS diagnosis	Current average age of child w/POMS
City 1—parents	5	2	40%	0	9	14
City 2—parents	3	2	67%	2	16	18
City 3—parents	4	3	75%	0	9	15
City 1—young adults—patients	5	5	100%	0	13	30
City 2—young adults—patients	5	3	75%	1	17	21
City 3—young adults—patients	4	4	100%	0	16	27
All parent groups combined	12	7	58%	2	11	16a
All patient/young adult groups combined	14	12	85%	1	15	26b
Total sample	26	19	73%	3	13	

[a]Parents in sample had children who were currently between 14 and 30 years, but were diagnosed with POMS.
[b]Young adults in sample were distinct from parent sample and ranged in age from 18 to 40 years, but diagnosed with MS as children or teenagers.

Views Regarding Cognitive Studies

Subjects reported previous cognitive study participation with psychosocial outcomes (eg, attention, memory, academic achievement) and shared factors for research consideration. Parents were worried about how their children would feel about research results. They did not want children to view findings as personal indictments. They also felt that cognitive tests on any given day might not accurately represent their child. Finally, they noted that such testing had potential to heighten anxiety, increase feelings of being "different" and undermine children's self-confidence. Parents were more likely to see the value of cognitive research if results could be used to track treatment response or to inform Individual Education Plans. Young adults had fewer concerns about participation in cognitive studies since they did not require additional medications. However, some noted these types of tests made them feel stupid or were long and boring. Finally, young adults suggested broadening exploration beyond cognitive experiences and delving into nutrition, mental health, social support, and comorbidities as potentially MS associated.

Discussion

The study described is the qualitative portion of a mixed-methods investigation of patient and family views regarding POMS clinical research. Results offered both shared and unique views between parents and young adults with POMS on research participation interests and concerns, research priorities and meaningful engagement in research.

Asking about experiences with the medical system provided a context for understanding priorities for and views on research participation. *Caring provider* was the predominant positive experience theme expressed by both cohorts. Caring referred to accessibility and frequent communication, as well as interest, compassion and knowledge of state-of-the-art MS treatments. Negative experiences centered on challenging pathways to accurate MS diagnoses, as well as behaviors of generalist clinicians lacking MS expertise. While the ways in which parents and POMS patients experienced a lack of knowledge or understanding were different, the negative impact was salient for both, and improving POMS education and knowledge among the broader healthcare system was a priority for both. This suggests that, particularly when designing studies of rare diseases, researchers should consider possibilities for using results to better inform general medicine providers to improve early experience of diagnosis and referral to specialists.

Parents and patients had similarities and differences with logistics pertaining to participation in POMS research. In general, each group spoke to visit frequency and location, the perceived belief in the broad efficacy and impact of study participation, and the type of participation incentives. Both groups preferred when research participation could be integrated with regular medical care and follow-up to limit patient fatigue and the burden of time away from work and other parental obligations. Interestingly, both groups spoke about incentives being important but not for their monetary value as much as for their compensatory value to families and as fun incentives for pediatric patients. More important than being compensated, parents and patients both spoke of the importance of knowing that their participation in research had real potential to improve outcomes or quality of life for all POMS patients. This highlights the importance of research informed consents that outline not only the specific risks and benefits to participants but detailed information about the rationale for the study and potential implications for the broader disease population.

When asked about participation considerations in placebo and two medication studies, parents emphasized minimizing

Table 3. Parent Versus Young Adult Patient Preferences.

Parents		Young adults	
Theme	Quote	Theme	Quote
Positive healthcare experiences			
Caring provider	*But they're always accessible. We have parent portals, we can access. He answers, he picks up the phone, he calls, he discusses. I'm thinking she's having a flare. He's like, "Well, this isn't really a flare." We discuss it over a week or so and then he says, "You know what? Let's go ahead and medicate and let's give her some steroids." So he is—it is, it's that being heard, yes. It really is.*	Caring provider	*Just the neurologist, like if there is anything she feels like we should try or we should know, just something to run by me maybe, I'm the first person to know. She is awesome with me, her staff, just everybody. I think it probably would have been a whole lot harder if I had terrible people to work with on top of dealing with such an awful thing, but everybody has been awesome.*
Negative healthcare experiences			
Difficult diagnosis	*When [my daughter] first had her first known relapse and I took her to her pediatrician, this was not anybody that was affiliated with the MS Center, and they put it down as a behavioral issue. And she was right hand dominant because of gross motor delays on her left side. She was right hand dominant from like under one year old. So when she lost the use of her right arm it was just so screaming obvious that there was something wrong, and yet they were like, "Oh it's a behavior. Just ignore it."*	Emergency rooms	*I ended up going to the ER about three times and they pretty much were asking me if I had accidentally sat on my leg and it fallen asleep. And I'm like, "For two weeks? Like really? Really?" And they were yeah, pretty—because I was a teenager so they were pretty much—it was a way for me to get out of school or something.* *For me, I think what's more stressful is going to the ER after getting a relapse and thinking that they'll help. And what I've noticed is they always ask me what drugs I need. So they won't even—they'll just ask me, "Oh, so what could I give you so you could pretty much leave?"*
Considerations for clinical study involvement			
Visit frequency/ logistics	*Nothing past two hours … If they need to be longer, at least split it another day.* *Doing it somewhere close… Or having even sometimes if people could come to your house or whatever.*	Visit frequency/ logistics	*"I think it depends on like how long the doctor's appointment is going to be and if I get paid."* *I would come for my appointment, like maybe come for the MRI early morning and then see the doctor and then after do the study stuff. So get it all at one go.*
Incentives	I think it might be nice depending on—if the child is involved, maybe some incentive for the child might be nice like age appropriate something, I think would go a long way.	Incentives	*"…minimal wait, and if I get, if they hand me $50 bucks."* *Diminishing the costs to participate, … just kind of reimbursing to get there. I think in all the studies that I've participated into being able to do my MRIs and have those be covered was appealing.* *… Make it fun (not boring)—Use technology (tablets, apps, etc) to make testing fun for kids*
Utility of participation	I feel like I also might be more willing to participate in a trial. I don't know, for some reason, eyes, the vision to me, is so much more like of a worry and a lot of the symptoms are visual related. So, if it was something that could prevent the loss of vision or the impact on his eyes, I think I'd be more willing to take—to participate as opposed to some other-	Utility of participation	*Yeah, [I want] frequent feedback … the thing that keeps me doing that is they send like little journals out to your house and it says, "Here's what our surveys are showing, the most recent things," even though they're not publications yet.*
Views regarding placebo studies			
Current medication continuation	Did not emerge as key theme	Current medication continuation	*…I didn't go off my medication, which I think if I had to go off it I would be more hesitant to [participate in a clinical trial.*
Information on medicine	Did not emerge as key theme		*I think I would want to understand how it's done in the adult community or if it was tested in the adult community, how effective it was. Is it new to the whole MS community or has it been existing…*

(continued)

Table 3. (continued)

Parents		Young adults	
Theme	Quote	Theme	Quote
Limit discomfort	*I think in terms of suffering, just nothing that involves suffering. Like tests, risk of further symptoms, anything that is painful, that's a big issue.* *I would not put them through that and have to suffer whatever amount of time it is. But like with my daughter, it never goes away, it's never going away. They get a little better, but like right now she is afraid to even tell me what is going on, because of missing school. She was out of school for a long time and she wanted to go back real bad, so I let her go back. I told her, "If you go back and you start saying you're having all these problems again it's going to be an issue because they're not going to let you just go out again, so we've got to make sure you're okay."*	Limit behavior change	I haven't had to change my behavior, because you need blood work every three months, well I already get that, or you need an MRI four times a year, I already do that. So, me participating had no effect on me. I'm not going to miss two tablespoons of blood and I already don't know who is looking at my MRI, so…
Views regarding two-medication studies			
Information on medicine	*"I'd feel safer with…knowing…what the medications are. As long as it came with the information of the side effects and what to expect."* *I think for me a big piece is understanding an honest representation of risk factors and short-term, long-term side effects. Which lots of times there aren't long-term side effects because we don't know, we haven't had it out long enough.*	Information on medicine	*For me, it would be more the understanding—the problems that I presented before with clinical trials, that would be—that's a higher factor to me than the compensation side. Because I worry more about the—what ifs.*
Medication administration route	*"…it hurts me to see that he is getting pinched, by injecting. I would prefer that he could take a pill."* *"…for the child who's used to taking pills and then now has to take a shot, that's kind of a big mental hurdle to get over. So I feel like it's a psychological thing for kids."* *"…she couldn't deal with the shots all the time. She was willing to try it, but she just couldn't do it. Now she is like a pro. She doesn't care for shots, but you do any kind of blood work or anything it don't bother her."*	Medication administration route	*"Anything that has to be with the blood drawn. I tend to be hesitant, but if it needs to be done and if it's—if it has any benefits for individuals that have MS, I would do it."*
Effectiveness of current medication	*It would also depend on what the current state of how my child is doing right now. Like have we tried everything and we've exhausted all options. Then I might be more willing to say I'm willing to try something new because we've tried the 13 other things that are out there and it's not working so let's try this.*	Effectiveness of current medication	Did not emerge as key theme
Views regarding cognitive studies			
Holistic approach	*Because she had an IEP and that way so they can get from me the information that I get from the doctors and we all share together so they understand—*	Holistic approach	Did not emerge as key theme

(continued)

Table 3. (continued)

Parents		Young adults	
Theme	Quote	Theme	Quote
Psychological impact	*[I] don't know if it's as much a burden to the child as much as putting them on the spot. We don't want to do that. They're already feeling different. And they don't need to be made to feel different again.* *"…sometimes kids don't show their real personalities or their real selves the first time they meet somebody. Would they need to get comfortable with that person first, like after a couple times, and then really be tested or questioned like they needed to be tested?"*	Psychological impact	*And looking at the tests, I want to do better than the next time. I don't want someone to tell me that I'm not good enough or that I'm stupid or that I don't know how to do something so I always work to the fullest.* *I hate those cognitive tests. They made me feel like stupid or whatever, because they're hard…* *I think there would be a lot of pressure on myself to try to be what's normal considered.*
Broader societal impact	*I mean, as long as—my daughter would probably say yes, let's do it, because she has a mentality as, "Mom, maybe this happened to me it's for a reason to help other children that don't know anything."*	Broader societal impact	*"…it's for the cause, and when you kind of look at it it's to make it better for the younger generation as well as the older generation. I mean there is people who are older than me who are worse off and there are people who are younger than me that are worse off. So, if you kind of think in the back of your head that this is for the common goal of making medicine that is going to make us all better that sometimes is win-win for me."*

Abbreviation: IEP, Individual Education Plans.

pain, discomfort, suffering, and risk to children. Both groups wanted the option to return to previous medications if symptoms recurred. This presents a challenge to the gold standard of a double-blind placebo study. Researchers and regulators may need to rethink notions of placebo studies being the standard of rigorous clinical trials and consider alternative designs, particularly for rarer diseases like POMS where participation and sample sizes are challenging and the impact and morbidity of disease is of high concern especially to parents. Together with expressed concerns about the burden of time for research participation, results of this exploration recommend that study design needs to include a balance of participant burden with scientific validity. Consideration of Sege and Devos' (36) broader pediatric research design matrix for evaluating evidence in a variety of formats beyond conventional clinical trials may facilitate further essential POMS research.

The most notable differences between parents and young adults were with perceptions of cognitive studies. Results highlighted concerns about dissemination and utilization of data, psychological impact on patients versus benefit, as well as broader societal knowledge impact. Both groups felt the risk of psychological discomfort should be outweighed by the potential usefulness. This again highlights the importance of providing subjects with detailed and understandable information on the purpose and expected benefits of research both for participants and for the disease population as a whole. And it highlights another benefit of integrating research participation into routine clinical care. Results of the study are especially relevant to other pediatric diseases where the impact on quality of life is understudied. When asked about additional areas of study potential, both groups highlighted quality of life and comorbidity research.

Overall, young adults hoped their experiences could inform future POMS research and treatment advances. They trusted that past suffering was not in vain and expressed a desire for on-going study feedback results. Parents' primary concern was their children's overall well-being and averting additional burden. Yet, they too realized the potential value of participation in future POMS research. In general, young adult patients had fewer reservations about research participation than parents as reflected in more frequent statements of altruism and general interest in research. Sharing patient perspectives with parents and patient advocacy groups might encourage research participation.

Our findings are limited in that they are applicable only to study participants, and, therefore, are not generalizable to a larger population. However, this study's focus groups were invaluable for gathering data to inform the next steps in understanding family perspectives on POMS research. From the categorical themes identified by the study, we developed and disseminated a survey for all NPMSC patients and parents.

This study also illustrated how patients incorporated social determinants of health in discussions about their health, treatment, and future participation in clinical and other studies. Future researchers ought consider and address such barriers to engagement. The study design could be used in other countries with significant concentrations of pediatric MS patients and eventually interregional

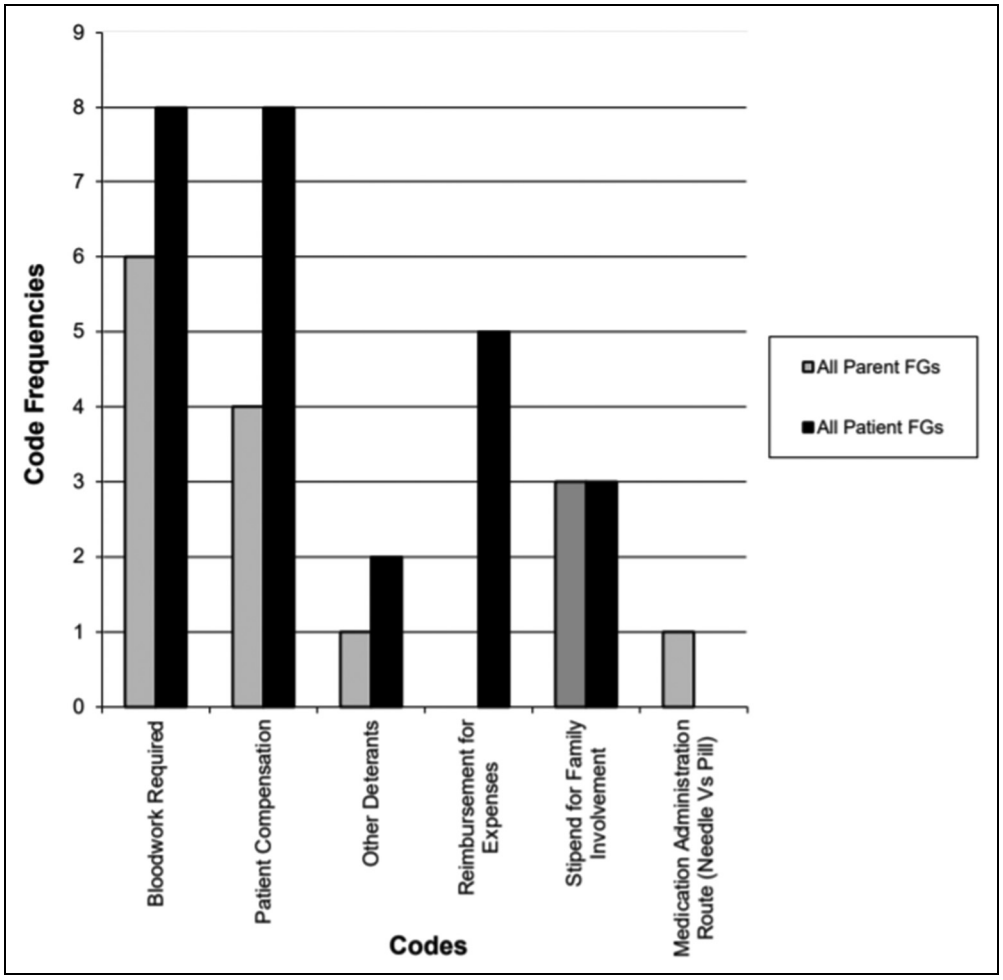

Figure 1. Parent versus patient considerations for clinical research participation.

results could be compared. Finally, the study model may inform other pediatric rare diseases, where maximizing recruitment and engagement is critical, and particularly for those in which clinical trials of new therapeutics are federally mandated, such as arthritis and inflammatory bowel disease.

Limitations

There may have been recall bias as participants were asked to remember prior healthcare and medication experiences, particularly for young adults whose perspectives may have changed over time. Further, given wide age range in patient participants, views may vary more broadly. Qualitative data also offers subjects' perspective at a particular point in time (34), still through data saturation, as well as clinical researchers' POMS experience, findings appear reliable. Given the scarcity of research on both parents' and pediatric patients' views of research participation, the benefits of a retrospective design likely outweigh limitations. Parents are too often used as proxies for pediatric patient perspectives. The inclusion of both patient and parent perspective on the same disease is a unique feature of this study and yielded notable distinctions.

We were not able to attract Latinx families, patients, and/or male subjects as anticipated. A broader sample would have enabled coding comparisons among cohorts (parents, patients, gender, and Latinx ethnicity) to determine possible differences. Still, we are confident that the data presented are robust and offer important information. More targeted culturally competent outreach, diverse staff and community-based data collection sites are warranted. These continued efforts will demonstrate commitment to achieving health equity for all POMS stakeholders.

Conclusions

Policy efforts designed to augment pediatric clinical research have had modest success. Recent recommendations of the International Pediatric Multiple Sclerosis Study Group suggest global consolidation of clinical trial designs (14). Policies such as The Patient Protection and Affordable Care Act of 2010 have facilitated Patient-Centered Outcomes Research (PCOR) as a means to assist patients, clinicians, and others in making informed health decisions through integrative, collaborative research (37), yet pediatric-

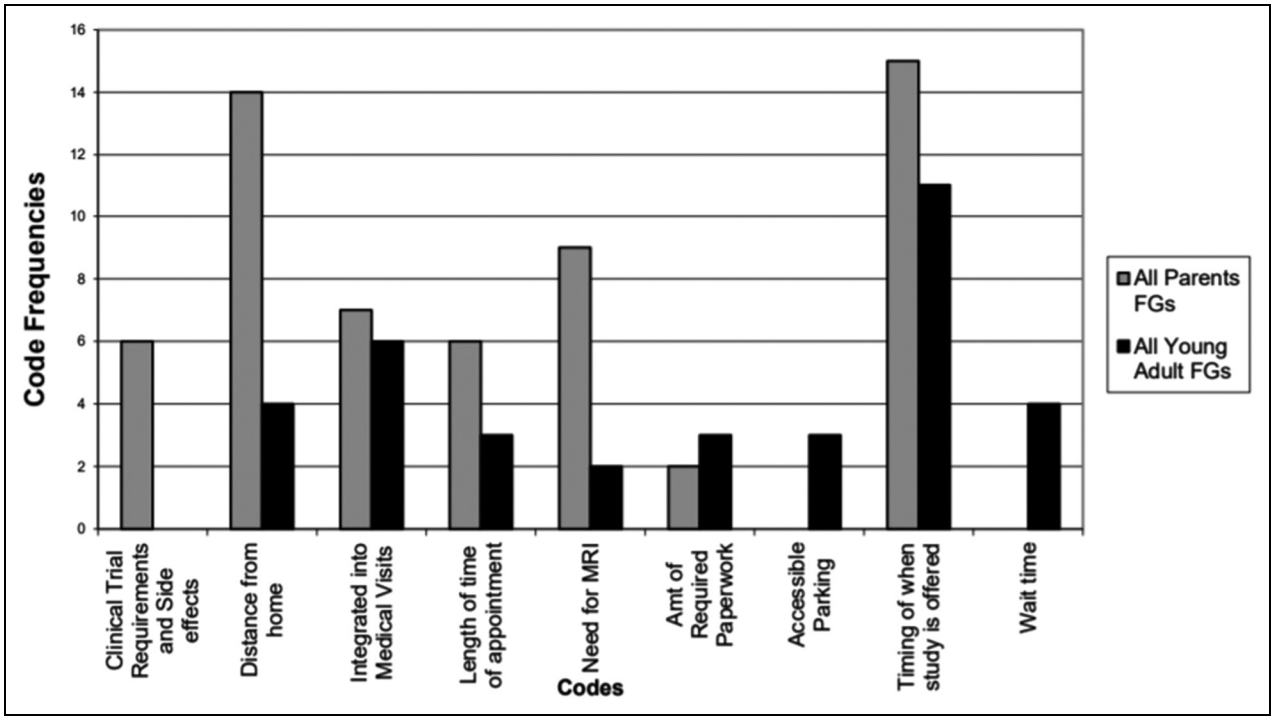

Figure 2. External factors impacting research participation interest.

focused PCOR is still lagging. A limited number of studies have reported that pediatric and adolescent patient engagement in their diagnosis, treatment, and clinical trial design is efficacious for both patients and researchers (38,39). However, few studies have engaged younger adult patients and families retrospective views to apply to future clinical study design. This study highlights the value of comparing and contrasting parent and patient perspectives. It also recognizes that a range of experiences within a disease course all color viewpoints and should be considered in research design.

Researchers must embrace changing times and recognize that closing a research gap, reducing health disparities, and promoting equity in pediatric clinical research is to engage patients and families in the research design process.

Acknowledgments

The authors would like to thank Katie Poulin for her assistance with study coordination and data coding. Other research assistants were: Michele Gomez, Madeline Grocott, and Ludmila Neves.

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 work was supported by the National Multiple Sclerosis Society: Health Care Delivery and Policy Research Contract.

IRB Approval

This study received IRB approval from the Mass General Brigham Human Research Committee and three affiliate Pediatric Multiple Sclerosis Centers. Protocol #: 2016P000430, PI: Chitnis, Tanuja/MGH, Approval Date: 04/11/2016. Written informed consent was received by all study participants.

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