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ORIGINAL RESEARCH

Unmet Therapeutic Needs of Non-Ambulatory Patients with Duchenne Muscular Dystrophy: A Mixed-Method Analysis

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Abstract

Objective Duchenne muscular dystrophy has been a launching pad for patient-focused drug development (PFDD). Yet, PFDD efforts have largely neglected non-ambulatory patients. To support PFDD efforts in this population, we primarily sought to understand the needs of non-ambulatory Duchenne patients and, secondarily, to examine these needs in the context of the PUL-PROM—a validated patient-reported outcome measure of upper limb functioning.

Methods Non-ambulatory Duchenne patients or their caregivers from eight countries answered open-ended survey questions about patients' needs related to their most significant symptoms and important benefits of new treatments. The PUL-PROM was used to evaluate patients' upper limb functioning and was compared to data collected on non-ambulatory stage and quality of life**.** We thematically analyzed open-ended data, descriptively analyzed close-ended data, and compared themes by non-ambulatory stage.

Results The study included 275 participants. Mean patient age was 24. Most patients were early-stage non-ambulatory (67%). Thematic analysis identified three congruent themes between significant symptoms and important benefits of new treatments: muscle functioning, especially upper limb function; body system functioning; and quality of life. Muscle functioning and body system functioning were endorsed more frequently in responses from early- and late-stage patients, respectively. Mean PUL-PROM total score was 22 with higher scores in early-stage patients ($p \leq 0.001$). Upper limb function positively correlated with quality of life ($r = 0.42$, $p \leq 0.001$).

Discussion Non-ambulatory Duchenne patients want new treatments that improve upper limb functioning and body system functioning, and not exclusively regaining ambulation. The PUL-PROM can be used as a patient-centric measure that accounts for the needs of later-stage Duchenne patients.

Keywords Rare diseases · Patient reported outcome measures · Patient-focused drug development

Introduction

Duchenne muscular dystrophy is a rare, degenerative genetic disorder [1–6] that leads to progressive muscle deterioration characterized by weakness and losses in ambulation and upper limb function [1–3, 7]. Most people affected by the disease become non-ambulatory and require a wheelchair by adolescence [1–3]. Upper limb weakness occurs first in the proximal muscles, progresses to a loss of function where movements are limited to the fingers, and affects performance of activities of daily living [8, 9]. Ongoing disease progression is further characterized by cardiomyopathy and respiratory insufficiency [1–3]. Patients affected by Duchenne typically die during the third decade of life due to cardiorespiratory failure [4].

There is currently no cure for Duchenne [18]. Standard of care includes use of oral corticosteroids that slow disease progression but can have serious side effects [10, 11]. Several therapeutic strategies [12–14], including some for non-ambulatory patients, are in development. These therapies primarily focus on muscular and cardiac functioning and target inflammation, stabilizing muscle structure, or restoring the expression of dystrophin (the underlying

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cause of Duchenne) [12, 14]. Regulatory approval of drugs that restore expression of dystrophin varies by country and region [12, 15–19].

New therapies for non-ambulatory patients are in the pipeline. However, most drug development efforts have focused on slowing disease progression for ambulatory patients and delaying the loss of ambulation. The benefits have often been assessed using the six-minute walk test, a functional mobility endpoint [20–22]. There are regulatory questions related to how drug development can address the needs of non-ambulatory patients. Patient-focused drug development (PFDD) is one approach employed by regulatory groups such as the US FDA to help include patients' experiences, perspectives, needs, and priorities in drug development and evaluation [23]. To elicit these perspectives, PFDD initiatives [24, 25] engage patients with the condition, as well as caregivers and advocates, to report on aspects of the disease experience, including questions related to unmet need, quality of life, and treatment experiences (for instance see summary report on Parkinson's Disease) [26]. Most PFDD efforts have neglected to focus on non-ambulatory Duchenne patients. Additionally, there is a need to understand non-ambulatory patients' needs as they relate to existing outcome measures validated for use among non-ambulatory patients.

We sought to explore the experience of non-ambulatory patients with Duchenne muscular dystrophy given the paucity of PFDD for this sub-population. We do this by identifying and describing the needs of non-ambulatory patients with Duchenne, and examining these needs in the context of the Performance of the Upper Limb Patient-Reported Outcome Measure (PUL-PROM) measure—an existing, validated patient-reported outcome measure of upper limb functioning. This research builds upon a decade of engagement with the Duchenne community [27–32]. Findings from this study will inform patient groups, regulators, and drug developers on the current experiences of non-ambulatory patients with Duchenne.

Materials and Methods

We applied principles of mixed-methods research across the design, analysis, and reporting of findings [33] to (1) understand the needs of non-ambulatory patients; and (2) examine these needs in the context of the PUL-PROM measure. Reporting adhered to the consolidated criteria for reporting qualitative research (COREQ) [34].

Data Source and Sample

Data for our study came from a cross-sectional survey of international patients with Duchenne or their caregivers. The survey was informed by a literature review and developed in partnership with a 16-member, international community advisory board comprised of patients, parents, and professional advocates [29]. It used a convergent design to concurrently collect open-ended and close-ended data [33]. The survey was administered through Qualtrics online platform and fielded remotely between October 2018 and May 2020.

Patient advocacy groups recruited participants for the survey using a variety of strategies that included social media, patient registries, snowball sampling, and word of mouth. Individuals were eligible to participate in the survey if they were (1) 18 years or older; (2) a male with Duchenne or a caregiver of a male living with Duchenne; and (3) currently residing in a participating country, which included Australia, Belgium, Canada, France, Italy, the Netherlands, the United Kingdom, or the United States. The survey was available in six languages/dialects to reflect the participating countries. The languages included English, Italian, French (Canadian, Belgian dialects), and Dutch (Netherlands, Flemish dialects). The eligibility criteria allowed for caregivers aged 18 or older to report on behalf of patients with Duchenne who were younger than 18. Among those who were eligible to respond to the survey and who did complete it, we limited the sample for the current study to non-ambulatory patients with Duchenne or caregivers of non-ambulatory patients. Patients were classified as non-ambulatory if they reported full-time use of a wheelchair.

Participants indicated their consent to participate by a one-question item on the first screen of the survey. All protocols for data collection and analysis were approved as research exempt by the Johns Hopkins Bloomberg School of Public Health (IRB8175) and The Ohio State University College of Medicine IRB (2019E0113). We worked with participating countries to determine if an additional, country-specific IRB review was needed, and each country determined that further ethical review was not necessary.

Open-Ended Survey Questions

Participants were asked to answer open-ended questions about their needs. These questions were similar to those asked by the FDA and the European Medicines Agency during their PFDD meetings and were intended to understand how drug development could be improved to fit patients' needs [29]. The questions were (1) "Thinking about your/your child's current Duchenne symptoms, which 3 symptoms have the biggest impact on day-to-day life? Please describe them here." and (2) "Think about day-to-day life over the past month. If a new treatment could cause a small but important benefit, what types of improvements would be important? Please list 3 small but important benefits." Each

question included its own open-text box where participants could comment.

Close-Ended Survey Questions

Close-ended survey questions were used to collect information about the demographic and clinical characteristics of patients including their age; medications used to manage Duchenne; experience participating in a clinical trial; and receipt of medication through a special drug access program via a biopharmaceutical company (which may vary by country given differences in regulatory drug approval). As described below, the survey included additional close-ended questions to assess patients' upper limb function and other measures of health status (ambulatory status, and health-related quality of life).

Performance of the Upper Limb Patient-Reported Outcome Measure (PUL-PROM)

Patients' upper limb functioning was assessed using the validated PUL-PROM [35, 36]. The PUL-PROM measures domains related to activities of daily living including food, leisure, self-care, and the household environment. The PUL-PROM includes 32 items with the following three response options that are assigned a score of 0 to 2 points: "impossible to do without help" (score = 0 points); "can do with difficulty" (score = 1 point); and "easy to do" (score = 2 points). A total PUL-PROM score was calculated by summing the scores for each response option. The total PUL-PROM score ranges from 0 to 64 where higher scores indicate better functioning.

Other Measures of Health Status

Ambulatory status was assessed using a measure of mobility developed to proceed the PUL-PROM. The measure contains 10 response options, and consistent with a previous study and guidance on care by stage, they were recategorized to reflect disease stages including early ambulatory; late ambulatory; early non-ambulatory; and late non-ambulatory [31, 37]. As stated above, this study focused on non-ambulatory patients, and patients were classified as non-ambulatory if they reported full-time use of a wheelchair. Patients were also classified as early- or late-stage non-ambulant. Patients were classified as "early-stage" non-ambulatory if they reported that they could use a wheelchair independently both indoors and outdoors. Patients were classified as late-stage non-ambulatory if they reported they were unable to go outdoors in some situations (such as cold weather) or control a wheelchair without help. Respondents were excluded from the analytic sample if they did not report on the patients' ambulatory status.

Patient's health-related quality of life was evaluated using country/language-specific 3-level EQ-5D instruments [38]. Patients completed the self-reported version of the measure (EQ-5D-3L) and caregivers completed proxy versions of the measure depending on the age of the patient (EQ-5D-Proxy1 for patients 12 years of age and older or EQ-5D-Y for patients aged 11 years of age and younger).

Analysis

In parallel and retrospectively, we thematically analyzed the open-ended data and descriptively analyzed the quantitative data [33]. The analyses are reported using a narrative-contiguous approach along with a comparison of qualitative findings by non-ambulatory disease stage [33]. We present summary statistics as proportions for discrete variables and the mean for continuous variables. Patients' demographic, clinical, disease-specific functional status, and health-related quality of life were compared by early- and late-stage non-ambulatory status using chi-squared tests for categorical variables and one-way ANOVA for continuous variables (significance defined as p value < 0.05).

Thematic Analysis of Open-Ended Data to Understand Patients' Needs

Data from the open-ended questions were exported into an Excel (Microsoft, Redmond, WA, USA) spreadsheet. Non-English responses were translated into English using multiple tools for triangulation, when necessary, and were translated before they were reviewed. Responses for each of the two open-ended questions were evaluated using interpretative phenomenological analysis, which is a qualitative research methodology used to make meaning of patients described, lived experience [39].

We used a multi-step process to code the data and identify themes. To code the data, we started first by reading and re-reading the comments from all participants, where participants' comments ranged in length (e.g., from short phrases to full paragraphs). This allowed us to become familiar with the overall account and become aware of repeated words or phrases. From there we identified and segmented the comments into meaningful, "chunked" responses—that is sets of words or statements that related to the same "central meaning." We then extrapolated the meaning of these chunked responses using a few words and finally encapsulated the central meaning of each chunked response in one or two words, which became our codes. From there we induced themes and thematic clusters first by connecting codes that related to the same central meaning and then by clustering themes according to similarities, nesting, and discordance.

We summarized the qualitative findings using representative quotes and by counting the frequency of responses

within each theme and thematic cluster. We also evaluated the frequency of responses by patients' non-ambulatory stage. In calculating the frequency of responses, we defined the denominator as the total number of responses. To contextualize the representative quotes and facilitate interpretation of the findings, we merged each representative quote with the close-ended data from the respective patients, including information about the patient's residence of location, functional status, PUL-PROM score, EQ-5D index score, and medication history.

Examining the PUL-PROM Distribution and by Non-ambulatory Status and Quality of Life

Building on the previously conducted validation study of the PUL-PROM [36], we evaluated the distribution of PUL-PROM total scores, looking at features such as skewness and percentage of responses at extreme values of the scale. We also explored the PUL-PROM among groups with clinically relevant differences in disease progression. We compared PUL-PROM total scores between patients of early- vs. late-stage non-ambulatory status. With the knowledge that patients' declines in functional ability can affect quality of life, we compared EQ-5D index scores to the PUL-PROM using a Pearson correlation. We used Stata SE version 14 (StataCorp LP, College Station, TX) for all analyses and defined significance as p value < 0.05.

Research Team

The research team was composed of professional patient advocates (RF and PF) as well as social scientists (AS, NC, and JB) who range from junior-level to senior-level academics with training in health services research, decision sciences, and economics, respectively. The team members are based in the U.S. Collectively, the team has deep knowledge of Duchenne muscular dystrophy and brings extensive experience with patient-focused activities in Duchenne, including community-engaged qualitative research [27–31, 40–44]. Two team members (AS and NC) independently coded and thematically clustered a random sample of responses to the open-ended questions. The team members compared findings and determined how to code moving forward. Disagreements were adjudicated through discussion with a third team member (JB). One team member (AS) then coded and thematically clustered the dataset. The other researchers reviewed the work in its entirety to assess the interpretation's validity. Two team members (AS and NC) completed assessments of the PUL-PROM.

Results

A total of 528 individuals were sent the survey between October 2018 and May 2020. Of the individuals sent the survey, 496 initiated it and 450 were eligible to complete it. Among those who were eligible to complete the survey and did complete it, 175 were excluded from our study because they were ambulatory. The final analytic sample included 275 participants where 101 were non-ambulatory patients and 174 were caregivers reporting on behalf of non-ambulatory patients (Fig. 1).

Table 1 presents characteristics of non-ambulatory patients overall and stratified by non-ambulatory-stage. Most patients ($n = 185$) were early-stage non-ambulatory (67%). Approximately one-fifth of patients resided in the U.S. (21%) and the majority of international patients resided in European countries or the U.K. (64%). Mean patient age of early-stage non-ambulatory patients was 21, compared to a mean patient age of 29 among late-stage non-ambulatory patients ($p < 0.001$). Early-stage non-ambulatory patients reported a mean PUL-PROM total score of 29 (18.7), which was significantly higher than that of late-stage non-ambulatory patients (7.5, 9.8) ($p < 0.001$). The mean EQ-5D index score reported by early-stage non-ambulatory patients was 0.35 (0.20), which was also significantly higher than that reported by late-stage non-ambulatory patients (0.29, 0.17) ($p = 0.018$).

More than a third of patients had participated in a clinical trial overall (39%), yet the percentage of patients participating varied significantly across non-ambulatory stage with only about 25% of late-stage non-ambulatory patients having participated ($p = 0.003$). Nearly one-fifth of patients overall had participated in an expanded access program (18%). Most patients reported using heart medications (88%). Late-stage non-ambulatory patients were significantly less likely to have used steroids to manage Duchenne (56.7% vs. 84.9%, $p < 0.001$) as well as nonsense-mutation medications (2.2% vs. 9.2%, $p = 0.033$) and exon skipping medications (2.3% vs. 9.3%, $p = 0.034$), which are medications that restore or replace dystrophin (medications that possibly directly affect DMD).

Symptoms that Have Biggest Impact on Day-to-Day Life

Of the 275 participants in the analytic sample, 231 answered the question about the symptoms that have the biggest impact on day-to-day life. Collectively, these participants made a total of 603 unique responses with 403 responses from early-stage non-ambulatory patients and 200 from late-stage non-ambulatory patients. We identified the following three overarching themes, listed in order of frequency of

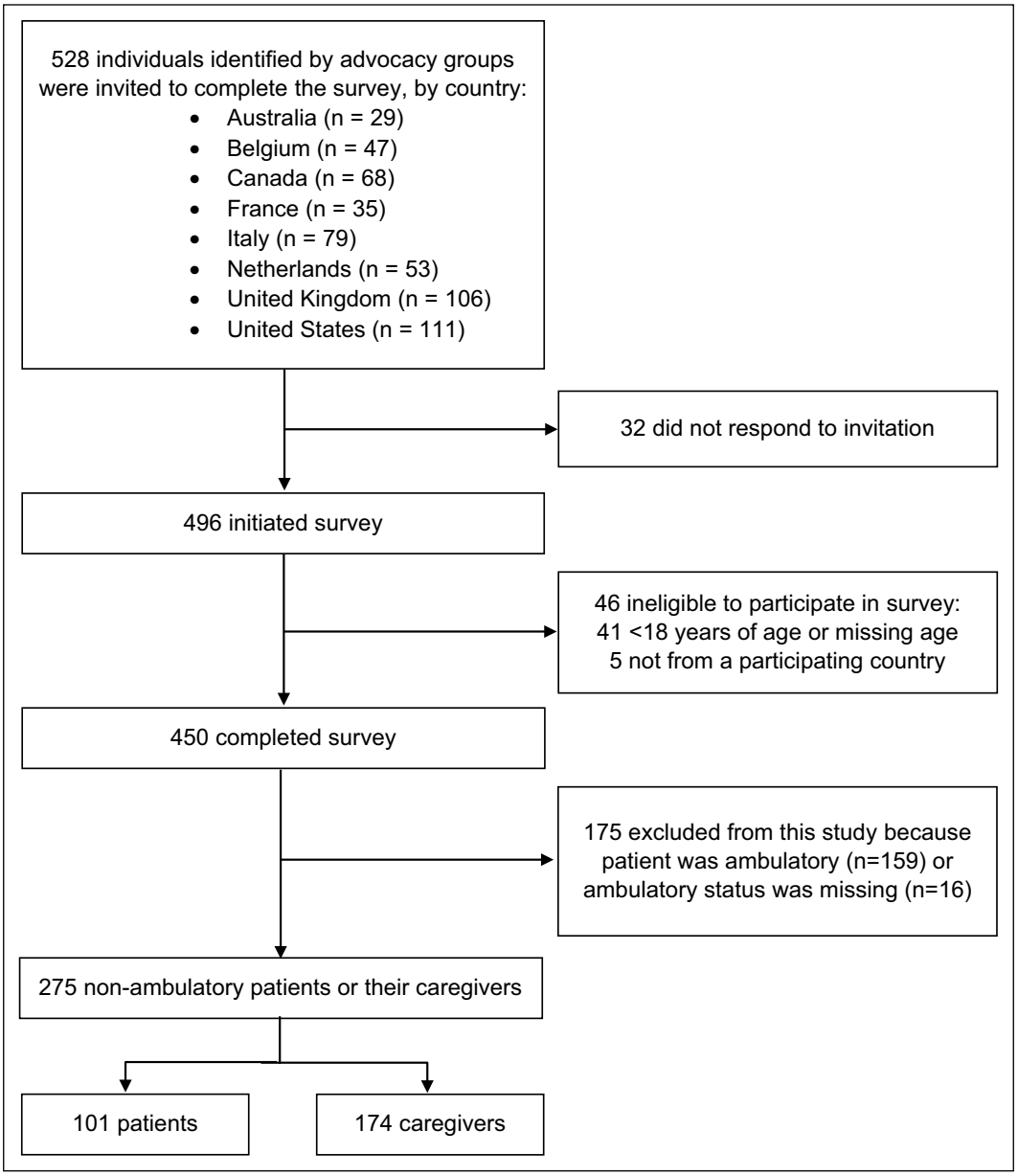

Fig. 1 Invited and initiated survey, screened, and included in final analytic sample

responses (Table 2): (1) functional impairment of muscles; (2) quality-of-life impairments; and (3) body system impairments. A sub-set of responses—categorized as "other"—did not align within these overarching categories. However, it is important to note that the responses from late-stage non-ambulant patients' endorsed body system impairment most frequently followed next by functional impairment of muscles. Next, we describe these themes in more depth.

Biggest Impact on Day-to-Day Life: Functional Impairment of Muscles

The symptoms we identified that related to functional impairment of muscles included immobility, upper limb function, and muscle weakness. The order of frequency was the same for responses reported by early- and late-stage non-ambulatory. Immobility encompassed poor range of motion, muscle stiffness, tightness, and/or contractures and was noted for having a big impact on day-to-day life because of the pain and discomfort attributed to it. Impairments

Table 1 Characteristics of survey participants ($n=275$)

Characteristic, %	All participants ($n=275$)	Early-stage non-ambulatory[a] ($n=185$)	Late-stage non-ambulatory[b] ($n=90$)	*P* value
Country				0.024
Australia	5.5	6.5	3.3	
Belgium	7.6	4.9	13.3	
Canada	10.2	9.7	11.1	
France	10.5	8.1	15.6	
Italy	13.8	15.1	11.1	
Netherlands	14.2	13.0	16.7	
United Kingdom	17.5	17.8	16.7	
United States	20.7	24.9	12.2	
Respondent				< 0.001
Adult with Duchenne	36.7	31.4	47.8	
Caregiver of adult	42.5	38.9	50.0	
Caregiver of minor	20.7	29.7	2.2	
Characteristics of patient				
Age of patient, mean (SD)	23.9 (8.0)	21.4 (7.2)	28.8 (7.3)	< 0.001
PUL-PROM total score, mean (SD)	21.8 (19.1)	28.6 (18.7)	7.5 (9.8)	< 0.001
EQ-5D, mean (SD)	0.33 (0.19)	0.35 (0.20)	0.29 (0.17)	0.018
Clinical trial participant	38.5	44.6	25.8	0.003
SAP participant	17.6	20.7	11.2	0.055
Heart medications	88.2	86.3	92.0	0.17
Steroids	75.6	84.9	56.7	< 0.001
Nonsense-mutation medication	6.9	9.2	2.2	0.033
ATP prod mod medications	12.9	13.1	12.5	0.89
Exon skipping	7.0	9.3	2.3	0.034
Vitamins	82.3	86.3	73.9	0.012

PUL-PROM PUL-PROM total score, *SAP participant* has been granted access to a drug through a special access program, *ATP prod mod meds* ATP production modulator medications

[a]*Early-stage* patient uses a wheelchair and can go indoors and outdoors

[b]*Late-stage* patient uses a wheelchair but unable to go outdoors in some situations or cannot control wheelchair without help

to muscle strength were described as weakness, lack of strength, or the progressive decline in muscle strength.

Of these three impairments, participants' responses most commonly elaborated on the impact of impairments to upper limb function. Upper limb impairments were described as loss of mobility and/or strength in arms, hands, and/or fingers. Some responses provided explicit examples of how loss of arm, hand, or finger function impacted day-to-day life. For instance, one patient from Canada who was early-stage non-ambulatory, had a total PUL-PROM score of 31, EQ-5D of 0.527, and had taken steroids and heart medications stated that:

> "The arm weakness is a real problem for me because I cannot reach for a lot of things that I would like to reach. It can get frustrating to have somebody help me every time I need to get something."

Biggest Impact on Day-to-Day Life: Quality-of-Life Impairments

The responses frequently referred to quality of life issues associated with Duchenne, which we categorized as dependency, fatigue, and distress. Responses related to both early- and late-stage non-ambulatory patients reported on dependency most frequently. In the majority of these responses, dependency was associated with being reliant on other people, especially for activities of daily living such as eating, dressing, showering, and using the bathroom.

Responses for early-stage non-ambulatory patients pertained to fatigue and distress at the same frequency, whereas responses from late-stage non-ambulatory patients were concerned with fatigue more frequently than distress. In relationship to responses about feeling tired or fatigued, some described how this feeling limited their

Table 2 Symptoms that have the biggest impact on day-to-day life ($n=603$ responses)

Theme	All $n=603$[a] %	Early $n=403$[a] %	Late $n=200$[a] %	Symptom (Freq, %[a])	Description	Relevant quotes
Functional impairment	40	45	35	Immobility (49%)	Stiffness or inability to move	"Range of motion" "Not being able to move" "Muscle tightness can cause pain and discomfort."
				Upper limb (34%)	Weakness of arms, hands, & fingers	"Struggling to lift arms without additional support for eating" "Loss of arm & especially hand function to be able to operate computer & chair."
				Weakness (17%)	Lack of strength	"No muscle strength" "Muscle weakness—too weak in all areas for normal functioning, losses continue to progress"
Quality of life	30	34	27	Dependent (58%)	Lack of self-sufficiency or autonomy	"Parents must always drive me when I have appointments." "Food must be chopped & fed to him." "Not able to go to the toilet whenever you want"
				Fatigue (23%)	Lack energy or extreme tiredness	"Tired all the time" "Fatigue causing me to need a little more sleep than most, doing certain tasks can be exhausting."
				Distress (19%)	Impaired mental health	"Depression" "Mental Health. Although this may not be currently considered a direct symptom of DMD, IT MUST BE."
System impairment	24	18	38	Respiratory (59%)	Difficulty breathing, ineffective cough	"Loss of ability to breathe on his own." "Weakening cough" "Decreased respiratory capacity" "Difficulty in expectorating cough"
				Digestive (22%)	Dysfunction in upper and lower tracts	"Swallowing difficulties" "Compromised gastrointestinal system—essential ongoing need to promote motility and manage bowel movements"
				Cardiac (19%)	Weakness of heart, poor circulation	"Decreased cardiac function" "Heart weakness affects way my heart pumps and I get heart palpations and PVC's, which greatly affect my daily life."

Table 2 (continued)

Theme	All $n=603^a$ %	Early $n=403^a$ %	Late $n=200^a$ %	Symptom (Freq, %[a])	Description	Relevant quotes
Other	6	3	0	Side effects (69%)	Complication from treatments	"Added problems from drug side effects" "Side effects of medications (cataracts, kidney stones, lack of natural growth)"
				Access (26%)	Impacts of immobility & wheelchair use	"Public areas are not chair accessible." "Biggest impact—public accessibility; home accessibility; home modifications; transportation; expense of all"
				Assorted (5%)	Range of symptoms or their impact	"Difficulties considering professional future" "Access to federal, state and local agencies that provide assistance. Very hard to find programs, get into them."

Early early-stage non-ambulatory patients, *Late* late-stage non-ambulatory patients

[a]*n* refers to total number of responses

ability to complete different activities, including school and socializing. The impact of Duchenne on distress stemmed from issues such as stigma, anxiety, isolation, depression, and learning challenges. One example of the learning challenges associated with Duchenne came from a patient in the UK who was early-stage non-ambulatory, had a total PUL-PROM score of 46, EQ-5D index score of 0.349, and had taken steroids and heart medications who said,

> "Some of the learning difficulties I have affect me greatly in some social situations and I have trouble with many complicated tasks."

Biggest Impact on Day-to-Day Life: Impairments of Body Systems

Overall, three symptom categories were identified that related to body system impairments: respiratory, digestive, and cardiac system. Respiratory problems were noted most frequently in the responses by both early- and late-stage non-ambulatory patients. The symptoms associated with respiratory impairments ranged from weakening cough and decreased respiratory capacity to the inability to breathe independently.

After respiratory problems, responses from early- and late-stage non-ambulatory patients differed in their order of frequency. Impairments to the digestive system were the second most frequently cited impairment in the responses from late-stage non-ambulatory patients. Digestive system problems were linked to swallowing and poor intestinal motility specifically.

Cardiac impairments such as poor circulation and heart rhythm irregularities constituted the second most frequently reported impairment in the responses from early-stage non-ambulatory patients. The responses that discussed cardiac symptoms often described the seriousness of the symptoms. As an example, a caregiver of a patient from Canada who was early-stage non-ambulatory, had a total PUL-PROM score of 22, and had taken steroids and heart medications stated:

> "Cardio-pulmonary decline. My son has just endured a life-threatening cardiac event. Chronic tiredness and shortness of breath continue to negatively affect quality of life."

Biggest Impact on Day-to-Day Life: Additional Symptoms

Finally, we identified responses that addressed issues beyond these three overarching categories (i.e., functional impairments of muscles; quality-of-life impairments, impairments of body systems). At times these responses did not seem to be symptoms, but were nonetheless issues exerting a significant impact on the lives of patients and their caregivers. These responses ranged from side effects of treatments to challenges related to wheelchair accessibility such as not being able to visit friends or access necessary medical

services (e.g., weight scales are not designed to take measurements of people in wheelchairs). These responses also addressed issues related to limited future opportunities and the lack of support services.

Important Benefits of a New Treatment

A total of 223 out of 275 respondents provided 571 responses to the question about small, but important benefits of a new treatment. There were 394 responses from early-stage non-ambulant patients or their caregivers and 177 responses for late-stage non-ambulant patients or their caregivers. The overarching themes that we identified were improvements to muscular functioning; body systems; and quality of life (Table 3). Again, however, responses from late-stage non-ambulant patients' endorsed body system impairment most frequently followed by functional impairment of muscles. The following sections describe the related sub-themes and responses as well as a group of responses that did not fall within these categories. The order of sub-themes did not differ between early- and late-stage non-ambulatory patients.

Important Benefits of a New Treatment: Muscular Functioning Improvements

Most responses indicated that improvements to upper limb functioning would be a small but important benefit of a new treatment. This included more strength and mobility in arms, hands, and/or fingers. The importance of regaining upper limb mobility and strength was associated with maintaining independence, facilitating passions, and supporting mental health. The mental health benefit associated with a new treatment that primarily impacts upper limb function was reflected in the following quote from a caregiver of a patient in Canada who was early-stage non-ambulatory, had a PUL-PROM total score of 22, an EQ-5D index of 0.123, and had taken steroids and heart medications:

> "Maintaining arm strength. There are both physical and psychological impacts as this progresses, more so it seems than losing the ability to walk."

Another quarter of responses indicated that maintaining or improving muscular strength would be a small, but important benefit of a new treatment. Over a fifth of responses identified that improvements to mobility and joint functioning would be a small but important benefit of a new treatment. Some participants explicitly expressed that those improvements in mobility and strength could enhance their quality of life.

Important Benefits of a New Treatment: Body System Improvements

We identified three specific body systems for small but important benefits of a new treatment in this order of frequency: respiratory; cardiac; and digestive. Related to respiratory functioning, the small but important benefits of a new treatment ranged from having a stronger cough and less congestion to having enhanced breathing capacity. In terms of cardiac functioning, some responses indicated a desire to preserve or stabilize heart functioning while others thought the benefit should result in improved heart functioning. Some responses inextricably linked improvements to both respiratory and cardiac function as illustrated by this quote from a caregiver of a patient who was from the U.S., late-stage non-ambulatory, had a PUL-PROM total score of 0, EQ-5D index score of 0.18, and had taken heart medications:

> "If medication restores some muscle strength especially to the lungs and heart so that my son can breathe on his own and not worry about having any heart issue."

For therapeutic improvements related to the digestive system, responses focused on supporting or regaining the ability to swallow as well as improving intestinal motility.

Important Benefits of a New Treatment: Quality-of-Life Improvements

Responses related to quality of life fell into three categories: independence, energy, and medications. The benefits of a treatment on independence were strongly tied to activities of daily living and had implications for patients' sense of privacy, especially related to dressing, showering, and using the bathroom. Some responses reflected a desire for a treatment to improve their situation so it would be safe for them to be alone. Even being able to turn over in bed would be important, as expressed in the following quote from a patient in Italy who was late-stage non-ambulatory, had a PUL-PROM total score of 26, an EQ-5D index score of 0.508, and had taken steroids and heart medications:

> "It would be important to be able to get up on your own and be able to move around in your home / car, or at least to be able to turn around on your own in bed."

Responses indicated that it would be beneficial for a new treatment to improve energy levels in ways such as reducing fatigue and facilitating better sleep. Finally, participants' responses conveyed a desire for new treatments to have fewer side effects—and explicitly side effects that affected their

Table 3 Small, but important benefits of a new treatment (n = 571 total responses)

Theme	All $n=571$[a] %	Early $n=394$[a] %	Late $n=177$[a] %	Symptom (Freq, %[a])	Description	Relevant quotes
Muscular function	40	43	35	Upper limb (56%)	Regain use of arms, hands, and/or fingers	"Able to continue to use arms properly" "Hand function to be able to operate computer and wheelchair as these are the most important functions to do my daily necessary activities."
				Strength (23%)	Increase strength	"Muscular force" "Have more strength" "Improved strength in any way" "Maintain the strength he has now"
				Mobility (21%)	Improve joint function	"Keep joints supple" "Be able to move a little more" "Ability to move in everyday life more easily and in a fun way"
Body systems	33	31	39	Respiratory (56%)	Increase lung functioning and basic cough	"Be less congested at respiratory level" "Strengthening respiratory muscles to restore basic coughing or to preserve function longer"
				Cardiac (30%)	Weakness of heart, poor circulation	"Preserve heart health" "Increase in heart function" "Stability of the heart muscle" "Improvements to benefit cardiac function"
				Digestive (14%)	Boost function of upper & lower tracts	"Increase bowel motility" "Improvement in bowel function" "Most important benefit would be to regain sufficient strength to swallow again"
Quality of life	20	20	20	Dependent (62%)	More self-sufficiency or autonomy	"Able to eat independently" "Being able to be alone at home" "Going to the bathroom by myself" "Preserve possibility of showering alone"
				Energy (20%)	Less fatigue and tiredness	"More energy" "Less tiredness" "Have less fatigue" "More effective sleep"
				Medication (18%)	Fewer side effects and/or less need	"Better skin (result of steroids)" "Replace the existing steroids with something equally protective in function, but without the weight gain side effect."

Table 3 (continued)

Theme	All $n=571$[a] %	Early $n=394$[a] %	Late $n=177$[a] %	Symptom (Freq, %[a])	Description	Relevant quotes
Other issues	6	6	6	Assorted (49%)	Range of benefits	"Improve body heat retention." "Improve ability to fight infections" "Medication to help urination easier" "No more need for compression socks"
				Disease progression (23%)	Slow or stop disease progression	"Delaying progression" "Slowing overall disease progress" "Slow down effects for those in chairs, not just those who are able bodied"
				Mental health (14%)	Improve cognitive, mental, & social	"Being able to socialise like peer group" "Less learning issues and easier concentration" "Be less anxious, angry and depressed"

Early early-stage non-ambulatory patients, *Late* late-stage non-ambulatory patients

[a]*n* refers to total number of responses

appearance such as weight gain or skin problems—or less frequent dosages because of the time required to take them.

Other Important Benefits of a New Treatment

Some responses referred to a variety of other small but important benefits that did not readily fit in with the other themes. In the instances where the benefit was mentioned in only one or two responses, we grouped them in a sub-theme titled "Assorted." Several responses identified that slowing the progression of the disease was a small but important benefit.

Assessing the PUL-PROM Distribution and by Non-ambulatory Status and Quality of Life

Figure 2 presents results from our assessment of the PUL-PROM. Figure 2A depicts the distribution of the PUL-PROM total score among patients. The total score spans the full range of possible scores (0 to 64), the distribution of the PUL-PROM total score is unimodal, right skewed

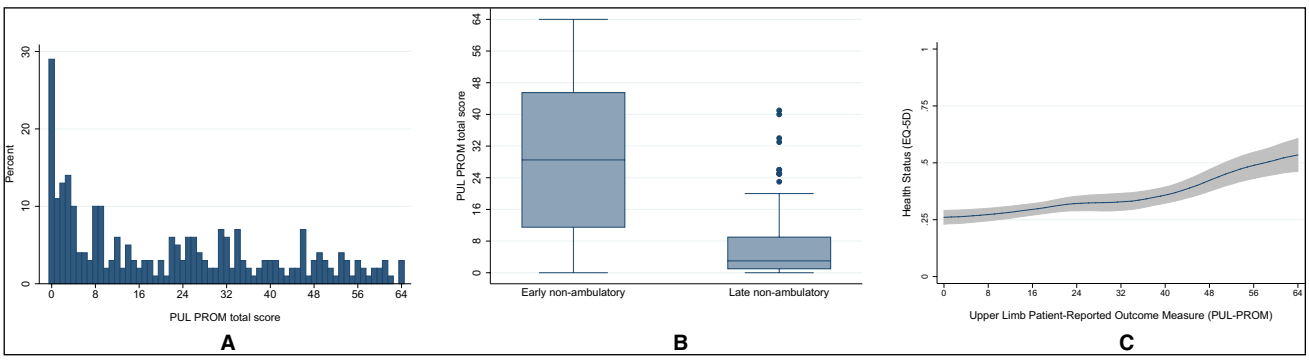

Fig. 2 Examining needs of non-ambulatory patients in context of PUL-PROM measure. **A** Distribution of the PUL-PROM total score among non-ambulatory patients. **B** PUL-PROM total score by early- versus late-stage non-ambulatory status. **C** Non-ambulatory patients' health-related quality of life versus PUL-PROM total score

with a mean total score of 22, and median total score of 18. We explored heterogeneity in the PUL-PROM total score based on early- versus-late-stage non-ambulatory status (Fig. 2B). Early-stage patients exhibited higher mean PUL-PROM scores as compared to late non-ambulatory patients (28.6 vs. 7.5, $p \leq 0.001$). Figure 2C shows that EQ-5D index score increased with the increase in PUL-PROM total scores. PUL-PROM total score was positively correlated with health-related quality of life ($r = 0.42$, $p \leq 0.001$). The mean EQ-5D index score increased by a factor of two (0.24 vs. 0.56) when comparing a PUL-PROM total score of 0 versus 64.

Discussion

This study makes an important contribution to the literature by innovating in PFDD with a survey-based approach to understand the needs and desires of non-ambulatory patients across international settings. It provides new insights into the burden of Duchenne in non-ambulatory patients overall and by non-ambulatory disease stage; it also provides insights into ways in which new treatments could alleviate that burden. Specifically, our findings demonstrated congruency in the frequency of symptoms reported and the treatments desired by non-ambulatory patients. In doing so it provides answers to regulatory questions that are relevant to PFDD.

Our findings reflect the progressive nature of Duchenne as well as the impact of deteriorating body system function to patients' day-to-day life and desired treatments. This is illustrated through differences we identified in the biggest impact symptoms that early- and late-stage ambulatory patients reported most frequently. Perhaps not surprisingly, late-stage ambulatory patients most desired treatments that would benefit body system functioning, whereas early-stage patients most desired treatments that would improve muscular function. The findings allude to how non-ambulatory patients' treatment priorities may change over the course of the disease.

Nonetheless compelling findings from our study were related to issues of muscle functioning—and specifically upper limb function—both as a symptom with the significant day-to-day impacts and as an area of treatment benefit. The Performance of the Upper Limb test (PUL 1.2 and PUL 2.0) is validated clinical measure of disease progression as assessed through upper limb function among ambulatory and non-ambulatory Duchenne patients [35, 45, 46]. New therapies for non-ambulatory patients are in the pipeline, but studies evaluating them have focused on the PUL.

Our study contributes to the evidence base about the PUL-PROM in the context of non-ambulatory patients' needs. The PUL-PROM was developed in parallel to the Performance of the Upper Limb test (PUL 1.2 and PUL 2.0), a validated clinical measure of disease progression as assessed through upper limb function [35, 45, 46]. It was intended that the PUL-PROM would be used in clinical trials alongside the PUL [35, 45, 46]. Yet, a review of ClinicalTrials.gov revealed that over the last decade eight studies on non-ambulatory patients used the PUL (either 1.2 or 2.0), but none of them used the PUL-PROM [47]. Our study provides support for use of the PUL-PROM as it can help contextualize patients' experience. Moreover, to our knowledge, our study is the first to assess the PUL-PROM in relationship to health-related quality of life and showed that the PUL-PROM was associated with differences in health-related quality of life. The observed relationship between the PUL-PROM and health-related quality of life adds important information about the consequence of protecting or restoring patients' ability to perform activities of daily living.

There are limitations to this study that should be considered when interpreting the findings. First, survey recruitment ended prematurely due to the demands placed on patient groups during the COVID-19 pandemic, even though the intent had been to create a sample that represented each participating country. As a result of ending recruitment early, we may have disproportionately limited the inclusion of the hardest to reach groups—older adults (as opposed to younger patients)—in our study because the adults took more time to recruit. As such we cannot be certain that the key themes we identified would have remained the same if more adult patients or caregivers of adult patients had participated. Another limitation is pooling participants' responses across different respondent groups (patients and caregivers) as well as heterogenous countries and languages. It is possible that the appropriateness of the disease-specific functional measures and health-related quality-of-life instrument may vary across the groups of respondents. It is also possible that the open-ended responses were more diverse across these subgroups of participants. That said, pooling and sharing data have become standard practice among cross-country patient advocacy organizations who are collaborating to unify approval and access decisions internationally.

This paper was targeted to a regulatory setting and as such did not explicitly address issues of economic burden or financial strain. However, these issues are of increasing focus and there is a need for further research on the financial and economic burdens facing patients with Duchenne and their caregivers. Another limitation pertains to our classifications of early and late non-ambulatory status. Our classifications reflect those used in previous studies, but we recognize that the community has not settled on common definitions for "early non-ambulant" and "late non-ambulant" patients.

While it was outside the scope of our study, future studies could investigate if the PUL-PROM could be used to help classify non-ambulatory stages. Also, as few studies have used the PUL-PROM to document disease outcomes in Duchenne, there is a need to further explore its general acceptability and sensitivity to detecting deterioration over time in community-based samples [20, 21]. Finally, given that the data are cross-sectional and capture information at a single point in time, we are unable to measure within subject changes in upper limb function over time. A longitudinal study that confirms PUL-PROM's relevance to disease progression would make an important contribution to the literature.

There are several implications for policy and PFDD efforts based on the findings of our study. First, our study indicates that non-ambulatory patients desire treatments that would preserve, or even improve, upper limb function, and were not explicitly interested in treatments that would restore ambulation. Given that new therapeutics are in the drug development pipeline for non-ambulatory Duchenne patients, drug developers should investigate the effect of these experimental treatments on upper limb function to address an identified need of non-ambulatory patients. Moreover, PFDD should continue to focus on treatments that address the underlying causes of Duchenne, so as to meet the needs of late-stage non-ambulatory patients who desire treatments that maintain or recover body system functioning. Moving forward drug development efforts should use the PUL-PROM in combination with the PUL. Not only would the use of the PUL-PROM provide meaningful information, but it would answer calls by regulatory agencies to engage patients more directly and to understand measures related to activities of daily living.

Conclusion

We found that impairments in upper limb functioning as well as body system impairments greatly impact non-ambulatory patients and improvements to both would be important benefits of new treatments. The results demonstrate how the PUL-PROM can be used as a patient-centric measure that accounts for the needs of later-stage patients with Duchenne. This study breaks new ground for PFDD given its international reach, survey-based approach, and focus on a neglected portion of a rare disease community. It provides timely evidence for regulators, advocates, and drug developers by describing the disease burden and treatment desires for non-ambulatory Duchenne patients. This work demonstrates the importance of understanding the experiences of subgroups of patients, even within a rare disease.

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Author Contributions

ALRS: Made substantial contributions to the conception or design of the work; analysis and interpretation of data for the work; and drafting and revising the work. She provided final approval of the version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. NLC: Made substantial contributions to the conception or design of the work; acquisition and analysis of data for the work; and revising the work. She provided final approval of the version to be published. RF: Made substantial contributions to the conception of the work; acquisition of data for the work; and revising the work. He provided final approval of the version to be published. PF: Made substantial contributions to the conception of the work; acquisition of data for the work; and revising of the work. She provided final approval of the version to be published. JFPB: Made substantial contributions to the conception and design of the work; acquisition and interpretation of data for the work; and revising of the work. He provided final approval of the version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declarations

Conflict of interest

NLC and JFPB have received funding from Parent Project Muscular Dystrophy. RF and PF are employees of Parent Project Muscular Dystrophy.

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