Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 30 (2020) 431–436

www.elsevier.com/locate/nmd

Workshop report

Patient and parent oriented tools to assess health-related quality of life, activity of daily living and caregiver burden in SMA. Rome, 13 July 2019

Eugenio Mercuri[a,b,*], Sonia Messina[c], Jacqueline Montes[d,e], Francesco Muntoni[f,g], Valeria A. Sansone[h], on behalf of all participants and the SMA PROM working group[1]

[a] *Centro Clinico Nemo, Fondazione Policlinico Universitario A. Gemelli IRCSS, Rome, Italy*
[b] *Pediatric Neurology Unit, Catholic University, Largo Gemelli 8, 00168 Rome, Italy*
[c] *Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy*
[d] *Department of Rehabilitation and Regenerative Medicine, Columbia University Irving Medical Center, New York, United States*
[e] *Department of Neurology, Columbia University Irving Medical Center, New York, United States*
[f] *Dubowitz Neuromuscular Centre, UCL Institute of Child Health & Great Ormond Street Hospital, London, United Kingdom*
[g] *NIHR Great Ormond Street Hospital Biomedical Research Centre, London, United Kingdom*
[h] *Neurorehabilitation Unit, University of Milan, Centro Clinico Nemo, Niguarda Hospital, Milano, Italy*

Received 31 January 2020; received in revised form 11 February 2020; accepted 26 February 2020

Twenty-five participants from Italy, United States, United Kingdom, Germany, Spain and Switzerland met to discuss Patient Reported Outcome Measures (PROM) in Spinal Muscular atrophy (SMA). The group included physicians and physical therapists with a specific experience in developing or validating PROMS in neuromuscular disorders, advocacy groups and representatives from pharmaceutical companies.

Eugenio Mercuri (Rome) and *Francesco Muntoni* (London) introduced the workshop, highlighting the aims of the workshop: (i) to explore the different PROMS currently or previously used in SMA, (ii) to better define the domains explored by each of them, also in relation to age and SMA type, (iii) to define a roadmap of possible tools to be used in different settings and iv) to define areas where further research is needed.

During the workshop, all participants contributed to review the published evidence in each area and to report current practice amongst the group.

Sonia Messina (University of Messina, Messina) provided the results of a critical overview of the existing tools, performed in collaboration with *Laura Antonaci* and *Annalia Frongia*, (Catholic University, Rome). The study included a review of the tools previously or currently used to measure not only health−related quality of life (HRQoL), but also of those assessing activity of daily living and caregiver burden, including specific tools developed for SMA. A total of 36 tools were identified. The majority of these assessed HRQoL; some of the tools focused on activities of daily living (ADL) ($n=5$) or on caregiver burden ($n=9$). Approximately a third of the questionnaires ($n=10$) included a combination of items related to HRQoL and others related to activities of daily living.

All ages were covered by the existing tools. While most of the tools were developed for adults or older children, a few of them had been devised to include also young children. Only 3 questionnaires and 3 surveys were specifically developed for SMA, while the others had been used in wider groups of neuromuscular disorders including SMA. The majority of the tools had only been partially validated and only few underwent Rasch analysis to establish their statistical robustness. The PedsQL and its neuromuscular module have been partly validated and are currently used in several SMA clinical trials. Based on the experience in Duchenne muscular dystrophy and in other disorders, the PedsQL provides important information on the overall quality of life and a number of health-related issues [1–3] but does not appear to show changes over time that are related to the changes observed on the functional scales [4].

* Corresponding author at: Pediatric Neurology Unit, Catholic University, Largo Gemelli 8, 00168 Rome, Italy.
E-mail address: eugeniomaria.mercuri@unicatt.it (E. Mercuri).
[1] Listed at the end of the report.

https://doi.org/10.1016/j.nmd.2020.02.019
0960-8966

The following session was dedicated to the analysis and an update of new tools currently used in clinical practice or in research settings with specific focus on new disease-specific tools (SMAIS, SMA HI) or on tools that have been recently used in SMA (PEDI-CAT) or assess aspects that are particularly relevant in SMA (e.g., fatigue).

Dylan Trundell and *Ksenija Gorni* from Roche presented the SMA Independence Scale (SMAIS), a new scale developed in an attempt to assess and record meaningful changes in daily functional ability (e.g., independence). The scale was developed following literature review and with input from internal clinical experts and patient advocates and qualitative interviews with caregivers and patients. The interviews were conducted in 2 rounds to allow concept elicitation and cognitive debriefing to permit testing of changes. The scale includes 29 items aimed at assessing the level of independence of SMA patients measured through the carers' report of the level of assistance needed to perform each activity. The items are grouped into sections: Bathing/Hygiene, Dressing, Eating and Drinking, Picking up, Moving objects, Mobility and Strength, Chores, Other tasks. The SMAIS was mainly devised for non-ambulant patients and can be used from the age of 2 years. At the meeting, there was some concern from the group that the validation of this new tool is still incomplete. The scale is however currently used in the clinical trial SUNFISH. The data collected at baseline are being used for further validation of the scale, including internal consistency, reliability, Item analyses to establish possible floor and ceiling effects; item-to-item correlations Exploratory Factor Analysis, Rasch (unidimensional) and Confirmatory Factor Analysis (bifactor model).

Further analysis will also provide information on the convergent validity with functional and respiratory measures.

Valeria Sansone (Nemo Center, Milan) reported the development of Spinal Muscular Atrophy Health Index (SMA-HI), as part of a collaborative group with *Chad Heatwole* at the University of Rochester, NY. The SMA-HI is a multifactorial measure of disease burden, it is not a measure of Quality of Life although the two concepts are intimately related. The SMA-HI was constructed in part based on the results of an in-depth analysis of what are the most relevant symptoms in SMA. In the PRISM-SMA (Patient Reported Impact of Symptoms) study [5], surveys were sent to 1438 adult SMA patients worldwide. 359 adult SMA patients responded and more than 80,000 patient responses regarding 207 symptoms, 20 themes, and 10 demographic features were obtained. Limitations with mobility or walking; inability to do activities; hip, thigh or knee weakness; problems with shoulders or arms; back, chest or abdominal weakness; fatigue and problems with hands or fingers were reported in more than 80% of patients and rated as having a significant impact of everyday life [5]. A portion of the symptomatic questions from the PRISM-SMA study were included in the SMA-HI based on their high level of prevalence, importance, psychometric properties, clarity, universal understanding, and potential responsiveness to therapeutic interventions. Beta testing was conducted with both adult and pediatric populations of SMA patients to ensure the usability of the instrument and known groups validity testing. Subscales were generated using confirmatory factor analysis and the internal consistency of each subscale was determined. The SMA-HI measures overall disease burden and 15 separate domains including: Hip, thigh, and knee function; Shoulder and arm function; Back, chest, and abdominal function; Social performance; Fatigue; Activity participation; Hand and finger strength; Social satisfaction; Emotional health; Pain; Breathing function; Swallowing function; Sleep; Gastrointestinal function; Mobility and ambulation (supplemental scale). Scores range from 0 to 100 with 100 representing the most severe disease burden in the symptomatic area and 0 representing no disease burden in the symptomatic area. A total score or individual subscales can be used to measure the impact of therapeutic intervention during clinical trials. The SMA-HI has been tested in children 8 years of age or older and is currently being used in multiple academic and pharmaceutical sponsored clinical trials.

The NEMO Center in Milan is collaborating with Dr. Chad Heatwole and the University of Rochester to validate the SMA-HI in Italy. Analysis on test-retest reliability and sensitivity to change are currently ongoing.

Amy Pasternak (Boston Children's Hospital) reported the PNCR experience using the PEDI-CAT (Haley 2012), a caregiver reported outcome measure intended for children with a variety of cognitive, motor and behavioral difficulties. The PEDI-CAT is an expanded version from the original PEDI (276 items versus 197 items), measuring mobility, daily activities, social/cognition and responsibility. The reported age range is from 1 to 21 years. Item maps are available for content-balanced and speedy versions have been introduced. Details of the changes on the PEDI-CAT and of its application in SMA have recently been published [6]. Age percentiles and T-scores are based on normative standardization sample for 21 age groups, scaled (criterion scores) based on data from the normative and disability sample. The scale is now available in software versions and can be easily used on tablet or computers. Dr. Pasternak reported the experience of the PNCR assessing test response and test information functions in SMA types I, II and III (Rasch analysis) of full PEDI-CAT. The Rasch analysis showed that the PEDI-CAT works best for Mobility & Daily Activities for type III as well Daily Activities for type II but less for type I, for which less difficult items need to be added to increase validity and sensitivity. It was also felt that the best window for the use of PEDI-CAT in SMA is probably from the age of 2.5 years but this needs to be confirmed.

There was a discussion on whether the duration of the test or the use of tablet may affect the results of the PEDI-CAT, but this was not the experience of the PNCR that found that the test was well accepted by all the families involved in their pilot study. The PEDI-CAT is currently being used in the Scholar Rock trial and further data will soon become available.

Table 1
Scales assessing fatigue in SMA.

Assessment	Age Group	Previous SMA studies	Validation in SMA
PedsQol Multidimensional Fatigue	Parent proxy, Child, Adult	Stam et al., 2018 Dunaway-Young et al., 2019	no
Fatigue Severity Scale	Adults	Noto et al., 2013 Werlauff et al., 2014 Montes et al., 2015 Dunaway-Young et al., 2019	no
PROMIS Fatigue short form	Parent proxy, Child, Adult	–	no
SMA – Health Index	Children>12 years, Adults	Mongiovi et al., 2018	In progress
Modified Fatigue Impact Scale	Adults		no

Jacqueline Montes (Columbia University, New York) provided a review of the tools used to assess fatigue differentiating tools assessing *perceived fatigue* (subjective) from the *physiological fatigue*, i.e., the decline in 1 or more aspects of performance during continuous or prolonged task. Perceived fatigue can be assessed with PROMS investigating feelings of mental and/or physical tiredness, including momentary perceptions of fatigue and more 'chronic' aspects, trying to distinguish between mental versus physical aspects of fatigue. The existing tools provide means of grading the severity of fatigue and the possible impact of fatigue on function.

Five tools were selected as the most frequently used or the most potentially appropriate to assess perceived fatigue in SMA [5,7–11] (Table 1).

The PedsQL multidimensional fatigue scale includes 18 items across 3 domains: general fatigue, sleep/rest fatigue and cognitive fatigue that also takes into account possible covariates of fatigue (i.e., depression, pain, weakness, and sleepiness).

The Fatigue Severity Scale (FSS) includes 9 questions mainly exploring the perception of fatigue as a disabling symptom and how it interferes with different aspects such as motivation, physical functioning, activities and, more generally, responsibilities, work, family, or social life [8,10]

The PROMIS fatigue scales includes a limited number of questions to assess experience of fatigue (frequency, intensity, duration) and its impact, limited to the past 7 days.

The SMA-HI is a measure of disease burden not specifically designed to assess fatigue however it includes questions on the presence of fatigue and its impact on function. The Modified Fatigue Impact Scale (MFIS) includes 21 items (3 domains) also exploring physical, cognitive and psychosocial aspects. Only the PedsQL multidimensional fatigue module and the PROMIS fatigue scales are available for young children, and while a few of the scales have been used in SMA studies, none has been formally validated in SMA populations.

A recent study by the PNCR group, using the PedsQL fatigue scale and the FSS showed that the majority of adults with SMA (78.6%) reported excessive perceived fatigue and half experienced severe fatigue [8]. Age, SMA type, or ambulatory status did not influence perceived fatigue, but perceived fatigue was not associated with function or QOL in type II and III patients or with fatigability (physiological fatigue) in ambulatory patients

Anna Lia Frongia (Catholic University, Rome) provided a review of other tools used in other neuromuscular disorders but not in SMA. Most of these tools have mainly been used in adults and may provide some suggestions on topics selected, questions to be asked or on the wording for the development of new tools.

Erik Henrikson (UC Davis) reported the CNRG experience in the correlation between PROMS and functional measures in Duchenne muscular dystrophy (DMD). Over the last few years there has been an effort to combine methodological aspects, from ICF model, to bioecological models of family development that have been reported in the 2018 DMD care considerations [12]. One of the biggest challenges has been to see how different PRO tools are responsive to functional changes. The experience of the CNRG group with PedsQL and PODCI indicates that PedsQL shows a wide variability over changes, when measured in patients also assessed on the 6MWT while the Pediatric Outcomes Data Collection Instrument (PODCI), a questionnaire designed to quantify functional abilities, provides a better correlation and much narrower variability. –PODCI was found to work properly both for ambulatory and non-ambulatory patients but the correlation was more obvious when patients were classified according to their functional status [13].

PODCI was also used to provide clinical meaningfulness to the functional changes found on the observer rated scales [14]. These findings, together with other studies also comparing the PedsQL with functional measures [4] suggest that in DMD functional changes are more likely to be associated with changes on tools also assessing functional abilities than to generic HR QOl tools. It is of interest that changes in mobility did not correlate with happiness – as this also dependent by other variables such as the multiple relationships existing with other parts of society (internally within the family, with extended family, with peers, with other patients, with the society/ environment and often by the possibility to find a balance between needs and adequate resources.

Mencía de Lemus, (Spain) reported the experience of the Spanish SMA patient association, FundAME, who are running a project aimed at building a Registry Module focused on Patient Relevance that will integrate their National Patient Reported Registry (Registro de Pacientes

con Atrofia Muscular Espinal de España, (https://wacean.com/registroame/). The project identifies those aspects of the disease that are more relevant or have a higher impact for patients. These include functional impact of the disease on mobility and independence, impact on well-being as well as other aspects more related to quality of life that should be captured in addition to the functional scales as part of PRO for SMA patients. The project has included an extensive literature review, field work through 6 focus groups, each of them between 8 and 14 participants representing the different age groups and levels of severity of the disease and has counted on the input of a Scientific and Patient Advisory Board. The outcome is a list of items of the areas considered to be relevant and important to be systematically measured as part of a PRO. These will form part of their registry and, more generally, will be made available for public use. Through the data gathering with the Registry, the selected items will be validated and will serve as a basis to draw a new or an add-on scale based on PROs.

Some of these aspects, such as mobility-independence, were related to activities of daily living such as personal care, washing, toilet, dressing, feeding, transfers from bed/chair/wheelchair or going outdoors alone. These activities reflect at the same time both the possibility to perform task but also the level of independence and the level of care/assistance needed. Others reflected aspects of endurance, such as the energy needed to go through student/professional day, maintaining position during the day or being able to perform activities /movements repeatedly (taking notes, using mobile phone) on a sustained way throughout the day.

Other aspects were related to the impact that some symptoms such as pain, contractures, breathing difficulties or scoliosis have on everyday life while others (vulnerability, stigma) were more related to the emotional burden of the disease.

The presentation helped to highlight a number of aspects that are not currently commonly assessed.

Nicole Gusset (SMA Europe, Switzerland) reported the results of their published first pan-European survey on disease impact on general well-being and therapeutic expectations of SMA patients [15]. Here, the impact of a patient's ability and inability to perform 10 pre-defined activities were described. Respiratory and bulbar functions as well as mobility were identified as the priority areas in which therapeutics should have an effect for SMA patients.

Together with the existing literature, this first survey was the basis for the development of a more comprehensive survey that was launched in July 2019. The *EUPESMA-2019* (European Patient Expectation Survey SMA) was designed to assess the SMA patient perception of well-being, the impact of particular ADL on their quality of life and the expectations regarding the effects of therapies on their daily activities. The EUPESMA-2019 includes items on demography and health status (including current and historic mobility), on the treatment status, and on the impact of pre-defined activities on individual well-being as well as on the individual expectation of treatment efficacy. The 41 ADL are divided in 7 areas: Dressing/Standing, Sitting, Lying/Eating, Drinking/Body Care/Toilet / Mobility in- and outside, Social Activities/Communication, Education.

Both surveys presented by the patient advocates focused on items that assessed the impact of activities of daily living and level of independence / care on the individual well-being but also on treatment efficacy. Thus, the outcome of these two ongoing studies might provide data-driven arguments to add or refine items in existing scales or tools, to complement existing indexes, to be selected for use in association with the observer rated scales in clinical trials and/or in registries, but also to provide a base to interpret results coming from existing scales in regard to the value for patients.

Mary Schroth, from Cure SMA (US) reported some results from their patients' survey exploring different aspects. Recent work has been devoted to enquiring about work productivity and activity impairment, measuring a number of aspects, namely absenteeism/presenteeism/work productivity loss/activity impairment. The results were subdivided according to the type of SMA, with SMA1 caregivers the most affected for absenteeism.

Other ongoing surveys explored health utilities index and fatigue. The results from the recent 2019 survey highlighted a list of important unmet needs reported by patients and families based on type:

(1) Gain muscle strength in types 1, 2, 3;
(2) Achieve motor function in types 1,2,3;
(3) Improve daily functioning in types 1, 2, 3;
(4) Improve fatigue in type 3;
(5) Improve respiratory function in type 1.

Marcus Droege (Avexis) provided an overview of companies' expectations or priorities, starting from the input available from EMA and FDA, both very supportive of the use of PROs to support label claims. In the EMA CHMP '*Reflection Paper on the Regulatory Guidance for the use of Health Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products'*, it is clearly stated that the information received through PROs can provide better understanding of impact caused by disease and treatment on the patient, which can lead to enhanced decision making.

Similarly, in the *Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. US DHHS, FDA,* it is reported that findings measured with well-defined and reliable PRO instruments that have appropriately designed investigations can be used to support a claim in medical product labeling, if the claim is consistent with the instrument's documented measurement capability.

Industries are keen to follow these suggestions stressing the importance that PROs/QoL measures should reflect relevant outcomes accurately and meet the Criteria in HA/HTA submissions (Validity, reliability, relevance, etc.) per FDA/EMA Guidelines. Such criteria include an assessment of the relevance of the data explored, of their accuracy and appropriateness to the scope to address appropriate questions.

These measures should undergo a process of validation both in terms of reliability and of content validity taking into account that content validity should be specific to the population, condition, and treatment to be studied.

Similarly, to the observer rated measures data from PROs should be reliable, with appropriate data sources and modalities of data collection and accurate data management and quality control.

Dr. Droege reported how some PROs fulfilling these criteria had been chosen for the RESTORE registry, a recent disease registry developed by their company.

Ivana Rubino (Biogen) introduced some specific considerations on why we want a PRO in SMA at the time new drugs are available and other trials are planned. The priority is to obtain information on aspects that translate what we observe in clinical settings, clinical trials in terms of function and ideally also have a measure on how this would reflect on costs related to the care of these patients. A pragmatic approach would be to have a system of add on modules that could be adapted to different settings, from more accurate modules for clinical trials to shorter and easier to use modules for real world data to be used even in non-tertiary centers.

One option could be to tailor the modules according to specific cohorts, following the principles of Goal attainment scales (GAS) used in rehabilitation and in other diseases.

The other participants agreed that such a format should be explored, postulating a multi-dimensional composite score that could be adapted according to the settings and the specific needs.

The last session of the workshop included a general discussion including all participants to draw conclusions on the presented topics and identify gaps. There was consensus that, in addition to the observer rated motor functional scales used in clinical trials, there is the need to use PRO to capture other aspects that cannot be easily captured in a clinical setting and are clinically meaningful to the patients and their carers. In general it was felt that, although new tools could be more strategically developed to address specific questions related to the changes observed with the new therapies, both for clinical trials and for disease or postmarketing registries, it is already possible to identify a roadmap of the exiting PRO that may be potentially used across the spectrum of age and severity of the different SMA types.

While each of the PRO available and currently or previously used in SMA have some advantages, not all are however relevant in a clinical trial setting or more generally, in a setting exploring their correlation with functional changes.

- There was agreement that Health Related Quality of Life measures are important and may have a correlation with function in SMA patients but, when used longitudinally, are less likely to measure changes that may mirror the functional changes observed on the motor scales. It was felt that most of the domains explored reflected aspects that would not easily show any change even in the presence of marked and meaningful clinical functional changes.
- In contrast scales assessing ADL and caregiver burden are more likely to capture changes that reflect the functional changes observed on the functional scales. Some of the existing scales assessing ADL, such as the PEDI CAT (full spectrum) or the SMAIS (> 12 years old for self-report; all ages for caregiver report) appear to be promising and should be further validated. ACTIVLIM and SMA-FRS also appeared to be promising. Other scales, such as the EK2, are effective tools to be used in clinics, but are less appropriate in a clinical trial setting.
- Scales assessing caregiver burden were also considered to be important. There is often an overlap with ADL scales, exploring the same aspect in a different way (e.g., are you able to feed yourself (ADL), how much help do you need when feeding (Burden). Some work is still needed to establish the correlations between these two different approaches. The results of clinical trials, in which the ASCEND scale is used in combination with observer rated functional scales, should provide information on its sensitivity to change and on the correlation with commonly used functional scales (HFMSNE, RULM). Increasing attention there is also on the SMA HI that is currently being validated in SMA patients.

The participants also highlighted a few gaps and challenges that should be further addressed:

- One of the challenges is to explore activities of daily living and care burden in infants in the first year(s) of life, as at this age even typically developing children require full support for care related to feeding, toileting etc. An analysis on how the level of care and of independence changes with increasing age in the typically developing infants may help to identify areas to be explored by new tools;
- This latter point will also be useful in view of the fact that clinical trials and new therapies are increasingly targeting presymptomatic infants and a detailed follow up including PROMs will be required;
- Other aspects that require attention concern the need to explore a patient's experience of reduced endurance or perceived fatigability. It was suggested to combine endurance scales (observer rated) with patient reported items, identifying items that can be easily explored, at all ages, and are related to important activities of daily living (maintaining a posture, maintaining an activity or performing a repetitive movement) or in older patients, holding a hair dryer, taking notes, being able to type a full text on mobile etc.);
- Further challenges come from the fact that many tools were designed before the advent of new treatments and now, in treated patients, may have a ceiling effect that should be investigated.The workshop ended with a number of suggestions on how to optimize training, instructions, education and on future collaborative work to promote

further validation of the existing scales and on how to address the existing gaps.

Workshop Participants/SMA PROM Working Group

Laura Antonaci, Rome, Italy
Matt Civitello, Orlando, USA
Giorgia Coratti, Rome, Italy
Mencia de Lemus, Madrid, Spain
Roberto de Sanctis, Rome, Italy
Marcus Droege, Avexis, Chicago, USA
Tina Duong, Stanford, USA
Richard Finkel, Orlando, USA
Anna Lia Frongia, Rome, Italy
Ksenija Gorni, Roche, Basel, Switzerland
Chad Heatwole, Rochester, USA
Nicole Gusset, Heimberg, Switzerland
Erik Henricson, California, USA
Anna Mayhew, Newcastle, USA
Chiara Marchesi, Biogen, Basel, Switzerland
Eugenio Mercuri, Rome, Italy
Sonia Messina, Messina, Italy
Jacqueline Montes, New York, USA
Francesco Muntoni, London, UK
Amy Pasternak, Boston, USA
Astrid Pechmann, Germany
Maria Carmela Pera, Rome, Italy
Ivana Rubino, Biogen, Cambridge, USA
Valeria Sansone, Milan, Italy
Mary Schroth, Illinois, USA
Dylan Trundell, Roche, Basel, Switzerland
Volker Straub, Newcastle, USA

Acknowledgments

The organization of the workshop and the preliminary work are part of iSMAC, the international SMA consortium partly funded by Biogen.

References

[1] Davis SE, Hynan LS, Limbers CA, Andersen CM, Greene MC, Varni JW, et al. The PedsQl in pediatric patients with Duchenne muscular dystrophy: feasibility, reliability, and validity of the pediatric quality of life inventory neuromuscular module and generic core scales. J Clin Neuromuscul Dis 2010;11:97–109.

[2] Dunaway S, Montes J, Montgomery M, Battista V, Koo B, Marra J, et al. Reliability of telephone administration of the PedsQl generic quality of life inventory and neuromuscular module in spinal muscular atrophy (SMA). Neuromuscul Disord 2010;20:162–5.

[3] Iannaccone ST, Hynan LS, Morton A, Buchanan R, Limbers CA, Varni JW, et al. The PedsQl in pediatric patients with spinal muscular atrophy: feasibility, reliability, and validity of the pediatric quality of life inventory generic core scales and neuromuscular module. Neuromuscul Disord 2009;19:805–12.

[4] Messina S, Vita GL, Sframeli M, Mondello S, Mazzone E, D'Amico A, et al. Health-related quality of life and functional changes in DMD: a 12-month longitudinal cohort study. Neuromuscul Disord 2016;26:189–96.

[5] Mongiovi P, Dilek N, Garland C, Hunter M, Kissel JT, Luebbe E, et al. Patient reported impact of symptoms in spinal muscular atrophy (PRISM-SMA). Neurology 2018;91:e1206–e1e14.

[6] Pasternak A, Sideridis G, Fragala-Pinkham M, Glanzman AM, Montes J, Dunaway S, et al. Rasch analysis of the pediatric evaluation of disability inventory-computer adaptive test (PEDI-CAT) item bank for children and young adults with spinal muscular atrophy. Muscle Nerve 2016;54:1097–107.

[7] Stam M, Wadman RI, Bartels B, Leeuw M, Westeneng HJ, Wijngaarde CA, et al. A continuous repetitive task to detect fatigability in spinal muscular atrophy. Orphanet J Rare Dis 2018;13:160.

[8] Dunaway Young S, Montes J, Kramer SS, Podwika B, Rao AK, De Vivo DC. Perceived fatigue in spinal muscular atrophy: a pilot study. J Neuromuscul Dis 2019;6:109–17.

[9] Montes J, Garber CE, Kramer SS, Montgomery MJ, Dunaway S, Kamil-Rosenberg S, Carr B, Cruz R, Strauss NE, Sproule D, De Vivo DC. Single-blind, randomized, controlled clinical trial of exercise in ambulatory spinal muscular atrophy: why are the results negative? J Neuromuscul Dis 2015;2:463–70.

[10] Noto Y, Misawa S, Mori M, Kawaguchi N, Kanai K, Shibuya K, et al. Prominent fatigue in spinal muscular atrophy and spinal and bulbar muscular atrophy: evidence of activity-dependent conduction block. Clin Neurophysiol 2013;124:1893–8.

[11] Werlauff U, Hojberg A, Firla-Holme R, Steffensen BF, Vissing J. Fatigue in patients with spinal muscular atrophy type ii and congenital myopathies: evaluation of the fatigue severity scale. Qual Life Res 2014;23:1479–88.

[12] Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Colvin MK, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. Lancet Neurol 2018;17:445–55.

[13] Henricson E, Abresch R, Han JJ, Nicorici A, Goude Keller E, de Bie E, et al. The 6-Minute walk test and person-reported outcomes in boys with Duchenne muscular dystrophy and typically developing controls: longitudinal comparisons and clinically-meaningful changes over one year. PLoS Curr 2013;5.

[14] McDonald CM, McDonald DA, Bagley A, Sienko Thomas S, Buckon CE, Henricson E, et al. Relationship between clinical outcome measures and parent proxy reports of health-related quality of life in ambulatory children with Duchenne muscular dystrophy. J Child Neurol 2010;25:1130–44.

[15] Rouault F, Christie-Brown V, Broekgaarden R, Gusset N, Henderson D, Marczuk P, et al. Disease impact on general well-being and therapeutic expectations of European type II and type III spinal muscular atrophy patients. Neuromuscul Disord 2017;27:428–38.