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# A critical review of patient and parent caregiver oriented tools to assess health-related quality of life, activity of daily living and caregiver burden in spinal muscular atrophy

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**Abstract**

The positive outcome of different therapeutic approaches for spinal muscular atrophy (SMA) in clinical trials and in clinical practice have highlighted the need to establish if functional changes are associated with possible changes of patient health-related quality of life or have an effect on activities of daily living and caregiver burden. The aim of this paper is to provide a critical review of the tools previously or currently used to measure quality of life, activity of daily living, and caregiver burden in SMA. We identified 36 measures. Only 6 tools were specifically developed for SMA while the others had been used and at least partially validated in wider groups of neuromuscular disorders including SMA. Twelve of the 36 focused on health-related quality of life, 5 on activities of daily living and 9 on caregiver burden. Ten included a combination of items.

The review provides a roadmap of the different tools indicating their suitability for different SMA types or age groups. Scales assessing activities of daily living and care burden can provide patients and carers perspective on functional changes over time that should be added to the observer rated scales used in clinic.


*Keywords:* Spinal muscular atrophy; Quality of life; Activity of daily living; Health related quality of life; Care burden, Personalized medicine.

## 1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder due to mutations in the *SMN1* gene, causing degeneration of motor neurons in the spinal cord, with subsequent muscle wasting and weakness. In

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the last few years there have been exciting advances with revised standards of care and clinical trials using different therapeutic approaches such as antisense oligonucleotides [1,2], small molecules or gene therapy [3], showing increased life expectancy and functional and respiratory improvements. In parallel, there has been an increasing pressure from regulatory authorities and from the SMA community to capture patients and caregivers perspective on the impact of the new treatments on their 'quality of life' [4].

In neuromuscular disorders however there is the need to address aspects which are not only specifically related to health related quality of life (HRQL), but also able to capture activities of daily living, level of independence or caregiver burden that may show some changes in response to intervention. These aspects are overall related to each other [5,6] but their constructs and their aims are different. HRQL is the degree to which a medical condition impacts on a multidimensional construct, consisting at the minimum of physical, psychological (including emotional and cognitive) and social health dimensions delineated by the World Health Organization. HRQL measures can be categorized as generic or disease−specific. Generic HRQL measurement instruments enable comparisons across pediatric populations and facilitate benchmarking with healthy population norms, while disease−specific measures enhance measurement sensitivity for health domains germane to a particular chronic health condition [7–10].

The term activities of daily living (ADLs), refers to activities an individual should perform to manage basic physical needs in order to live independently [11–13]. These generally include a number of area related to physical functioning [14,15]: feeding, personal hygiene, dressing, toileting, transferring/moving around indoors and outdoors.

More complex activities, such as meal preparation, using public transportation, doing household chores, and grocery shopping ADLs are more often explored in adults and are referred as Instrumental ADLs [16–18] and are often explored in adults with possible cognitive impairment.

The term caregiver burden is generally used to include not only the physical burden related to the care but also the psychological, social and financial burden that is experienced when providing care [19–21]. When caregivers are within the family, their role is more complex and associated with multidimensional responsibilities and a higher psychological and emotional involvement. More recently there has been an effort to separate 'objective' burden that mainly refers to the more physical or instrumental aspects of care, from 'subjective burden', referring to the emotional or psychological aspects.

While each of these aspects is important, the construct of these measures is very different and the question has arisen if and how the possible changes observed on these tools reflect functional changes on the outcome measures used in clinical routine and in clinical trials.

This is particularly true for the HRQL questionnaires that often include social and economical items which are often not related to changes in functional abilities [22].

Another point of discussion is that, as SMA is a very heterogeneous disorder, spanning from non ambulant young children to ambulant adults, the individual scales may not be suitable for all SMA types and ages but may be more appropriate for a specific type or for distinct functional abilities (e.g. ambulant/non ambulant).

The aim of this study is to perform a critical review of the existing tools, including HRQL, ADLs, and caregiver burden questionnaires, in order to establish the domains assessed in each of the scale and their relevance to each SMA type.

## 2. Method

### 2.1. Search approach

A comprehensive search of the following electronic databases was performed: MEDLINE, CINAHL, PsycINFO, and EMBASE.

We also searched the web-based the TREAT NMD website dedicated to outcome measures (http://www.treat-nmd.eu/research/outcome-measures/rom/). Information on the tools used in the recently completed and ongoing clinical trials were also extracted from clinicaltrial.gov.

The primary search terms 'spinal muscular atrophy and 'neuromuscular disorder' were combined with keywords 'health−related quality of life', 'quality of life', 'activity of daily living' and 'caregiver burden'. All electronic searches were limited to the English language and to publication years 1980 to 2018. Reference lists of relevant articles were searched to identify any other further assessment tool or other studies evaluating their properties.

Furthermore, we also searched for the tools currently used in natural history and clinical trials in SMA. Fig. 1 shows the flow diagram developed using the PRISMA approach.

### 2.2. Inclusion / exclusion criteria

To be included, an assessment tool had to meet the following inclusion criteria: (1) to be related to HRQL, ADLs or caregiver burden; (2) reported in studies in SMA or pediatric neuromuscular disorders including SMA or (3) used in registered natural history studies or clinical trials and (4) the assessment was available for use.

### 2.3. Data management and quality assessment

The titles and abstracts of articles were screened by the first authors (ALF, LA, SM). As it was not always possible to ascertain details of the questionnaires from the abstract, we first identified all papers of interest and the full text of articles were then examined to obtain details of each domain of the tools and of their application.

A panel of experts (ALF, LA, SM, MCP, GC, EM) categorized, for each questionnaire, if domains were more related to HRQL, ADLs, or caregiver burden. When possible,

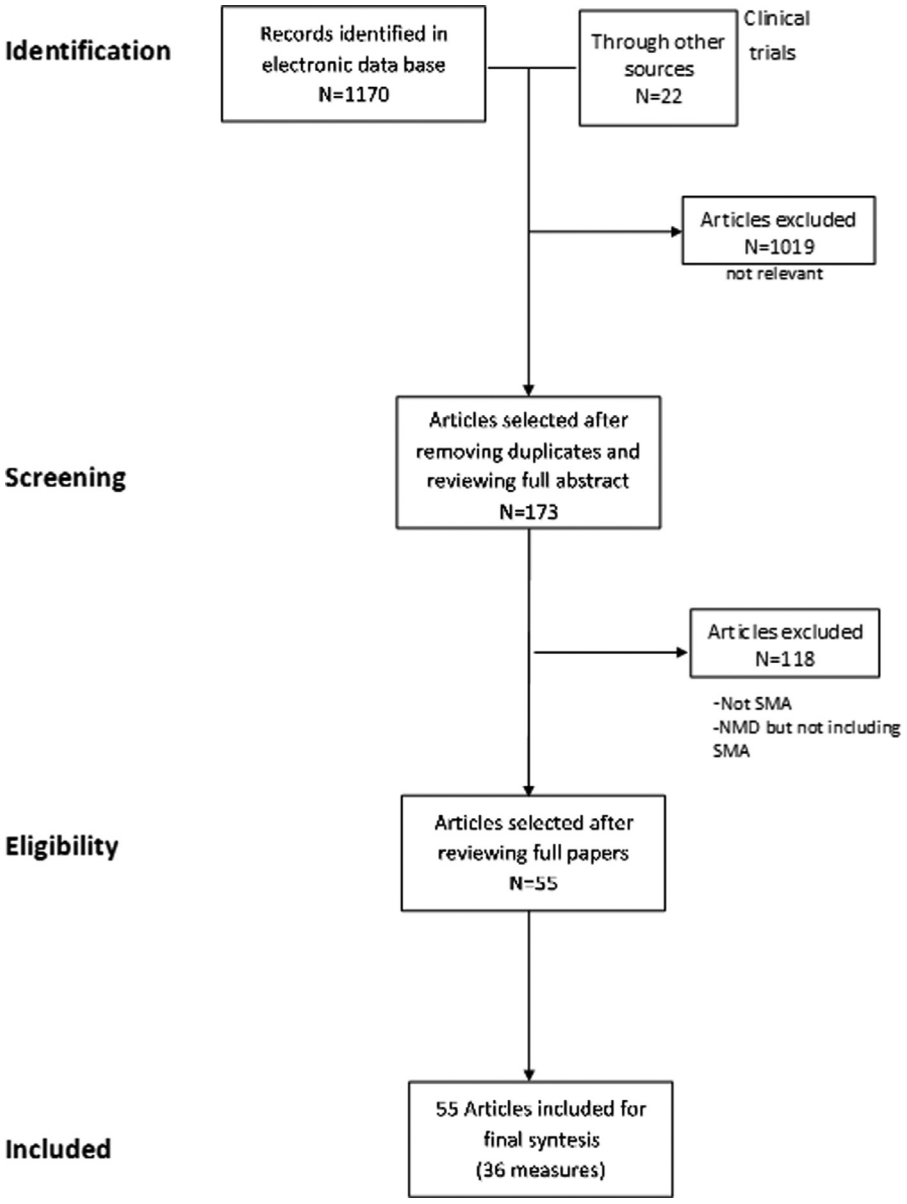


Fig. 1. PRISMA flow diagram illustrating the selection process of the included articles.

we also established if they were more appropriate for i) SMA Type 1, 2 or 3, or ii) specific age groups.

Finally, we searched for reliability and validity data reporting if the tool had already been used in longitudinal studies in SMA or other pediatric neuromuscular populations.

Data extracted included the name of the assessment tool, name of domain, designated population, validation in SMA, use in clinical trials.

## 3. Results

From the review of the literature, a total of 1170 articles were preliminarily selected based on their title. After reviewing the full abstracts, 173 were selected for review of the full paper. After reviewing the full paper, 55 papers were selected, reporting a total of 36 measures previously used in SMA or cohorts on neuromuscular disorders including SMA (Fig. 2).

We also identified another 4 measures, Work Activity Work Productivity and Activity Impairment (WPAI), SMA Independence Scale (SMAIS), Infant Toddler Quality of Life Questionnaire (ITQOL47) and SMA Health Index (SMA HI) that had not been published in full papers in relation to SMA or other pediatric neuromuscular disorders but have been used in recent or ongoing SMA natural history studies or clinical trials.

This resulted in a total of 36 measures identified (Tables 1–4 and Fig. 2). Twelve of the 36 focused on HRQL, 5 on ADLs and 9 on caregiver burden. Ten measures had a combination

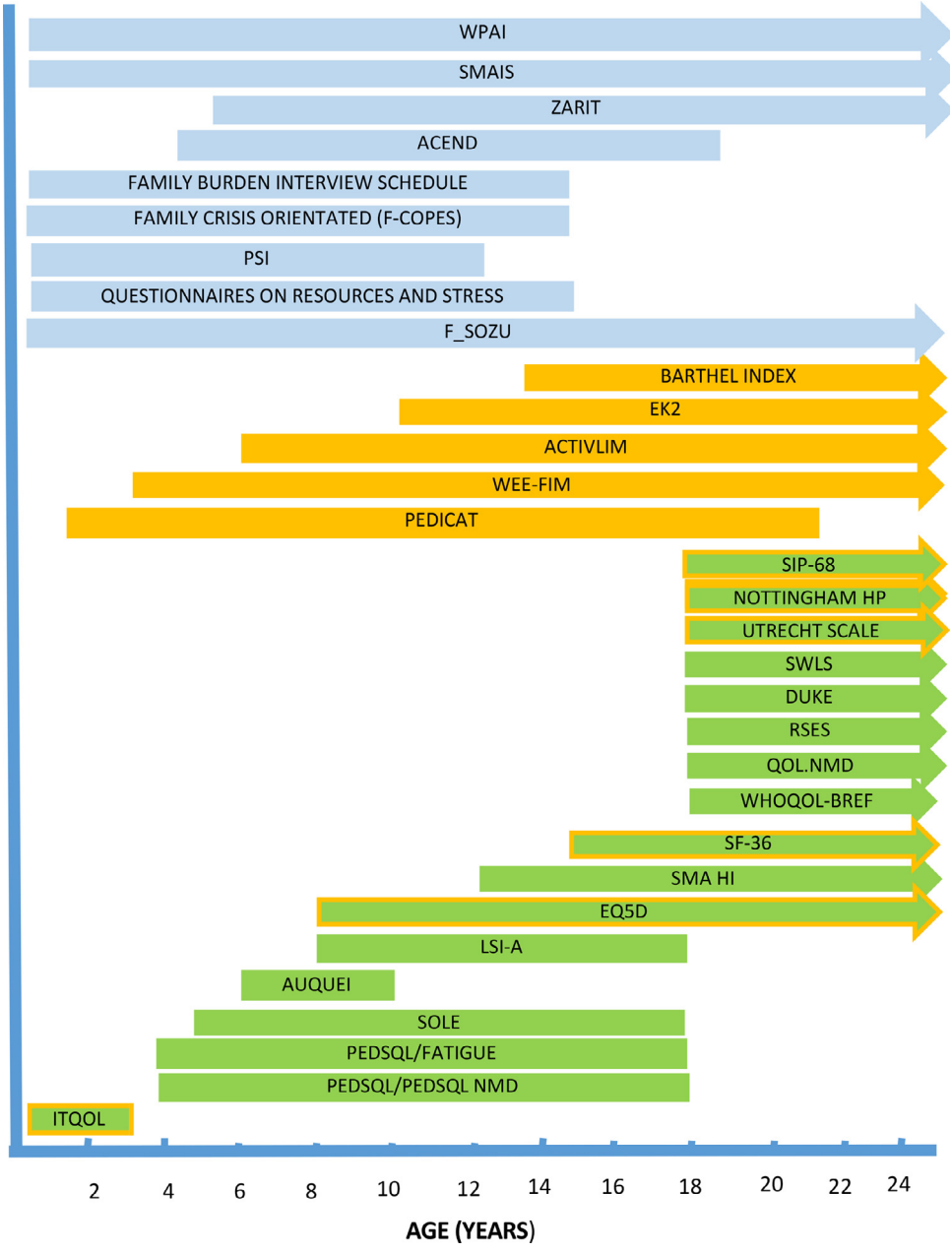


Fig. 2. Details of the measures included and of their possible application in different age groups. Key to figure: Measures assessing quality of life are shown in green, those assessing activities of daily living in orange and those assessing caregiver burden in blue. The measures in green with orange border indicate scales with items assessing both quality of life and activities of daily living.

of items related to quality of life and others related to ADLs or caregiver burden. Four were primarily developed as survey rather than outcome measures (reported at the end of Table 2 in bold).

### 3.1. Specificity for SMA

Six tools (SMA HI, SMAIS, FLASH SURVEY SMA, Patient Reported Impact of Symptoms in Spinal Muscular Atrophy "PRISM-SMA", International survey 1–2) were specifically developed for SMA.

Twenty were not specifically designed for SMA but had been used and at least partially validated in SMA cohorts while the others were used in neuromuscular cohorts including SMA patients.

Six of these measures underwent a Rasch analysis – modern psychometric analysis - (Egen Klassifikation 2 Scale "EK2", Activlim, Pediatric Evaluation of Disability Inventory Computer-Adaptive Test "PEDI-CAT", Pediatric Quality of Life Inventory generic core/NMM "PedsQL", Quality of Life in Neuromuscular Diseases "QoL–NMD") based on results obtained in neuromuscular cohorts.

Table 1
Details of the tools assessing Quality of Life reported in studies including SMA patients. (ADL: activities of daily living).

| | QoL | ADL | CARE BURDEN | SMA TYPE | Details/comments | References | used in SMA trials/NH studies |
|---|---|---|---|---|---|---|---|
| Pediatric Quality of Life Inventory Generic Core Scale | ✔ | | | 1,2,3 | Child self-reported (5–18 years) and caregiver reported (or children ages2-18 years). Generic tools to assess HRQL in children. | [26,31,33,34,60,80–82,84] | NCT02908685 NCT02628743 NCT02594124 NCT00227266 NCT01166022 NCT00443066 |
| Pediatric Quality of Life Inventory Neuromuscular | ✔ | | | 1,2,3 | Child self-reported (5–18 years) and caregiver reported (for children ages 2–18 years). Disease-specific modules for NMD (SMA, DMD). | [26,28,31,33,56,60,86,85] | NCT02908685 NCT02628743 NCT02594124 NCT01302600 NCT01494701 |
| Pediatric Quality of Life Inventory Multidimensional Fatigue Scale | ✔ | | | 2,3 | Self (5–18 years) and proxy-reported (for children ages 2–18 years). Specifically developed to measure quality of life and perceived fatigue. | [82,83] | NCT01166022 |
| Quality of Life Neuromuscular Disorders | ✔ | | | 2,3 | Patient self-reported (>18 years). Specifically developed for NM disorders. | [42,61,62] | no |
| World Health Organization Quality of Life questionnaire | ✔ | | | 2,3 | Patient self-reported (>18 years). Generic questionnaire to assess HRQL. | [42,61,62] | no |
| Autoquestionnnaire Qualite ´de Vie Enfant Image | ✔ | | | 1,2,3 | Child self-questionnaire (from 6 to 10 years of age). Generic tools to assess QoL in children. | [36] | no |
| Life Satisfaction Index for Adolescents | ✔ | | | 1,2,3 | Self (8–18 years) and caregiver-reported (5–18 years). Wide range of functional status. Developed for DMD. | [63] | no |
| The Strips of Life with Emoticons | ✔ | | | 1,2,3 | Self-reported questionnaire (5–18 years). Developed for children with NMD. | [25] | no |
| Rosenberg Self-Esteem Scale | ✔ | | | 2,3 | Self-reported questionnaire more oriented for adults (>18 years of age). Generic tool to assess individual's self-esteem. | [64] | no |
| Duke Health Profile | ✔ | | | | Self-administered questionnaire more oriented for adults. Generic instrument. | [65] | no |
| Satisfaction with Life Scale | ✔ | | | 2,3 | Self-reported questionnaire more oriented for adults. Generic tool to assess psychological well being. | [64] | no |
| SMA health Index | ✔ | | | 2,3 | Self-reported>12 years | Proceedings Cure SMA 2018 | natural history |

## 4. Discussion

The aim of this study was to review the existing PROMs used in SMA. In order to do so we expanded the search beyond the term 'health related quality of life' in order to identify other tools related to ADLs, independence and care burden that also have an impact on quality of life. The rational beyond this 'extended' review was that we wished to explore which aspects were assessed by the available measures and to establish a roadmap of their appropriateness in relation to age and functional status in SMA. This has become important at the time there is the need to explore the impact of new drugs on various aspects of patient and caregiver experiences that may not be captured by functional assessments performed in a clinical setting.

Our review showed that very few tools have been specifically developed for SMA. These tools have the advantage that, being disease specific, can better address the specific issues related to the disease and be more sensitive to possible interventions. Their number and data on their full validation is however still very limited. A number of more generic patient/carer reported measures that can be potentially used in SMA is also available and many of them have been at least partly validated in SMA or in groups of neuromuscular cohorts including SMA.

We also found that none of the scales had a full validation process and only few underwent Rasch analysis that in recent years has been increasingly used to establish the statistical robustness of different outcome measures.

Table 2
Details of the Quality of Life tools including items assessing activities of daily living reported in studies including SMA patients. (ADL: activities of daily living). The shaded areas report the 4 measures, developed as surveys.

| | QoL | ADL | CARE BURDEN | SMA TYPE | Details/comments | References | used in SMA trials |
|---|---|---|---|---|---|---|---|
| The Short Form 36 Health Survey | ✔ | ✔ | | 2,3 | Self-reported questionnaire, form includes questions more oriented for adults (minimum age 14 years). Generic functional health and quality of life, instrument. | [43,47–49,51,66,82] | NCT02628743 NCT01166022 |
| EuroQol-5D 5L, 5D, 3 | ✔ | ✔ | | 2,3 | Self-reported questionnaire and caregivers-reported module. Generic instruments to assess health status in a wide range of ages (children to adulthood). | [45] | NCT02908685 NCT02628743 |
| Nottingham Health Profile | ✔ | ✔ | | 2,3 | Self-administered questionnaire more oriented for adults person. Generic instrument to measure health related quality-of-life. | [43,44,67] | no |
| Sickness Impact Profile 68 | ✔ | ✔ | | 2,3 | Self-reported questionnaire. General health measure. | [6]8 | no |
| Utrecht Scale | ✔ | ✔ | | 3 | Self-reported questionnaire for adults (>18 years). Generic tool to assess participation. | [64,66] | no |
| Infant and toddler quality of life questionnaire | ✔ | ✔ | | 1,2,3 | Parent-completed 2–72 months).Generic profile measure. | | NCT02913482 |
| **FLASH SURVEY** | ✔ | ✔ | | **2,3** | **Self-reported and care giver reported developed to appraise the expectations on current therapeutic developments in type 2 and 3 SMA patients.** | **[52]** | **no** |
| **International survey (1)** | ✔ | ✔ | | **2,3** | **Self-reported and care giver reported. Specifically developed to assess the meaningfulness of functional items and the expectations on current therapeutic developments in type 2 and 3 SMA patients.** | **[53]** | **no** |
| **International survey (2)** | ✔ | ✔ | | **2,3** | **Self-reported and care giver reported.** | **[55]** | **no** |
| **Patient reported Impact of symptoms in Spinal Muscular Atrophy** | ✔ | ✔ | | **2,3** | **Self-reported (adults) assessing how different symptoms affect adult life in SMA.** | **[54]** | **no** |

We identified 36 PROMS that in most cases could be classified into one of the different categories (HRQL, ADLs, caregiver burden). Only 10 tools had a combination of items falling into more than one category.

Twelve were classified as HRQL tools. As recently reported by a recent systematic review focusing on HRQL in SMA, we also found that there were no published disease-specific HRQL tools [23]. Since the publication of the previous review, a newly developed scale, the SMA HI, specifically adapted for SMA has become available. The SMA HI has been presented at international conferences and is currently being validated in SMA teen agers and adults from the age of 12 years.

The available non disease specific HRQL measures cover a wide age range, from tools designed for carers of very young infants (ITQOL-SF47) [24] to others covering the whole pediatric spectrum and beyond. The Strips Of Life with Emoticons (SOLE) questionnaire [25] uses a graphic approach with cartoons that may prove to be more accepted by young children.

The PedsQL, including the generic and neuromuscular modules, is the most commonly utilized tool in children with neuromuscular disorders [22,26–34]. This tool had some validation in SMA [26], and is currently used in several clinical trials. The results of the ongoing trials will help to establish if and how the different domains of the PedsQL relate to functional abilities on the functional assessments used in the trials, often also used in SMA clinical routine, and which effectively capture the drug-related improvements. This is an important point to address as a recent study in Duchenne

Table 3
Details of the tools assessing activities of daily living reported in studies including SMA patients. (ADLs: activities of daily living).

| | QoL | ADL | CARE BURDEN | SMA TYPE | Details/comments | References | used in SMA trials |
|---|---|---|---|---|---|---|---|
| Egen Klassification 2 Scale | | ✔ | | 2,3 | Self-reporting questionnaire for non ambulant teen agers and adults. Specific tool designed to measure functional ability in wheelchair person with DMD and SMA. | [39,40,69–72] | no |
| ACTIVLIM | | ✔ | | 1,2,3 | Self-reported and parents version (6–80 years. Specific tool designed to assess activity limitations in patients with NMD. | [38,73,74] | no |
| Pediatric Evaluation of Disability Inventory Computer Adaptive Test | | ✔ | | 1,2,3 | Caregiver-reported form for a wide age range (1 to 21 years) and functional status (non sitters to ambulant).Generic tool to assess the performance level for children and young adults with disabilities. | [41] | no |
| Barthel index | | ✔ | | 2,3 | Self-reported or caregiver-reported >12 y. Generic tool to evaluate physical disability. | [25,42–45,61] | no |
| The Functional Indipendence Measure | | ✔ | | 1,2,3 | Self or proxy- reported questionnaires (children up to 3 years of age to adult ages). Generic instrument to assess functional independence level in children and adults. | [57,67,75,76] | no |

muscular dystrophy showed a poor correlation between the changes on the PedsQL and functional changes, with the exception of the domains assessing fatigue [22].

The possible correlation with fatigue appears to be particularly relevant for SMA as fatigue has been reported to be frequent in SMA patients, with both clinical and neurophysiological evidence on the six-minute walk test (6MWT) and on repetitive nerve stimulation [35]. Perceived fatigue, a person's subjective report, was not related to function or quality of life in SMA types II and III or objective fatigue measured on the 6MWT in ambulatory patients.

A poor correlation between functional measures and quality of life scales has also been found using the Autoquestionnnaire Qualitè de Vie Enfant Image (AUQUEI) [26], another non disease specific HRQL tools used and validated in children with SMA from the age of 5 or 6 years.

A number of PROMS explore activities of daily living. The review of these tools confirms a recent trend to develop new tools or modify existing tools to assess activities of daily living in neuromuscular disorders [37,38] often developed as an integration to the observer rated scales administered in the clinical setting. These new tools include a list of items reflecting activities of daily living that cannot be easily assessed in a clinical setting.

One of these scales, the EK2 [39,40], explores ten categories, each contributing to an overall picture of function, including different aspects such as swallowing, breathing, trunk mobility. The items included in the scale however are not specific for SMA and mainly reflect the original intent of using it in non ambulant patients, particularly with Duchenne Muscular Dystrophy.

The PEDI-CAT [41], has the advantage to capture typical performance across a wide range of ages (1–21 years) and abilities, measuring mobility, daily activities, social/cognition and responsibility. The assessment targets children and youth across all diagnoses, conditions and settings. The PEDI-CAT is reported to be useful for measuring mobility and daily activity skills in Type II/III SMA, but further studies are needed to establish its sensitivity to detect small functional changes over time.

The Barthel index has also often been used in SMA [42–45], measuring functional independence in the daily functioning by assessing ten basic ADLs. It is largely used in health research [46] and in rehabilitation to establish a baseline level of functioning and, by repeating the test periodically, improvement in the chronically ill.

Other HRQL instrument measures, like the SF-36, have been used in a large number of studies on neuromuscular diseases including SMA patients [47–51].

Even if strictly cannot be defined as outcome measures, there has been a recent effort to develop questionnaires to be used as surveys [52–55,68]. These have been designed to assess disease impact on the general well-being of Type II and Type III SMA patients and how the ability to perform individual activities of daily living has an impact on their life [52–55]. The most recent ones also explore how the patients feel about preserving or improving individual functional capacities in relation to possible trials.

Table 4
Details of the tools assessing care burden reported in studies including SMA patients. (ADL: activities of daily living; * the reference is related to a paper describing the scale in another disease).

| | QoL | ADL | CARE BURDEN | SMA TYPE | Details/comments | References | used in SMA trials |
|---|---|---|---|---|---|---|---|
| Assessment of Caregiver Experience with Neuromuscolar Disease | | | ✔ | 1,2,3 | Caregiver-reported, form includes questions for a wide range (4–18 years) of age and functional status (non sitters to ambulant). Instrument specifically designed to assess the caregiver burden of children with NMD. | [77] | NCT02594124 |
| Zarit Burden Interview | | | ✔ | 1,2,3 | Caregiver-reported (> 5 years). Generic tool non specific for NMD. | [45,57] | no |
| Parenting Stress Index | | | ✔ | 1,2,3 | Caregiver-reported. For children aged 1 month to 12 years.Generic tool designed to evaluate the magnitude of stress in the parent–child system. | [34] | no |
| Fragebogen zur sozialen Unterstutzung (F-SOZU) | | | ✔ | 1,2,3 | Caregiver-reported questionnaire. General instrument to assess social support. | [58,78] | no |
| Questionnaire on Resources and Stress | | | ✔ | 1,2,3 | Parents-reported questionnaire. General tool to evaluate perceived stress in parents of children with disabilities. | [55,75] | no |
| Family Crisis Orientated Personal Evaluation Scale | | | ✔ | 1,2,3 | Parents-reported questionnaire. General tool created to identify problem solving and behavioral strategies utilized by families in difficult or problematic situations. | [55,75,59] | no |
| Family Burden Interview Schedule | | | ✔ | 1,2,3 | Parent-reported questionnaire. General tool to assess impact on the family of different pediatric disorders. | [51] | no |
| Work productivity and Activity Impairment Questionnaire | | | ✔ | | Caregiver-reported, form includes questions for a wide range of age and functional status (non sitters to ambulant). | [79]* | NCT02908685 NCT02628743 |
| SMA Index Scale | | | ✔ | 2,3 | Self and caregiver-reported (>12 years). | | NCT03032172 NCT02908685 |

A number of tools focus on caregiver burden in SMA, considering the socio-economic burden more than the psychological impact of the disease [34,45,56,59]. New scales, such as the SMAIS, have been specifically developed for SMA and have recently been proposed for clinical trials and appear to have a number of items that are relevant for SMA but data on their validation are not yet available.

Our results provide, for the first time, a general overview of the PROMs in SMA, expanding the previous reviews focused on quality of life only.

Having a large library of PROMS exploring different aspects provided the opportunity to design a roadmap including different tools that could be used in different settings. There has recently been a lot of discussion on the costs of the new therapies and on their impact on patients and their carers. Possible changes in motor function, that are increasingly observed with new therapies both in clinical trials and in real world data [87], are more likely to be mirrored by changes in activities of daily living and on care burden than by general measures of quality of life [22,36]. This is particularly true for scales assessing activities such as transfers from wheel chair or turning in bed that cannot be easily assessed with an observer rated scale in a clinical setting and have a big impact on the level of independence for patients and for their carers.

QOL measures in contrast provide additional information on more specific health related issues that may also be useful in more general socio-economic studies.

We also reported the suitability of these measures for different age groups and different functional level that could be used at the time of selecting one or more measures in a research setting or to explore additional clinical information in different clinical groups. Some tools appear to be more appropriate for specific subgroups (non ambulant patients) with many of them developed for adults. For the time being there are no specific scales for type I, probably related to the fact that until recently type I infants had a very limited survival.

At the time new phenotypes are emerging as the result of the new disease-modifying approaches, there is the need to cover additional aspects that are not captured by the observer rated functional scales. Combining effective tools

such as ADLs and caregiver burden may allow us to further strengthen the patients and carers perspective, capturing additional information on gains or losses of complex functions most clearly relevant to patients every−day life.

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